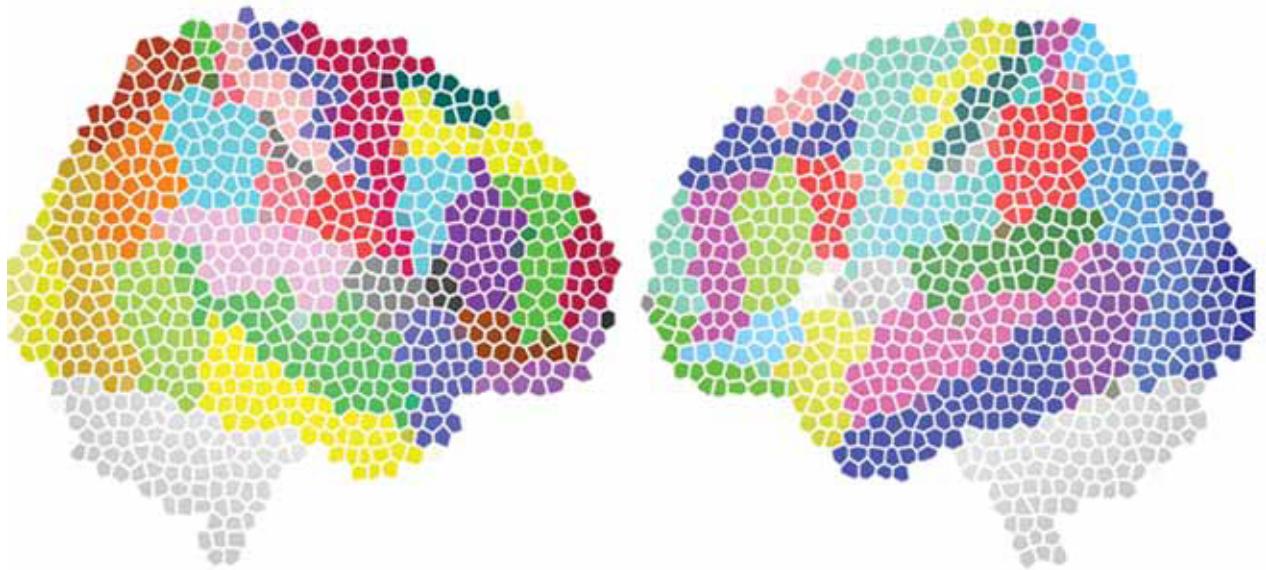


# The Two Halves of the Brain



Information Processing in the Cerebral Hemispheres

edited by Kenneth Hugdahl and René Westerhausen

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**edited by Kenneth Hugdahl and René Westerhausen**

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## Preface

The current volume is a follow-up to the two previous MIT Press volumes on hemispheric asymmetry and brain laterality in 1995 (Davidson & Hugdahl: *Brain Asymmetry*) and 2003 (Hugdahl & Davidson: *The Asymmetrical Brain*). The main reason for an update is that the field is rapidly expanding again, after a resting period in the last decade, attracting the interest of a new generation of researchers. This renewed interest in hemispheric asymmetry is coming both from new theoretical approaches and applications to new areas and from the development of new measuring techniques. Another new trend in the literature is the increasing number of international researchers engaged in hemispheric asymmetry research. The current volume clearly reflects these trends with a mix of well-established and young researchers, reflecting both continuity and novelty. There are 21 contributions from 11 countries (the United States, Japan, the United Kingdom, Germany, Italy, New Zealand, France, the Netherlands, Finland, Norway, and Sweden), and four different continents, covering the range of asymmetry research from the molecular to the cognitive and clinical level of explanation. It has been the ambition of the editors to present a comprehensive update on the field. With all the challenges and pitfalls inherent in such an ambitious undertaking, we think that the current volume has been successful in achieving its goals.

Kenneth Hugdahl and René Westerhausen  
Bergen, Norway, May 2009



## **Introduction and Overview**

**Kenneth Hugdahl and René Westerhausen**

### **Aims and Objectives**

In this general introduction we outline a theoretical umbrella perspective on the 21 chapters in the book, to emphasize novel theories, methods, and applications of research devoted to hemispheric asymmetry and laterality. Despite all the research devoted to hemispheric asymmetry and laterality over the last decades, this is an area in which big questions remain with respect to understanding the neural underpinnings of cognition, and the questions being addressed in this field are ones that come up for almost any cognitive science researcher. Moreover, it is not possible to advance a theoretical understanding of brain-behavior relations without taking asymmetry and laterality into account. Similarly, issues related to asymmetry and laterality penetrate most theories and models of neuropsychology and neurocognitive aspects of the major neurological and psychiatric diseases and disorders. However, despite the large amount of empirical data accumulated over the last decades (see Davidson & Hugdahl, 1995; Hugdahl & Davidson, 2003), theoretical understanding of the behavioral significance and the neural basis of laterality remains limited. Thus, the questions of "why," "how," and "what" are as valid today as they were 30 years ago (e.g., Bradshaw & Nettleton, 1981; Bryden, 1982; Harnad et al., 1977; Porac & Coren, 1981).

Our objective when compiling the current volume has therefore been not only to update the reader on the latest data and empirical results but also to provide a coherent theoretical perspective whenever possible to put the different chapters and contributions into perspective. The field of hemispheric asymmetry has more or less exploded in recent years with ever new data and applications, but there has not been a corresponding explosion of theoretical advances. In this introduction, we comment on the different contributions from a theoretical perspective, moving from molecular, genetic, and evolutionary to cognitive and clinical factors in the understanding of one of the most fascinating phenomena in neuroscience, neuropsychology, psychiatry and neurology, and cognitive sciences.

## Functional Segregation and Integration in an Asymmetrical Brain

The issue of functional segregation and integration in the brain has a long history in neuroscience, with the observations of Broca and Wernicke as classic examples for the localization of language areas in the left hemisphere. However, it was not until the development of the hemodynamic neuroimaging techniques that the concept of functional segregation also gained acceptance in mainstream cognitive psychology and cognitive neuroscience (Friston, 2005). Before this development, it was not uncommon to find statements like “Where is memory localized in the brain?—Everywhere and nowhere” in standard textbooks in psychology and neuroscience. Such statements have almost totally disappeared from the literature following the introduction of positron emission tomography (PET) and functional magnetic resonance imaging (fMRI) as well as modern analysis techniques—for example, source localization, to supplement magnetic- and electroencephalographical (EEG) methods, such as magnetoencephalography (MEG) and EEG/ERPs. Frith (1997) provides several arguments as to why segregation, rather than integration, is the guiding principle behind the functional organization of the brain, taking arguments from evolution, economy, and the complexity of the design of the brain.

In his review of EEG/MEG measures of hemispheric asymmetry, Alfredo Brancucci (chapter 8) shows how EEG was the first “objective” measure to be used to infer asymmetry of neuronal firing in the two hemispheres by comparing EEG responses obtained from the left and right side of the scalp. The later development of newer recording techniques, for example, the use of MEG, opened up opportunities for more fine-grained analyses of direct neuronal correlates of behavioral asymmetries seen in response to auditory and visual tasks. A general conclusion to be drawn from all electrophysiology studies of hemispheric asymmetry, with a variety of recording and analysis measures, is that the two cerebral hemispheres show different patterns of activation when provoked by specific stimuli or tasks.

## A Historical Perspective

Looked at from a more narrow perspective, the study of hemispheric asymmetry and brain laterality has had a long tradition in the neurosciences, and in psychology, biology, and medicine (see Davidson & Hugdahl, 1995, for an overview). The fact that the vertebrate nervous system is divided into two halves has attracted the attention and has sparked the speculation of numerous generations of scientists, actually further back than typically recognized (see Harrington, 1995). In her treatment of the history of research on hemispheric asymmetry, Harrington (1995) argues that many of the fundamental assumptions regarding the “unquestioned truths” about differences between the cerebral hemispheres have their roots in 19th-century theories of what

was called localization theory, which in modern terminology would translate to brain "structure-function relationships."

It is not possible to discuss the history and theory of hemispheric asymmetry without mentioning the speculations of Franz Joseph Gall, who perhaps more than Paul Broca and Carl Wernicke personifies the idea that the brain is divided into functionally segregated regions with their own cognitive and emotional processing specializations. Gall's ideas with respect to localization theory were not supported by later empirical research, and his views are today mostly forgotten, except in historical overviews. However, as correctly pointed out by Harrington (1995), it was Gall who changed the at that time religiously influenced view that all mental capacities were hierarchically organized with the less "divine" mental faculties like sexual and animal-like behaviors at the bottom and more divine faculty like language and prayers at the top. He also changed the view that the human mind was a holy unity by claiming that it could be broken down into "brain-based building blocks."

### **Imaging the Asymmetry of the Mind**

The notion of localization and specialization of the mind and that different mental capacities could be anatomically localized in the brain along a left-right gradient received new interest with the introduction of functional imaging in the beginning of 1980 (see Friston, 2003). That the functioning of the mind could be visualized on a template brain anatomy image was a revolution in itself but that it also would show differential effects on brain metabolism across the hemispheres depending on the nature of the cognitive task further attested that the human mind was not a holy unity that could not be broken down into its subcomponents. The introduction of functional neuroimaging techniques also ended the view held by many neuroscientists of what could be called the "equipotentiality" and "mass action" principles, originally introduced by Karl Lashley in the 1940s and 1950s (Lashley, 1950). The equipotentiality principle stated that all cortical areas can substitute for each other as far as higher cognitive functions are concerned, as in, for example, learning. The principle of mass action similarly stated that the reduction in performance for a given cognitive function, for example, the ability to learn, is proportional to the amount of brain tissue destroyed, and the more complex the cognitive task, the more disruptive brain lesions would be.

Thus, while the behavioristic view of the functioning of the mind and the brain was a nonlocalized and nonspecialized view, the view of Gall and later brain imagers was a localized and specialized view, in particular, one in which the two cerebral hemispheres had different functions (see also Huettel et al., 2004). However, modern views of specialization of the hemispheres are focused not only on finding specific areas or regions within or between the hemispheres that may show functional

specificity but also on understanding the functional relationships, or connectivity, between different areas and regions in a network perspective. In this regard, the terms functional versus effective connectivity have been used (e.g., Frackowiack et al., 2004). Functional connectivity means the statistical correlation between two areas in the brain with regard to observed signal strength to a common cognitive task, while effective connectivity means how a certain brain region may have a causal influence on another region, or regions, which will require knowledge of possible alternatives, set by knowledge of functional brain anatomy.

An extension of the notion of connectivity is the identification of a resting state, or the default-mode cortical activation network in the absence of explicit external (or internal) stimuli (Raichle et al., 2001; Raichle & Snyder, 2007). An fMRI default-mode network analysis is applied to the study of hemispheric asymmetries in the chapter by Nathan Swanson, Tom Eichele, Godfrey Pearlson, and Vince Calhoun (chapter 20). The analysis of asymmetry of default-mode activation (also during activation) is a novel application of fMRI data for the study of hemispheric asymmetry that could have important theoretical as well as clinical consequences. Theoretically, it could mean that the hemispheres differ in their “idling” state, which could have consequences for increases or decreases in activation in a “running” state when the brain is required to process certain stimuli or instructions. Clinically, it could help us understand how hemispheric asymmetries differ between different clinical states and diagnostic categories, as well as why patients in a specific diagnostic category may shift hemispheric asymmetry pattern across time.

### Cortical Structural Asymmetries and White Matter Tracts

Recent years have also brought us new methods to look at structural asymmetries between the two hemispheres, namely, cytoarchitectonic mapping (Amunts & Zilles, 2001) and diffusion-tensor imaging (DTI; see Jones, 2008; LeBihan, 2003) that have significantly widened our perspective on the brain’s asymmetry. Based on cytoarchitectonic analysis of postmortem brains, it was shown that macroanatomical landmarks often do not allow for an exact localization of functional modules of the cerebral cortex and that there is a substantial interindividual variability in the exact location of these modules. This observation not only led to the development of cytoarchitectonic maps that support a probabilistic localization of functional cortex modules (see Eickhoff et al., 2005) but also advanced the understanding of asymmetries in the cerebral cortex.

Structural brain imaging results are summarized by Katrin Amunts in chapter 6, in which she reviews the available evidence about brain structural asymmetries. In her comprehensive review, she comes to the conclusion that structural asymmetries are to be found in many, perhaps all, other brain regions (e.g., visual cortex, parietal

cortex, hippocampus); that such previously thought to be static differences are subject to dynamic modulation through environmental influences; and that the degree of asymmetry differs with respect to brain region, handedness, gender, and disease.

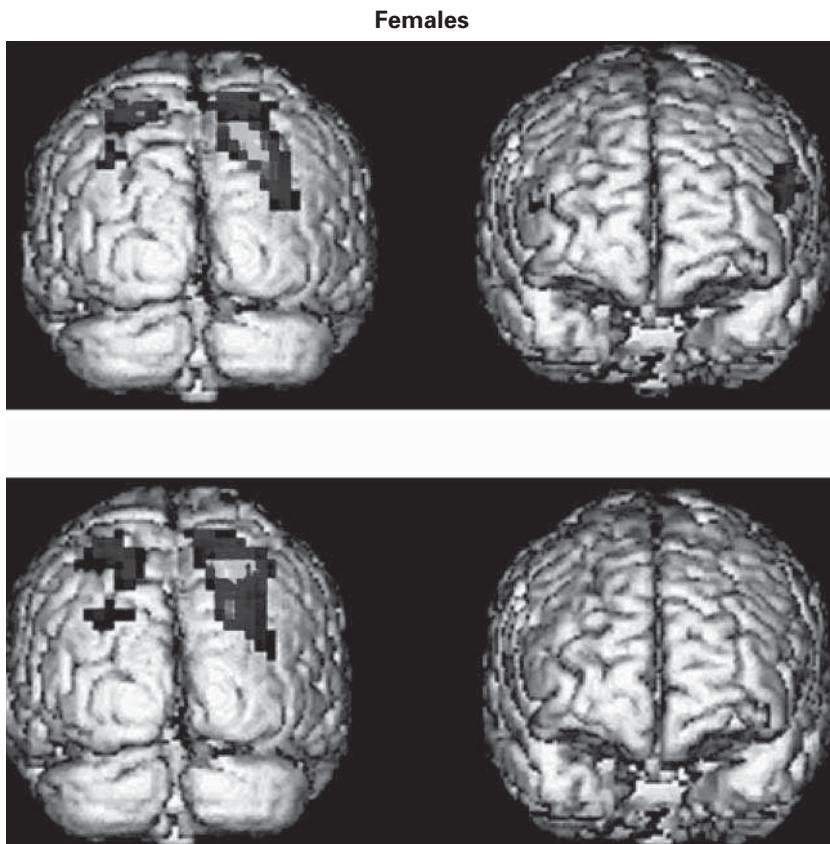
Marco Catani, Stephanie Forkel, and Michel Thiebaut de Schotten (chapter 7) advance a hodological view on hemispheric asymmetry, that not only the functional modules of the brain networks but also the anatomical connections between the spatially distributed modules are of importance. Studies regarding brain hodology were until recently limited to studies on the effect of lesions or postmortem dissection of the brain white matter. However, with the introduction of DTI into neuroimaging about 10 years ago and its “boom” during the last 5 years, it is now possible to non-invasively examine white matter brain connections. DTI allows researchers to calculate indices representing white matter tissue characteristics (e.g., anisotropy) that are supposed to reflect factors like axon myelination and fiber density (Beaulieu, 2002). Moreover, it allows researchers to track white matter fiber bundles throughout the brain and thus to assess the connections between distant cerebral cortex areas. Marco Catani and colleagues demonstrate that DTI fiber tracking can be used to reveal hemispheric asymmetries in structural connections and gain information that goes beyond the knowledge derived from the more traditional approaches.

### **Effects of Asymmetry on Inter- and Intraindividual Differences**

Figure I.1 (plate 1) shows an example of superior activation in the right posterior parietal lobule when healthy subjects solve a three-dimensional mental rotation task (Hugdahl, Thomsen, & Ersland, 2006), attesting to the specificity of functional segregation in the brain. Interestingly, the lower panel of Figure I.1 shows that while female subjects in addition activated speech production brain regions overlapping with Broca’s area, no such activation was seen in the male subjects. Thus, fMRI also highlights sex differences in hemispheric asymmetry that had been observed in psychological experiments over a long period of time. Thus, it seems that males and females utilize different processing strategies when approaching the same task, with females using a verbal, or language-guided, approach, and males using a spatial, or perceptually guided, approach.

The results seen in figure I.1 may lend themselves also to a discussion of the origin of hemispheric asymmetry in an evolutionary perspective. Perhaps the different brain activations in males and females seen in figure I.1 are modern variants of a functional division of labor made necessary from the need to socialize the next generation of offspring into a language-guided culture versus the need to orient in three-dimensional space to localize prey and to find the way back home to feed the members of the culture.

The important issue of sex differences in hemispheric asymmetry is further reviewed and discussed in the chapter by Iris Sommer (chapter 10), who provides an updated



**Figure I.1 (plate 1)**

Functional magnetic resonance imaging/blood-oxygen-level-dependent activations in males and females to a three-dimensional mental rotation task. Note the profound right-over-left parietal asymmetry in both males and females and the unique female left asymmetry in the frontal cortex.

review and meta-analysis of existing research on sex differences, coupled with a thorough discussion of a possible underlying mechanism in a more bilateral brain in females. Such an underlying mechanism would explain why there are more boys than girls with language-related disorders such as dyslexia and specific language impairment. It would also explain why more males than females are affected by psychiatric dysfunctions and disorders like autism, attention-deficit/hyperactivity disorder (ADHD), and schizophrenia. A problem, as pointed out by Sommer, is that although such a hypothesis is theoretically reasonable, it has been difficult to provide empirical evidence supporting it.

Sex differences in hemispheric asymmetry can be seen as a variant of individual differences, which is further elaborated on by Markus Hausmann and Ulrike Bayer (chapter 9) in their chapter on the effect of sex hormones on hemispheric asymmetry and interhemispheric integration. Thus, the authors address a factor influencing brain asymmetry previously neglected or treated as error variance to be ignored. By systematically investigating the effects of sex hormones on brain function and hemispheric asymmetry, Hausmann and Bayer show that sex hormones are important modulators of performance asymmetries and that this reveals an intraindividual variation (the different phases in the menstrual cycle) in addition to interindividual variation (males vs. females). Thus by focusing on the change in performance on tasks involving the differential engagement of the right and left hemisphere, Hausmann and Bayer show how new theoretical advances are made in the understanding of what previously was labeled errors not of interest for asymmetry research.

The chapter by Maria Casagrande (chapter 11) further pushes our understanding of state-dependent asymmetries by showing how hemispheric asymmetry patterns and interactions vary with sleep and different sleep stages. Casagrande's research extends the notion of hemispheric asymmetry to altered states of consciousness as in sleep states.

### **Genes and Evolution—Are Humans Unique?**

One the most important developments in asymmetry research was the discovery in 2005 by Tao Sun (see also chapter 1 in the current volume) of a possible link to a specific gene (LMO4) which is differentially expressed on the right and left side of the brain in the perisylvian region. This region of the brain overlaps both Wernicke's functional area for speech sound perception and the planum temporale structural area in the brain.

This raises again the issue of the uniqueness of human asymmetry and asymmetry for language as the dominant principle of organization of the two cerebral hemispheres. Such a view is supported by Crow (1997; see also chapter 21, this volume). However, the findings by Gannon et al. (1998) that chimpanzees have a larger left than right planum temporale call into question a human uniqueness for language asymmetry. Thus, on the one hand, it can be argued that the neuronal underpinning for language and speech processing is not uniquely human. This then raises the question of what evolutionary pressure would have caused primates not to develop language. It has been speculated that an upright body position (see Lieberman, 2006) was necessary for the development of language, because of the need for a critical length of the vocal tract for production of the sounds necessary for speech. Primates have the head tilted forward compared to humans, with a corresponding shortening of the vocal tract, probably a consequence of the need for using both arms and legs when

walking and climbing. An alternative explanation may be that planum temporale asymmetry developed for some other (unknown) purpose in both species and that it later took on a speech-related function in humans but not in the great apes.

Since efficient speech perception presupposes the existence of an equally effective speech production module (it would not make sense to have a perception module if no one was speaking), the absence of a structural asymmetry for Broca's area (but see chapter 6 by Amunts, this volume) could speak to the independent nature of speech perception and planum temporale asymmetry. Sun makes the important observation in chapter 1 that

even though genetic models of human handedness have been proposed, the "genes" that may control preferential hand use in humans have not been identified. Taking advantage of large-throughput screening approaches, we are beginning to uncover the differential gene expression in human left and right hemispheres. These candidate genes can serve as references in revealing the molecular mechanisms of brain asymmetry and handedness in humans and animal models.

Thus, recent advancements in genetic and molecular techniques such as microarray methods for observation of gene expression in brain tissue increase the probability that we will be in a position to identify the genes responsible for hemispheric asymmetry. It seems that the available empirical evidence would suggest that the left and right hemispheres in humans show differences in gene expression and that this can be seen early in fetal development. What is, however, still not resolved is how such differential gene expression is related to structural and functional asymmetries as seen in speech perception, visuospatial coordination, or handedness to take a few examples.

In his chapter on the evolutionary origin of hemispheric asymmetry, Michael Corballis (chapter 3) asks the question of whether there is "a middle ground" between the opposing views held by proponents of a unique humanness for hemispheric asymmetry (e.g., Crow, 1997) and, for example, Rogers (2004) making the argument that asymmetry seen in the chicken brain has similar functional consequences as asymmetry seen in the human brain. Corballis starts by stating that no one would deny that there "are some asymmetries that are distinctively human," but he then considers the issue from the opposite direction, beginning with two functions that are generally considered unique to our species. These functions are manual dexterity and language. Both are represented asymmetrically in the human brain, and he examines the possible evolutionary and genetic sources of these asymmetries, invoking concepts like genetics of handedness, mirror neurons, and manual gestures as possible sources for language asymmetry in humans.

In chapter 2, Patrick Gannon approaches the topic from still another angle. He looks at the evolutionary origin of language and any signs of asymmetry in language areas, such as the leftward asymmetry seen in the planum temporale in the posterior

temporal lobe, citing evidence from paleontology that Wernicke's area may have been represented in the brains of our prehistoric ancestors. It is, however, not entirely clear whether other anatomical landmarks of asymmetry for language, such as the different slopes of the sylvian fissure on the left and right side of the brain, are also found in the primate brain. This may be dependent on the measuring method used and should be carefully considered whenever comparisons between species are made. As also pointed out by Gannon in his chapter, statistical correlations and statistical significance are not the same as inference of functionality and theoretical significance. Gannon moreover points out the importance of having blinded procedures when investigating anatomical differences in human and nonhuman brains, something which is difficult in postmortem studies. The issue of human uniqueness for hemispheric asymmetry is a difficult question to answer since in order to disqualify a unique human perspective, observed asymmetries in other species should be possible to interpret in a similar frame of reference as is relevant in the human case. An emerging view is, however, that the homologues of human brain areas for language also existed in ancestors of ours who are far more distant from us than the primates, which may mean two things: Either these species had the necessary brain preparations for developing language, or the so-called language areas in the brain are independent of actual language use, at least when it comes to nonhuman species.

### **Asymmetry as an Evolutionary Advantage?**

As mentioned above, an unanswered question in research on hemispheric asymmetry is what evolutionary advantage would have been gained through a division of labor between the two cerebral hemispheres. Several theories have been suggested over the years, most pointing to the advantage of not having a competition for processing between two identical messages (Hugdahl, 2000; Cook, 1986). This implies that there would be an advantage to having a single information-processing system which facilitates communication at high speed and to avoiding having identical forms of cortical representations. The simultaneous activation of homologous areas in each hemisphere would run the risk of attenuating and blurring information, thus slowing down sensory processing and subsequent motor output.

A variant of this is to say that evolution of higher cognitive functions pushed for a division of labor between the hemispheres, forcing the development of the two hemispheres as a result of a demand for processing speed and efficiency (Ringo et al., 1994). This would have been accompanied by an increase in neural capacity, since specializing one hemisphere for a particular function leaves the other hemisphere free to perform other functions. Thus, lateralization may have been a way to increase brain capacity to carry out simultaneous, parallel processing without the mutual inhibition

and information loss that may have been the case in a situation where information would have been duplicated. An extension of this argument is that it would also have been advantageous to avoid shuffling information across long distances, which would mean the loss of processing speed. It would therefore be preferable that information be processed in a single hemisphere with the involvement of spatially restricted neural networks as discussed above.

### Auditory and Visual Asymmetries

Apart from the question of the existence of language-like asymmetry structures in the brain of nonhuman species and the evolutionary origin of language and handedness, a range of other asymmetries have been observed in nonhuman species; perhaps the best known examples are auditory asymmetries in songbirds and visual asymmetries in pigeons as covered in the chapters by Isabell George (chapter 4) and Onur Güntürkün and Martina Manns (chapter 5), respectively. An important issue in all cross-species comparisons is whether there is an early common origin of lateralization and hemispheric asymmetry. An aspect of this is that population-based asymmetry biases (favoring one direction over the other) are the result of a social constraint (Ghirlanda & Vallortigara 2004) emphasizing that unidirectional biases will favor social communication among members of the same species.

For example, gestures to communicate in baboons elicit a right-hand bias (Meguerditchian & Vauclair 2009). Animal models of hemispheric asymmetry may more easily allow for an understanding of the underlying neuronal circuitry and will more easily allow such experimentation. As argued by George, “songbirds … form a unique model because they allow experimental investigation of the interplay of neurobiological substrate and the behavior that characterizes them, that is, song, which is a learned behavior whose critical function is to communicate with other birds.” In this respect, the study of song behavior in songbirds provides a particularly important model for the understanding of the underlying mechanisms of hemispheric asymmetry across species when it comes to communications, whether this is phonetic language as in humans or song as in birds. Recent advances in research on songbirds may therefore cast new light on the eternal issue of language lateralization in both humans and nonhumans.

Güntürkün and Manns (chapter 5) show in their chapter that genetic models alone cannot explain the development of hemispheric asymmetry since environmental factors act as important modulator of biologically inherent laterality effects. In this respect, hemispheric asymmetry is a form of brain plasticity (cf. Steinmetz et al., 1995). Güntürkün and Manns demonstrate that pigeons show distinct asymmetry for various visual tasks where the left and right hemispheres differ in the capacity for detailed, fine-grained analysis of the visual environment for stimulus discrimination, memory,

and other aspects of visual processing and that these behavioral asymmetries can be related to the development of the visual system at the neuronal level. These findings then raise the question of whether a common underlying principle for the existence of a lateralized brain is to optimize adaption to the ecological niche each species occupies. That chickens show visual asymmetries for grain picking, when occluding one eye may be as ecologically important as the use asymmetry of a phoneme based language in humans. Seen in this perspective, the controversy of whether functional asymmetry is a unique human trait could be resolved into saying that it depends on the specific function studied and the position of a certain behavior–function in a response–function hierarchy for a particular species. Thus, a common underlying cause for lateralization may be the need for processing efficiency and the need to avoid task duplication, which occupies processing resources and delays speed of processing.

In the chapter by Joseph Hellige, Bruno Laeng, and Chikashi Michimata (chapter 13), visual asymmetries are further discussed, from a human perspective, focusing on the underlying spatial properties that give rise to object perception and how these features are lateralized in the human brain. Specifically, left- and right-hemisphere specialization for processing categorical versus coordinate spatial relations, respectively, are the focus of Hellige's and colleagues' discussion, following the original suggestions by Kosslyn (1987) of a lateralization gradient regarding categorical versus coordinate classification of object perception. This is followed by a discussion of hemispheric asymmetry in processing high versus low ranges of visual spatial frequency and how this relates to the processing of categorical versus coordinate spatial relations. Through the understanding of such features as categorical versus coordinate relations, and high and low spatial frequencies, new theoretical advances have been made in the understanding of asymmetries of object recognition and asymmetries in the processing of spatial relations.

Patricia Cowell takes a different approach in chapter 12 and looks at linguistic and cultural factors that impact laterality of speech perception. It is interesting to note in this regard that such “basic” lateralized processes as language and verbal behavior are also influenced by modulatory factors, which Cowell discusses at length. She states that

two important themes emerge from the research of the past 10 years. First, the degree and direction of lateralization in speech perception involve a rich interplay between biological and experiential influences; this has taken scientific inquiry beyond the search for “main effects” and more deeply into the study of multifactorial interactions. Second, the nature of the stimuli that evoke lateralized neural and behavioral responses in speech perception is more complex than originally believed; thus, lateralized speech processing appears to involve a range of functions from the processing of acoustic input to the processing of integrated input such as words and phrases.

### Top-Down Modulation of Bottom-Up Asymmetries

A classic view of hemispheric asymmetry is a bottom-up, or stimulus-driven, view of the functional bias of the cerebral hemispheres, supported by structural asymmetries in the brain that would facilitate the processing of a certain class of stimuli, or cognitive functions rather than other classes. This is, however, a static view, leaving little room for environmental influences, that is not in accordance with research on the plasticity and dynamic change across development of cognitive capacities. For example, if speech perception were completely decided by the processing characteristics of the left hemisphere, and in left perisylvian region, the understanding of another person speaking to me would be impossible if there are more than two sources of input at the same time, as in the well-known “cocktail party phenomenon” wherein several people speak at the same time.

Humans, and perhaps also other species, solve this situation quite easily by directing attention to a single source of input, mentally “filtering out” other sound sources occurring simultaneously (see also Westerhausen and Hugdahl, chapter 16). This is a cognitive, top-down modulation of the complex speech signal input that is necessary in order to gain intelligibility of speech perception. Dichotic listening studies—which can be said to mimic the cocktail party phenomenon in that they entail presenting two simultaneous sources of speech sound input, one in the left ear and one in the right ear—have shown that preliterate children have problems in using attention to shift from a bottom-up, stimulus-driven, right-ear report in the dichotic listening situation to a left-ear report (Hugdahl & Andersson, 1987; Hugdahl et al., 2001). Thus, these studies show that the ability to use top-down cognitive strategies to modulate a stimulus-driven laterality effect is dependent on the cognitive maturation of the brain.

Heikki Hämäläinen and Fiia Takio (chapter 14) take a top-down modulation of a stimulus-driven laterality effect by showing how auditory and visual asymmetry are integrated and that there is a default right-sided bias for spatial perceptual and attentional capacity. This phenomenon is seen in its severest form as hemispatial neglect and/or extinction after right parieto-temporo-frontal disorders/lesions. Hämäläinen and Takio argue that this bias is multimodal including auditory and visual space and that it is present in childhood and in old age. They propose that the early developing asymmetricity in cognitive ability is balanced by later developing executive functions and cognitive control functions. The asymmetricity again becomes evident in old age with the decline of executive functions.

Stefan Pollmann (chapter 15) addresses top-down modulation of the right-ear advantage in dichotic listening by asking the question of whether it is primarily the auditory input or an attentional signal which is exchanged via the corpus callosum

and whether the right-ear advantage in reality is caused by attentional modulation and the transfer of information across the corpus callosum.

Still another aspect of cognitive functioning is asymmetry of memory, as described and discussed by Grégoria Kalpouzos and Lars Nyberg (chapter 17), who take their starting point in the notion of episodic memory (Tulving, 1972), which is the memory of past personal experiences and events, not necessarily shared by others. The use of fMRI and other neuroimaging techniques for the study of lateralization of episodic memory has implicated the medial temporal lobe and suggests that the left and right side are stimulus specific, such that the right medial temporal lobe, and the hippocampus, is activated for items containing visuospatial features while the left medial temporal lobe is recruited for verbalizable items, and that this seems to be related to both encoding and retrieval. However, not only does lateralization of memory follow a verbal/visuospatial gradient but asymmetry of episodic memory is also contingent on novelty versus familiarity and on depth of processing, that is, semantically versus perceptually encoded materials.

As can be seen in the emergence of the hemispheric encoding/retrieval asymmetry (HERA) model (Tulving et al., 1994), another brain structure that has played a key role in recent theoretical models of lateralization of memory is the prefrontal cortex. Although the HERA model has been challenged, and there are other more recent models, it is still a reasonable model for the theoretical understanding of how asymmetry of episodic memory is organized in the frontal cortex.

### **Altered Asymmetry—Clinical Perspectives**

Any theory or model of clinical disorders related to language and speech processing, as, for example, dyslexia and other language neuropediatric disorders, will be unfinished business without taking hemispheric asymmetry into consideration. This is covered in the chapter by Deborah Moncrieff (chapter 19). Similarly, several neurological disorders clearly have a lateralized component, perhaps the most well-known being visual neglect and the neglect syndrome, covered in the chapter by Victoria Singh-Curry and Masud Husain (chapter 18). Recent developments in both structural and functional neuroimaging of patients with schizophrenia and psychotic disorders have moreover shown a greater degree of brain morphological abnormality, particularly in temporal and frontal areas, than previously thought (Williams, 2008). Of particular interest in this context is the fact that areas in the left temporal lobe, overlapping with the planum temporale and Wernicke's regions, seem to be the most vulnerable brain regions in schizophrenia. Since these areas also involve the regulation of language and speech perception, it is a short step to infer that abnormal lateralization of language in schizophrenia may be a critical factor behind the disorder as suggested in chapter 21 by Tim Crow.

It is also of theoretical interest why the same brain region, the planum temporale area, shows structural abnormalities in both schizophrenia and dyslexia, two disorders that from the outside have very little, if anything, in common from an etiological point of view. The important question about similarities in brain asymmetry in individuals with different diagnostic disorders is further pursued in the chapter by Moncrieff, who states that as more and more data are accumulated with neuroimaging techniques like fMRI and PET, it has become more and more apparent that similarly abnormal brain structure is evident in children diagnosed with different developmental disorders, such as autism, ADHD, and dyslexia. She then goes on to ask whether overlapping findings could potentially be due to errors in diagnostic classification of study subjects or whether they may represent systematic and similar alterations occurring in neural systems across several pediatric disorders. The involvement of the same brain structures and similar asymmetries across diagnostic categories is a critical issue in the understanding of hemispheric asymmetry and may also point in the direction of dimensionality rather than categorization when it comes to psychiatric diagnostics and treatment.

A clinical perspective is also evident when it comes to the specialized function of the right hemisphere. Singh-Curry and Husain (chapter 18) point to the interesting fact that it took a long time after the discoveries of Broca and Wernicke that the left hemisphere was specialized for language and verbal functions for researchers to explore whether the right hemisphere could also have corresponding specializations (although this had already been hinted at by Broca). As stated by Singh-Curry and Husain, it was not until the 20th century that the evidence for a special role of the right hemisphere in visuospatial functions began to develop (e.g., De Renzi, 1982). A series of investigations which started in the 1930s and 1940s demonstrated that while insults to the left hemisphere resulted in difficulties with verbal ability, damage to the right hemisphere consistently led to poor performance on tests involving the manipulation of geometrical figures, completion of missing parts of shapes and patterns, and other tasks incorporating the analysis of form, distance, and spatial relationships. These discoveries subsequently led to the realization that damage to the right hemisphere, in particular right posterior parietal lobe lesions, could lead to clinical symptoms related to visuospatial function, the so-called neglect syndrome (see also Heilman, 1995).

As also stated by Curry-Singh and Husain in their chapter, "such a striking deficit in the visuospatial representation of the external world following right-hemisphere damage has fueled the proposal of a special role of the right hemisphere in visuospatial and, more generally, spatial functions." An important consequence of studies of the neglect syndrome is that they have shed new light on the underlying functional organization of the right hemisphere related to attention, visuospatial function, and spatial working memory. This is a nice example of how a clinical syndrome can con-

tribute to advancing our theoretical understanding of the functional integrity of the cerebral hemispheres.

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## I Genetic and Evolutionary Perspectives on Hemispheric Asymmetry



# **1 Differential Gene Transcription in the Left and Right Cerebral Cortex**

**Tao Sun**

A striking asymmetrical brain function in humans is preferential handedness, with more than 90% of the population more skillful in using the right hand, which is controlled by the left hemisphere. The preferential right-hand use is even detectable during fetal development. Some more sophisticated cognitive functions are also preferentially localized in the left or right hemisphere; for example, the left hemisphere is dominant for language and the right hemisphere excels in spatial recognition. Moreover, anatomical asymmetries, for instance, the sylvian fissures and the planum temporale, have been mapped in human brains using imaging techniques such as magnetic resonance imaging (MRI).

In the past decade, using genetic tools and animal models, researchers have demonstrated causal relationships between genes and behaviors. Whether brain anatomical and functional asymmetry is regulated by genetic programs is unclear. Even though genetic models of human handedness have been proposed, the “genes” that may control preferential hand use in humans have not been identified. Taking advantage of large-throughput genetic screening approaches, we are beginning to uncover the differential gene expression in human left and right hemispheres. These candidate genes can serve as references in revealing the molecular mechanisms of brain asymmetry and handedness in humans and animal models.

## **Genetic Patterning of the Cerebral Cortex**

During the development of the central nervous system (CNS), the forebrain is organized into a three-dimensional structure with anterior-posterior (A-P), dorsal-ventral (D-V), and left-right (L-R) features (Grove & Fukuchi-Shimogori, 2003; Levitt & Eagleson, 2000; O’Leary, Chou, & Sahara, 2007; O’Leary & Nakagawa, 2002; Rakic, 1988; Sun & Walsh, 2006; Sur & Rubenstein, 2005). Our knowledge of early brain patterning is largely from investigations of rodent brain structures and functions using genetic tools. Brain patterning is initiated by molecules secreted from patterning centers. At least three patterning centers have been identified: (1) The ventral features

are regulated by Sonic hedgehog (Shh) secreted from the mesendoderm beneath the forebrain (Chiang et al., 1996; Machold et al., 2003), (2) the anterior features are controlled by the fibroblast growth factor 8 (Fgf8) expressed in the anterior midline of the forebrain (Fukuchi-Shimogori & Grove, 2001; Garel, Huffman, & Rubenstein, 2003), and (3) the dorsal features are regulated by bone morphogenetic proteins (BMPs) and Wnts expressed in the dorsal midline in the cortex (Bulchand, Grove, Porter, & Tole, 2001; Golden et al., 1999; Gunhaga et al., 2003; Hébert, Mishina, & McConnell, 2002; Monuki, Porter, & Walsh, 2001; Zhao et al., 2005). Recently, another potential patterning center, the cortical antihem, was identified at the lateral cortical field (Assimacopoulos, Grove, & Ragsdale, 2003).

Along the A-P axis in the cortex, molecules secreted from patterning centers induce downstream gene expression, such as transcription factors. These transcription factors normally have gradient expression; for example, Pax6 is expressed in an anterior-high and posterior-low gradient, while Emx2 and an orphan nuclear receptor chicken ovalbumin upstream promoter-transcription factor 1 (COUP-TF1) are expressed in an anterior-low and posterior-high gradient (Armentano et al., 2007; Bishop, Rubenstein, & O'Leary, 2002; Liu, Dwyer, & O'Leary, 2000; Zhou, Tsai, & Tsai, 2001). Even though it is unclear how gradient expression of transcription factors is established, the proper expression pattern of these transcription factors is essential for organizing distinct cortical functional areas. Mutation in Pax6 produces expansion of posterior cortical region, resulting in smaller motor cortex in the anterior (Bishop, Goudreau, & O'Leary, 2000; Muzio et al., 2002). Altering cortical expression levels of Emx2 alone causes a larger or smaller visual cortex in the posterior (Leingärtner et al., 2007). As a result, mice with altered Emx2 cortical expression display impaired sensory detection and motor coordination (Leingärtner et al., 2007). These results indicate that the proper anatomical formation and functional performance of mouse brains are controlled by precise gene expression and regulation during development.

The organization of functional areas in human brains is more complex than in the mice. Based on conserved functions between human and mouse genes, similar patterning mechanisms in mouse brains may nevertheless apply to humans.

### Differential Gene Transcription and Human Brain Asymmetry

If the anterior and posterior organization of functional areas in developing brains is regulated by genetic programs, does the establishment of asymmetrical structures and distinct functions between the left and right hemispheres also have a molecular base?

The molecular regulation of the left-right asymmetry of visceral organs of vertebrate bodies, such as the heart, lungs, and intestines, has been thoroughly studied (Levin, 2005; Wright, 2001). Signaling pathways, for instance, Shh, Fgf8, and Nodal

and their downstream genes, have been shown to play a critical role in left-right body determination (Capdevila, Vogan, Tabin, & Izpisua Belmonte, 2000; Hamada, Meno, Watanabe, & Saijoh, 2002). An interesting question is whether genes involved in visceral organ asymmetry have differential expression between human left-right hemispheres. If they are differentially expressed in human brains, they likely play a conserved role in regulating brain asymmetry as in controlling visceral organ asymmetry. In a preliminary study, expression patterns of candidate genes for body asymmetry, such as Pitx2 and Wnt molecules, have been tested in 17- to 22-week-old human fetal brains (Geschwind & Miller, 2001). However, no significant differences in gene expression have been observed between the two hemispheres.

A recent study directly measured gene expression levels in the left and right hemispheres of human fetal brains using a genetic screening approach (Sun et al., 2005). In this study, levels of gene transcripts were quantified using the total RNA extracted from the perisylvian regions, the presumptive language center, of human fetal brains at 12, 14, and 19 weeks. To compare expression levels of almost all transcripts either with high or low abundance without bias, gene expression libraries were created using a technique called serial analysis of gene expression (SAGE; Sun et al., 2005). Interestingly, a majority of differentially expressed genes in the left-right hemispheres function in regulating cell signaling or cell communication and in controlling gene or protein expression (Sun, Collura, Ruvolo, & Walsh, 2006). The differential expression of candidate genes was further verified in additional 12-week-old human fetal brains using either real-time reverse transcription polymerase chain reaction (RT-PCR) or *in situ* hybridization. Twenty-seven genes that show consistently higher expression either in the left or right hemisphere were identified (Sun & Walsh, 2006).

These studies provide two interesting findings: (1) The human left and right hemispheres already have differential gene expression levels at early fetal stages (as early as 12 weeks), and (2) these differentially expressed genes may play a role in neurogenesis and neural connections by regulating cell signaling and gene expression during early brain development. Identifying more differentially expressed genes in human left-right hemispheres and verifying their expression levels in human brains at different developmental stages will create a comprehensive picture of the molecular signature of human brain asymmetry.

Additionally, genes critical in visceral organ asymmetries, such as molecules involved in SHH or NODAL pathways, are not identified as differentially expressed in human fetal brains using this SAGE screening approach (Sun et al., 2005). Previous work has shown that Shh and Nodal play a patterning role in visceral organ asymmetries at very early embryonic stages (Capdevila et al., 2000; Hamada et al., 2002). The earliest stage of the SAGE analyses is in human fetal 12-week-old brains. Differential gene transcription between left-right hemispheres may have an early onset,

earlier than 12 weeks in the human fetus. Thus, even though molecules regulating body asymmetries might also be differentially expressed in human embryonic brains, they may not be detectable in 12-week-old human fetal brains. Whether brain asymmetry and body asymmetry share conserved signaling pathways still remains a question.

Differential gene transcription in a specific human brain region has also been detected recently. Using genome-wide screening approaches, such as cDNA microarrays, 44 genes were identified with enriched expression in frontal cortex and superior temporal regions of human fetal brains (Abrahams et al., 2007). Gene coexpression relationships in specific human brain regions and cell types have also been carefully examined using microarrays (Oldham et al., 2008). Even though these microarray analyses do not reveal genes that directly regulate brain asymmetry, gene transcription profiles generated in these studies will help us better understand human brain development and will provide databases for comparing brain development and evolution in humans and nonhuman primates (Vallender, Mekel-Bobrov, & Lahn, 2008). Moreover, the accumulation of gene expression profiles in different human brain regions from two hemispheres will allow comparisons of differential gene transcription in mirrored brain regions between left and right hemispheres.

### Potential Mechanisms Regulating Brain Asymmetry

The screening approach has identified many genes that are asymmetrically expressed in human fetal left and right hemispheres. Most of them are expressed in postmitotic cells based on their cellular functions (Sun et al., 2006). Are there early initiating signals that are active in neural stem cells or progenitors between the embryonic left and right hemispheres? The initiating signals may be important in breaking early symmetry and in inducing asymmetrical expression of downstream genes that maintain brain asymmetry (Palmer, 2004).

The critical step of early development of the CNS is to form a tube structure called the neural tube (Tanabe & Jessell, 1996). The forebrain (cerebral cortex) is located in the most anterior region of the neural tube. The potential molecular candidates that break the neural symmetry might be signals from the midline structures, such as the notochord and the floor plate (Dodd, Jessell, & Placzek, 1998). In the forebrain, a structure anterior to the notochord is called the prechordal plate (Rubenstein, Shimamura, Martinez, & Puelles, 1998). Secreting molecules such as Shh from the notochord or the prechordal plate may have uneven distribution between the left and right forebrain and break neural symmetry (Tannahill, Harris, & Keynes, 2005). Additionally, the roof plate in the neural tube is a resource for morphogens, for example BMPs and Wnts (Chizhikov & Millen, 2005). The anterior neural ridge located in the most anterior cortical region transiently expresses the growth factor Fgf8 (Fukuchi-Shimogori & Grove, 2001). Together, these secreted molecules, such as

BMPs, Wnts, and Fgf8, may play an early patterning role in the left and right forebrain asymmetry.

Recent studies have demonstrated that different cell division rates are observed in distinct regions of the primate and mouse cortices and may contribute to the formation of different cortical functional areas (Lukaszewicz et al., 2005; Polleux, Dehay, Moraillon, & Kennedy, 1997). Is cortical asymmetry simply a result of different proliferation rates of progenitors and, subsequently, temporal and spatial difference of neural differentiation and connections between the two hemispheres? One important function of morphogens, such as Shh, BMPs, and growth factors, is to regulate proliferation. The uneven distribution of morphogens between two hemispheres may cause different proliferation rates. Differentially expressed genes in human fetal 12- to 19-week-old brains, identified by the SAGE screening approach (Sun et al., 2005), may reflect the temporally and spatially distinct neuronal differentiation and connections between the two hemispheres. Because consistent asymmetry is mostly detected in human brains, testing these potential mechanisms of brain asymmetry directly in humans remains a challenge.

### Detecting Differential Gene Expression in Nonhuman Brains

While it is difficult to directly test the molecular regulation of brain asymmetry using experimental approaches in humans, revealing differential gene expression and mechanisms of laterality in nonhuman brains is favorable.

Biased hand use is also observed in nonhuman primates, such as chimpanzees. Because most studies on preferential hand use have entailed investigating manual tasks of captive great apes, whether there is consistent handedness at a population level in wild apes is arguable (Hopkins & Cantalupo, 2005; McGrew, Marchant, Wrangham, & Klein, 1999). A recent study of wild chimpanzees living in the Gombe National Park has provided some new insights into hand preferences in nonhuman primates. It appears that handedness in wild chimpanzees varies depending on the type of tool use and the specific manual task (Lonsdorf & Hopkins, 2005). These variations make it difficult to identify genes that may be associated with handedness in nonhuman primates.

Interestingly, several recent studies have shown asymmetries of the planum temporale and Broca's area in the brains of chimpanzees and great apes (Cantalupo & Hopkins, 2001; Gannon, Holloway, Broadfield, & Braun, 1998; Hopkins, Marino, Rilling, & MacGregor, 1998). These anatomical asymmetries in the simian brains resemble those of humans. Even though the functional relevance of simian brain asymmetry, for example, related to "language ability," remains a question (Hutsler & Galuske, 2003), genes that contribute to the asymmetrical structural formation in the primate cerebral cortex may have similar roles in regulating asymmetries in human

brains. Thus, using primate brain tissues may help us identify differentially expressed genes, map their expression patterns, and gain insights into conserved gene expression and function in human brain tissues. However, the difficulty of developing genetic primate models hurdles further examination of gene functions in brain asymmetry using primates.

The rodent is an ideal animal model for studying brain development and functions because of low cost, well-developed genetic tools, and established behavioral tests. However, consistent anatomical and functional brain asymmetries have not been well described in rodents. A biased food reaching task, called paw preference, is often observed in an individual mouse with preferential use of either the left or right front paw. However, paw preference becomes randomly distributed at a population level (Biddle, Coffaro, Ziehr, & Eales, 1993; Signore et al., 1991). By breeding mice that exhibit consistent paw preference, mouse lines showing strong lateralized food reaching have been created (Collins, 1991). However, these mice still do not have a consistent 9:1 ratio of preferential hand use at a population level as reported in humans. These studies indicate that a genetic program of brain asymmetry may exist in rodent brains but it is not preferentially biased to either the left or right hemisphere. Nevertheless, since the techniques of creating transgenic and gene mutant mice are becoming conventional in many laboratories, examining functions of differentially expressed genes, detected in human and primate brains, in mouse models is a promising direction for understanding the genetic mechanisms of brain asymmetry.

The epithalamus, a structure of the diencephalon, consists of the habenula and the pineal complex and shows left-side asymmetries in zebra fish. The molecular regulation of the epithalamus asymmetry in zebra fish has been revealed (Concha & Wilson, 2001; Halpern, Liang, & Gamse, 2003). Consistent with the role of the Nodal pathway in the molecular regulation of body asymmetry, Nodal-related genes Cyclops and Nodal downstream genes lefty1 and pitx2 have been shown to control the asymmetry of the diencephalon in the zebra-fish brain (Bisgrove, Essner, & Yost, 2000; Concha, Burdine, Russell, Schier, & Wilson, 2000; Essner, Branford, Zhang, & Yost, 2000; Halpern et al., 2003). Developing behavioral tests relevant to the epithalamus asymmetry in zebra fish will help us better understand the significance of biological functions of asymmetrical gene expression in zebra-fish brains.

Moreover, lateralized song production has been observed in songbirds. Denervation of the left syrinx, the vocal organ of songbirds, has been shown to result in the loss of 90%–95% of song syllables in canaries (Hartley & Suthers, 1990; Nottebohm, Manning, & Nottebohm, 1979; Nottebohm & Nottebohm, 1976). Lesions to the high vocal center on the left canary cortex, but not the right, also cause dramatic loss of song components (Nottebohm, Stokes, & Leonard, 1976). It appears that canaries display lateralized song production, with dominance on the left side. It is unclear

whether genetic programs contribute to this laterality in songbirds. Since brain tissues for songbirds are relatively easy to collect at different developmental stages, identifying genes that are differentially expressed in left and right hemispheres may provide insights into lateralized song production. Moreover, since the neurocircuitry of song production in songbirds is well understood (Bottjer, Halsema, Brown, & Miesner, 1989; Nottebohm, Kelley, & Paton, 1982; Nottebohm et al., 1976), developing techniques to alter gene expression in songbird brains can further reveal how the lateralized song system is established.

### **Approaches to Identifying Genes Involved in Human Brain Asymmetry**

#### **Forward Genetic Approach**

A forward genetic screen is based on the identification of mutated genes that produce certain phenotypes. Mapping genes that are associated with disrupted body and brain asymmetries in humans may help us identify the genetic controls that lead to normal asymmetries. Complete reversal of normal organ position, such as heart and lungs, is called situs inversus (SI). Anatomic and functional MRI studies have shown that the left-hemisphere dominance for language is detected in individuals with SI as frequently as in normal subjects (Kennedy et al., 1999). Moreover, Kartagener's syndrome, a disorder caused by cilia with decreased or total absence of motility, represents 50% of SI cases (Carlén & Stenram, 2005). However, these SI individuals with Kartagener's syndrome are found with normal ratio of dominance for right handedness (McManus, Martin, Stubbings, Chung, & Mitchison, 2004). These studies suggest that individuals with abnormal body asymmetry can have normal asymmetrical brain function and handedness. It appears that the genetic regulation of visceral organ asymmetries may be distinct from that of brain asymmetries and handedness (Hobert, Johnston, & Chang, 2002; C. McManus, 2005). Therefore, identifying genes involved in visceral organ asymmetries using forward genetic approaches may not help us understand the molecular mechanisms of human brain asymmetry.

Directly mapping genes that are associated with disrupted brain asymmetry may be a better approach to identifying the molecular regulation of brain laterality in humans. Reduced and reversed anatomical brain asymmetry has been reported in individuals with schizophrenia, autism, and dyslexia (Falkai et al., 1992; Galaburda, Menard, & Rosen, 1994; Herbert et al., 2005; Hugdahl et al., 1998). Whether abnormal brain asymmetry is the cause or result of these neurological disorders is unknown. Recently, research into the causal relationships between genes and autism has made promising progress (Geschwind, 2008; Walsh, Morrow, & Rubenstein, 2008). Examining functions of candidate genes of autism may provide insight into not only the causes of autism but also functional connections of these genes to brain asymmetrical development.

Additionally, several recent case reports have shown that polymicrogyria (PMG), characterized by an excessive number of small gyri in the brain, occurs only on one side of the cortex, called unilateral polymicrogyria (Chang et al., 2006; Pascual-Castroviejo, Pascual-Pascual, Viano, Martinez, & Palencia, 2001). The presence of several pedigrees in which the disorder is present in more than one individual of affected families suggests that unilateral PMG appears to be caused by gene mutations (Chang et al., 2006). Mapping genes involved in unilateral PMG using forward genetic approaches may reveal their role in normal formation of brain asymmetry in humans.

### **Microarrays**

Microarray is a method to generate high throughput gene expression profiles. To detect gene expression levels, DNA oligonucleotides corresponding to various regions of a specific gene are attached to glass slides. Slides are hybridized with fluorescence-labeled complementary DNAs (cDNAs) or complementary RNAs (cRNAs) and scanned with fluorescent readers. Usually the slides are hybridized simultaneously with cDNAs/cRNAs derived from two samples, for instance, with samples from the left and right hemispheres. The fluorescence intensities for each cDNA are quantified and compared between two samples. Gene transcripts that are either up- or down-regulated in the left or right hemisphere can be detected. Thus, microarray is an effective method for measuring expression levels of known genes between samples. Microarrays have been used to comprehensively characterize distinct gene expression in different brain regions in both mice and humans (Oldham et al., 2008; Sunkin & Hohmann, 2007). Using the microarray technique, one can identify genes with differential transcriptions between left and right hemispheres of human brains.

### **Serial Analysis of Gene Expression**

SAGE is a method for the comprehensive analysis of gene expression levels without the prior knowledge of gene transcripts. SAGE has been successfully used to identify genes with differential expression levels in specific tissues in many systems, including human fetal left and right brains (Blackshaw, Fraioli, Furukawa, & Cepko, 2001; Sun et al., 2005; Velculescu, Zhang, Vogelstein, & Kinzler, 1995; Ye, Usher, & Zhang, 2002). The advantages of using SAGE versus microarrays are as follows: (1) SAGE can detect transcripts at low expression levels that may be undetectable by microarrays, and (2) SAGE can easily compare gene expression levels among multiple samples. For instance, once SAGE libraries are created from the left and right hemispheres of developing human cortices, they can be compared at different developmental stages in one side of the brain or between left and right hemispheres. To reveal the evolutionary mechanisms of brain asymmetry, SAGE has been used for the comparison of gene expression levels across species—for example, between human and primate brains (Sun et al., 2006).

### **MicroRNA Microarray**

Recently, a class of about 22 nucleotide (nt) endogenous noncoding small RNAs, called microRNAs (miRNAs), has been identified (Lee, Feinbaum, & Ambros, 1993; Wightman, Ha, & Ruvkun, 1993). Mature miRNAs are processed from precursor miRNAs into imperfect RNA duplexes, and subsequently one strand is preferentially loaded into the RNA-induced silencing complex (Hammond, 2005; Hutvagner, 2005; Kim, 2004). Mature miRNAs recognize the 3'-untranslated region of their target messenger RNAs (mRNAs), inhibit protein translation, and in turn shut off protein production of targeted genes (Kloosterman & Plasterk, 2006). Thus, miRNA function represents a novel posttranscriptional machinery of gene regulation.

Many miRNAs have enriched expression in embryonic and adult brains in humans, nonhuman primates, rodents, and zebra fish (Landgraf et al., 2007; Miska et al., 2004; Wienholds et al., 2005). Abnormal miRNA biogenesis has been associated with the etiology of some human neurological disorders (Chang & Mendell, 2007). For example, several miRNAs are found to be more highly expressed in the prefrontal cortex of schizophrenic patients than normal subjects (Perkins et al., 2007). This preliminary research has implied the importance of miRNA function in normal brain development and under disease conditions. Thus, it is interesting to know whether miRNAs have differential expression levels between human fetal left and right hemispheres. Examining miRNA expression and function may reveal a new layer of gene regulation network in brain asymmetry.

### **Proteomic Approaches**

Proteomics is a method for a high throughput analysis of protein expression levels. It is through proteins that genes exert their functions. Even though measuring gene transcription levels—for instance, using microarrays—can reveal mRNA expression, the protein level is not always correlated to the mRNA level. Thus, revealing protein expression profiles in a certain brain region will provide accurate evaluation of gene functions in brain development. The rapid development of mass spectrometry techniques and bioinformatics makes the proteomics a practical and effective method for studying normal brain development and for examining the causes of human neurological diseases (Móron & Devi, 2007; Tannu & Hemby, 2006). The combination of detecting differential gene transcripts and identifying distinct proteins between the left and right hemispheres will provide a comprehensive picture of the molecular regulation of brain asymmetry.

### **Perspectives**

High throughput screening approaches allow us to identify asymmetrical gene transcription, differential microRNA expression, and distinct protein levels between

human left and right hemispheres. These gene and protein expression profiles will help us assess the underlying mechanisms of brain asymmetry at a molecular level. Revealing differential gene transcription in human brains at different developmental stages can also help us understand the molecular onset and progression of human brain asymmetry. Moreover, the forward genetic approach will identify and confirm candidate genes that are directly associated with brain asymmetry in humans. Even though we can't test how anatomical and functional brain asymmetries develop in humans using experimental approaches, we can begin to understand functions of asymmetrically expressed genes identified in human brains by generating genetically engineered animal models. These animal models will provide valuable insights into the molecular mechanisms of brain asymmetrical development and lateralized behaviors.

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## 2 Evolutionary Depth of Human Brain Language Areas

Patrick J. Gannon

### History of Brain Asymmetry for Language

The beginning of it all was concomitant with Charles Darwin's *Origin of Species* (Darwin, 1859). Before that, Franz Joseph Gall's early-nineteenth-century discipline of phrenology was semiscientific analysis of bumps on the skull, but because it was so controversial, it was in the public eye. As such, it served to set the stage for more formal science-based advances. Interestingly, Gall had assigned his "language area 33, skull bump" to where the inferior frontal gyrus lay, just a little anterior to where Broca placed it later.

Pierre Paul Broca and Marc Dax were leaders of the vanguard that led the "science" of language away from Gall's deeply rooted "bumps on the skull" phrenologic approach and toward functional localization of the brain itself. Dax had noted brain language area phenomena as early as 1836, but Broca brought it independently to the scientific community (Broca, 1861). Dax's son brought it to the scientific literature too late for it to be termed Dax's language area (Dax, 1863). Broca had many problems with the French Christian majority who opposed his research, and he was labeled a heretic, especially after he formulated a society of free thinkers. Within the era of Darwin's *Origin of Species*, Broca appeared to have been guided by the science of evolutionary biology; like Darwin, he denied the immutability of race and species and supported the theory of evolution. His reactionary and personal mantra may have showed in a renowned aphorism which stated "I would rather be a transformed ape than a degenerate son of Adam" (Sagan, 1986).

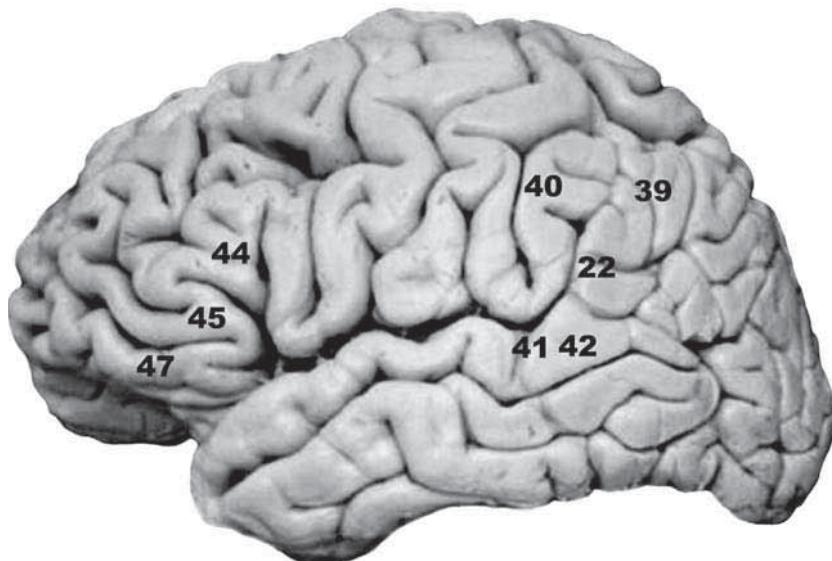
Broca's findings were based essentially on the ( $n = 1$ ) postmortem observations of the brain of a patient who was unable to speak anything but the word "tan" repeatedly (for which he became affectionately referred to as "Tan") but was able to understand spoken language. Tan had suffered from neurosyphilis, wherein one of a series of brain lesions had eroded, in particular, his inferior frontal gyrus. After postmortem observations, Broca assigned a region of Tan's left inferior frontal gyrus as a brain language area (Broca, 1861, 1863). A brain language area was not

only described scientifically for the first time but was shown to be lateralized to the left hemisphere. It should be remembered that neither Dax nor Broca were the first to observe speech or language disorders (usually after local trauma), as these had been noted consistently since being referred to in documents as early as the Smith Surgical Papyrus of 3500 B.C. and the Hippocratic Corpus of 400 B.C. (Benton, 1964).

Shortly thereafter, Carl Wernicke, a German neuropsychiatrist, was following the currently hot theme of brain language areas research. He had observed in his patients' brains (postmortem) that some types of language disorders did not obey the regional rules set forth by Broca. Henry Charlton Bastian had reported findings of similar disorders but at this time without clear notes of localization (Bastian, 1869). Based on observations of individuals who could speak and hear but not comprehend spoken language, Wernicke characterized the cerebral location and the nature of the disorder as "sensory aphasia" versus the "motor aphasia" described by Broca 13 years earlier (Wernicke, 1874). This region of the left hemisphere, which, of course, became known as Wernicke's (sometimes, but less so, Bastian's) area, is located on the posterior superior temporal gyrus immediately adjacent to the primary auditory cortex. Over the ensuing years, Wernicke expanded his approach to other language areas to understand better their systemic anatomical and functional signature (Wernicke, 1910). These cross-centennial decades were located around the time of a formal birth of the discipline of aphasiology (derived from the Greek word *aphatos* meaning "speechless") in the scientific community.

Also around the same time period, Korbinian Brodmann published his masterpiece of a cellular-level (cytoarchitectonic) map of cerebrocortical areas that is still referred to today, lacking an alternative since it was such a monumental piece of work of a single brain (Brodmann, 1905, 1909). Broca's region is currently referred to primarily as Brodmann's areas 44 (pars opercularis), 45 (pars triangularis), and 47 (pars orbitalis). Wernicke's area is referred to as Brodmann's areas 39 (angular gyrus) and 40 (supramarginal gyrus). Further, the region adjacent (posterior to Heschl's sulcus) to primary auditory cortex (Brodmann's areas 41 and 42), and Brodmann's area 22 (planum temporale) is an auditory association region that is involved with processing multisensory language and is the core of Wernicke's area that channels information for level 2 processing to regional association areas and beyond (see figure 2.1). What an incredible time period package for evolution, brain, language, and beyond: Darwin, Broca, Wernicke, Brodmann.

As part of Wernicke's area, the planum temporale is likely the most leftward asymmetrical cortical area of the human brain (Galaburda & Geschwind, 1980; Geschwind & Levitsky, 1968; Habib & Galaburda, 1986). The leftward asymmetry of planum temporale is also manifested as a longer left sylvian fissure (lateral sulcus) in humans and some apes (Galaburda, LeMay, Kemper, & Geschwind, 1978; LeMay, 1976). These



**Figure 2.1**

Left hemisphere of a human brain. Brodmann's areas 44, 45, and 47 are part of Broca's spoken language area; 41 and 42 are primary and secondary auditory cortex, respectively; superior part of 22 is planum temporale; 22, 39, and 40 are auditory (or multisensory) association cortex as part of Wernicke's receptive language area.

observations were among the first in the modern literature to compare indicators of human language areas to nonhuman primates.

#### **Evolution of Brain Language Areas in Humans versus Nonhuman Primates**

Answers to the questions of when, where, and how the organizational platform for language was created in the brain have fascinated us for more than a century. The word "language" itself has caused much ado since some would prefer that its use be restricted to humans. I'm not sure that Carl Von Frisch, who described the (dance) "language" hypothesis for honeybees and, for this and more, won the Nobel Prize in 1973, would have agreed with such a narrow and restricted usage. Further, the term "ape language" is used commonly by scientists to refer to the amazing abilities of great apes such as the bonobo Kanzi and the chimpanzee Washoe. These apes access human language through devices such as lexigrams and signs, which appear to me to represent a good fit (Gardner & Gardner, 1969; Savage-Rumbaugh et al., 1993). Let's wait to decide on usage until a good polyspecific (multisensory) definition of language is formulated (Foxe, 2008). "Communication," the obvious and well used alternative, is

correct but much too broad. Even life forms such as the “social” amoeba *Dictyostelium* communicate and respond to valium just like us (Anjard & Loomis, 2005). Regardless of valium users, a closer connection of language in our brains to those of common ancestors among our distant primate ancestors 40 million years ago, or to those more proximate in our common ancestors with great apes around 8 million years ago, is a much better fit.

If the form of language is characterized as that used by humans, then there is no problem since that indeed is unique, so be specific, call it “human language” and be done. We cannot hope to have our closest living relatives master our form of language and neither could we hope to master their form of (ape) “language” anytime soon. Both species are very good at what they do. Beyond debate on use of the “language” term, the cognitive divide between us, the ancestors we shared with great apes, and recent human ancestors over the course of eight million years shows that cognition likely drove the adaptive trajectory toward advancement of interindividual discourse.

### Approaches Used to Study Brain Evolution for Language

Now let’s consider some of the unique evidence-based approaches that have provided windows into answers to the when, where, and how questions. These are paleoneurology and comparative neurobiology. A third would be archeological evidence, such as tools and art, as a window into the mind of the time, but that is not addressed here. As is often the way of science, the answers may not be as big as the questions.

#### Paleoneurology

The paleoneurological approach provides the only direct evidence since it uses the fossil record. However, there is no such thing as a true fossil brain since that organ and its covering (the meninges) putrefy rapidly and are transported away by macroscavengers, leaving an empty bony vessel, the inside of the cranium (endocranum). The ideal situation is if the endocranum fills with sediments (via the foramen magnum) that eventually harden by the process of fossilization. This process creates a “natural endocast,” which essentially is a cast of the outer surface of the meninges since this (secondarily) in life reflects the surface of the brain on the endocranial (inner bony) surface of the skull. The most commonly used alternative is to create a plaster cast of an empty endocranial cavity, or parts thereof, as partial cranial fossils. Either way, since the main component of the meninges, the dura mater, is quite robust and thick at 1/2 to 3/4 mm (Zyablov et al., 1982), gross details of the cerebrocortical surface transferred to the cranium may not be as clearly represented as would be ideal. However, for consideration of brain surface representation of language areas, which

are quite robust and are prominently leftward asymmetrical (in modern humans), there is good evidence that some of these characteristics are present in the fossil endocasts record of human ancestors.

There are several key players in the endocast arena. One of the leading paleoneurologists is Phillip V. Tobias. He explored a relatively enlarged brain in a landmark report with Louis Leakey and John Napier that named a new species in our own genus, *Homo habilis* (Leakey, Tobias, & Napier, 1964; Tobias, 1964). The species name, which means "handy man," was suggested for use by Raymond Dart based on evidence of stone tool use. Tobias reported the endocranial (brain) volume of this type specimen (new species model) (Olduvai Hominid 7, OH-7), which was based mostly on reconstruction from parts of an incomplete cranium, to be around 675 to 680 cc. This size was in between the largest australopithecine and the smallest *Homo erectus*. This value qualified it for membership in the family hominidae, and the *Homo* genus club. As had been noted, the "cerebral Rubicon" (for membership in the *Homo* club) had previously been set at 700 cc by Weidenreich, 750 cc by Sir Arthur Keith, and 800 cc by Vallois, so a revised species diagnosis was required. Later, it was proposed that an endocranial volume of even 600 cc, or evidence for "possession of language as inferred from endocranial casts," did not necessarily meet all the requirements for membership in *Homo* (Tobias & Campbell, 1981; Wood & Collard, 1999). However, this significant finding by Tobias was followed by many other reports by him on brains of early human species. Much of his early work focused on the relative increase of brain volume compared to members of the genus *Australopithecus* and later *Homo* species. Discovery of many new specimens of early *Homo* and a long series of controversial articles culminated in publication of a classic two-volume set wherein all the evidence for language areas in the brains of early *Homo* was characterized (Tobias, 1991). A chapter on endocasts (VIII) noted that both Broca's and Wernicke's brain language areas were well represented in *Homo habilis* for the first time in the hominid fossil record. In contrast, endocasts of *Australopithecus* did not show language areas at the same level. My favorite piece of volume 4 was chapter IX: 5, titled: "*Homo habilis*: A Speaking Primate." Here Tobias discusses the need for efficient transfer of "complicated cultural mechanisms" observed in *Homo habilis*. This would require a more efficient method like spoken language, rather than use of example or imitation, to teach the next generation (Tobias & Campbell, 1981). Although it is clear that Tobias's main point is transfer of sophisticated information between the more cognitively advanced members of this species, I would argue that spoken language is not necessary to achieve that goal. Maybe the brain cares not so much about the mode of information transfer but more about its level (Deacon, 1997). The stance of "brain evolution drives language evolution and vice versa" always reminds me of grandmother's expression "Don't speak about more than you know, or you will look foolish." In other words, it's not adaptive.

The classic report by Gordon Hewes “Primate communication and the gestural origin of language” suggested that gestures were the platform that other modalities were built upon (Hewes, 1992). Similarly, the work of Michael Corballis has promoted a shift from gestures (“a behavioral fossil”) to speech during hominid evolution, essentially supporting the old idea of freeing the hand for other functions such as toolmaking (Corballis, 2003a, 2003b; Gentilucci & Corballis, 2006). The endocast work of Tobias inspired another leader, Ralph Holloway (Columbia University, New York), during his sabbatical trip to Africa in 1969, to use this investigative tool and start a lifetime of paleoneurological research (Holloway, 2008). Holloway soon became the epitome of endocasts workers and followed from endocranial volume to publish many studies that dealt with the issues of cerebral advancement toward the human condition and, of course, the onset of brain areas for human language in human fossil ancestors. One of Holloway’s central themes was pursuit of the legendary “lunate sulcus” that is seen in fossil endocasts along the human lineage (Holloway, 1983). A more posterior position of this critical landmark served as an indicator of the expansion of the parietal association cortex that is important to functions within brains that are more evolved toward the human condition. For example, second-level (polysensory) processing of language is an example of high-order functions in this region. Much opposition over many years was offered for this controversial position by those with alternate views of the progression of brain evolution from apes to early human ancestors (Falk, 1983b).

Surprisingly, it was noted by Holloway that in many endocasts, such as Neanderthals and *Homo erectus*, key parts of brain surface convolutions such as the sylvian fissure (also termed lateral sulcus; that indicate the presence of a leftward asymmetrical human brain language region, Wernicke’s area) and that these are not easy to describe, with confidence (Holloway, 1981). This did not necessarily mean that they did not exist. Perhaps the robust nature of the dura mater around these prominent brain regions blurs their anatomical signature. However, a key cross-disciplinary review article of brain asymmetries by Galaburda and coworkers noted that a prominent leftward asymmetry of the sylvian fissure had been described in endocasts of the La Chapelle-aux-Saints Neanderthal (*Homo neanderthalensis/Homo sapiens neanderthalensis*) and in Peking man (*Homo erectus*; Galaburda, LeMay, et al., 1978). Many different versions of hemispheric asymmetry for the sylvian fissure have been discussed in many primate species from living monkeys and apes to humans. These are discussed below.

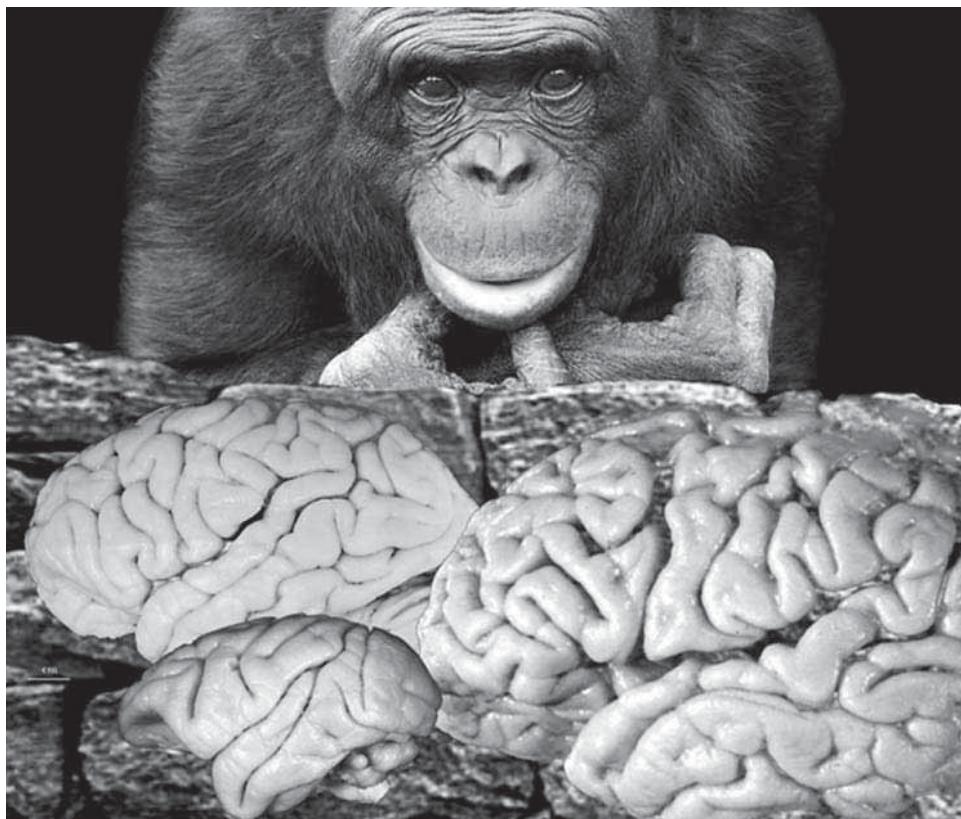
During his life-changing sabbatical trip to South Africa in 1969, Holloway was invited by Drs. C. K. “Bob” Brain and Tobias to assess a new endocast (natural) specimen from the Swartkrans fossil site (SK 1585), thought to be a member of the robust australopithecines species *Australopithecus boisei* (Holloway, 1972; 2008). Holloway noted that the parts of the inferior frontal gyrus showed a more complex frontal

lobe, particularly in Broca's region, that is, the second key brain language region involved with the production of spoken and signed human languages. Although the several components that are seen on human brains were not discernible, the region appeared larger and more rounded than in great apes. Similar findings for Broca's area were presented by Dean Falk for an endocast from the Koobi Fora region of Kenya (Falk, 1983a). This specimen (KNM-ER 1470) was originally assigned to *Homo habilis*, then later to *Homo rudolfensis*. Falk described the unique nature of the sulcal pattern in the left inferior frontal gyrus (Broca's area) in KNM-ER 1470 as being similar to modern humans and unlike *Australopithecus* and living great apes. It had been noted earlier that endocasts of *Australopithecus* were not organized toward the progressive design of *Homo* (Falk, 1980).

### Comparative Neurobiology

The comparative neurobiology approach provides indirect evidence since it uses the brains and behaviors of living primates to infer the evolutionary trajectory of brain evolution that occurred after diversion from common ancestors. As you look at figure 2.2, which portrays the main players in the building blocks of brain evolution, human, chimpanzee, and monkey, you should think about why the monkey brain is up front and why the human brain is blended into the wall. Answers to the question might lie in temporal distance, stasis, adaptation, and ongoing changes.

When one is applying the approach of comparative neurology, it must always be remembered that the rules of homology (basic rules of multifactorial similarity within adaptations along the lines of a Hennig style transformation series) must be adhered to whenever possible, and the likelihood of homoplasy (analogy; independent recurrence of similarity; not derived from a common ancestor and can include convergence, parallelism, or reversal) be accommodated (Hennig, 1965). In the classic text *Principles of Animal Taxonomy*, George Gaylord Simpson laid out a series of nine criteria that could be used to establish historical homology hypotheses, specifically for use with neuroanatomical data (Simpson, 1961). These criteria include similarities, within the neurons that form the group, of (1) topology, (2) topography, (3) axonal connections (hodology), (4) relationships between the group of neurons in analysis to some consistent feature of the species analyzed, (5) embryological derivation, (6) morphological features, (7) neurochemical attributes, and similarities in (8) physiological properties and (9) behavioral outcomes of neuronal activity. Without availability of a transformation series, which is often the case, particularly in the nervous system, the possibility of homoplasy, which includes the processes of convergent, parallel, or reversal evolution, is very difficult to rule out. A similar "processual approach" which combines multifactorial evidence to support a hypothesis of homology was proposed (Begin, 2007). However, the problem is usually dealt with by assuming that homology exists "in the absence of contrary evidence" (Butler & Hodos, 2005).



**Figure 2.2**

Kanzi the bonobo contemplates the building blocks of brain evolution with brains of human, ape, and monkey. Why is the monkey brain up front, tight, and intact while the human brain is loose, incomplete, and blending into the wall?

Lacking the support of fossil evidence with the absence of great ape/human ancestor endocasts, can we assume that the brains of living chimpanzees or bonobos, our closest living relatives, are good living models of the common ancestor we shared 5 million to 6 million years ago? The only endocast is that of Proconsul, reported to have looked like a cross between living Old World monkeys and gibbons, and is a species that lived around 23 million years ago in Kenya (Begun & Cordos, 2004). Similarly, if you take a comparative trip back to common ancestors with Old World monkeys in the Oligocene epoch sometime around 30 million years ago, the problem might be magnified. The tools of comparative neurobiology that compare brain similarities from cells to sulci across diverse species are utilized to determine homology and adaptations. The Hennig and Simpson tool kits help comparative neurobiologists

in their effort to bridge the evolutionary chasm. At least six of Simpson's nine criteria are assumed in my research discussed below.

### Gross Asymmetries of the Primate Brain

#### Overview

The broadest way to infer whether there are brain regions that are expanded on one hemisphere versus the other is to consider items such as relative hemispheric width and/or anterior–posterior length. It is widely considered that such global measures may indicate broad expansion of cerebral regions beyond what may be more subtle regional manifestations. For example, expression of hemispheric “petalia” or “torque” in humans refers to extension of the left occipital lobe beyond that of the right in combination with extension of the right frontal lobe beyond that of the left (Chiù & Damasio, 1980). Similar findings have been reported in fossil humans and great apes (LeMay, 1976). An interpretation of left occipital polar extension’s being associated with language areas makes some sense since these are represented by their larger size on the left hemisphere, at least within the temporal lobe as the planum temporale of Wernicke’s area. However, what is not discussed is why extension of the right frontal lobe fits into the same language function story since it would make more sense for the left frontal lobe to extend more to express the leftward volumetric asymmetry of Broca’s area. Similarly, right handedness in fossil human ancestors such as *Homo erectus* has been inferred from petalia (Holloway, 1980). Since handedness is a left-hemisphere motor function (frontal lobe, precentral gyrus, motor cortex) specialization mostly in right-handed and the majority of left-handed humans, perhaps like for language, a left frontal lobe extension would likely be manifested if this region were larger. Using different measures, including magnetic resonance imaging (MRI), it was shown that individuals with a left-hemisphere dominance of handedness had larger right anterior frontal, and left occipital widths (Kertesz, Polk, Black, & Howell, 1992). However, others have demonstrated, using CT imaging in living humans, that handedness and cerebral asymmetries such as petalias and hemispheric widths are independent variables (Chiù & Damasio, 1980).

Recent discussions of torque/petalia in humans have even suggested that the evolutionary redesign process of the early *Homo* brain that manifest as “torque” gave rise to language along with schizophrenia as a by-product of “language at the end of its tether” (Crow, 1997, 2000, 2008). This may be interpreted to mean that adaptations for full-blown human “language” were moving so fast that the brain was overwhelmed (human brain evolution still in process; see figure 2.2).

Measures of petalia and hemispheric width have also been made in apes and monkeys using a myriad of approaches from endocasts (dry skulls of living species), whole cadaveric brains, and MRI. For example, it was demonstrated in a large sample

of rhesus monkey endocasts that right frontal petalia was significant with occipital petalia less so except in association with frontal petalias (Cheverud et al., 1990; Falk et al., 1990). One example of a distinct technique, which measured petalias and hemispheric width in a large sample of perfusion fixed macaque brains, showed no frontal but some occipital petalias and no frontal or parietal lobe hemispheric width asymmetries (Gannon, 1995). These and many other results across species and approaches are compelling except that some, at least, may fall into the category of functionality inferred from broad anatomy. After all, correlations alone do not have to translate to functionality. For example, I prefer to place patterns of petalia into the physical domain across species; the preferred drainage route of the cerebral venous system is to the right, from the superior sagittal sinus along the transverse to sigmoid venous sinus. The larger relative bulk of the right transverse sinus physically persuades the whole right hemisphere anteriorly; voila, petalia (Henneberg & Symons, 1992).

### **Asymmetries of Primate Brain “Language” Areas**

The cross-specific approach to characterize language areas in brains of nonhuman primates has followed the trajectory from gross to microscopic anatomy to functional localization. The sylvian fissure (lateral sulcus) has served as the historical gold standard for assessment of hemispheric asymmetry as an indicator of the purported homologue of Wernicke’s receptive language area in humans. The sylvian fissure is significantly leftward asymmetrical in humans and some great apes and is considered to represent the marked asymmetry of the planum temporale, an auditory association area that is involved with language and perhaps multisensory processing (Galaburda, LeMay, et al., 1978; LeMay, 1976). The planum temporale is around one third larger on the left hemisphere in 65% versus 11% on the right hemisphere of human brains (Galaburda & Geschwind, 1981; Galaburda, LeMay, et al., 1978; Geschwind & Levitsky, 1968). On the next rung down the evolutionary ladder, so to speak, in our closest living relatives, chimpanzees, an even greater leftward asymmetry of the planum temporale was demonstrated in 17 of 18 brains (94%) (Gannon, Holloway, Broadfield, & Braun, 1998). This discrepancy may have been due to measurement of lateral linear versus whole planar profiles in humans and chimpanzees. The chimpanzee method has yet to be repeated in humans.

### **Gross Brain “Language” Area Asymmetries in Monkeys**

In Old World and New World monkeys, there have been a variety of reports based on endocasts and both immersion and perfusion fixed brains. Using three-dimensional surface imaging analysis of ten macaque endocasts, significant leftward asymmetry of the sylvian fissure was shown (Falk, Cheverud, Vannier, & Conroy, 1986). Similarly, a study that used direct measures of sylvian fissure length from fixed brains of five species of New and Old World monkey showed significant leftward asymmetry

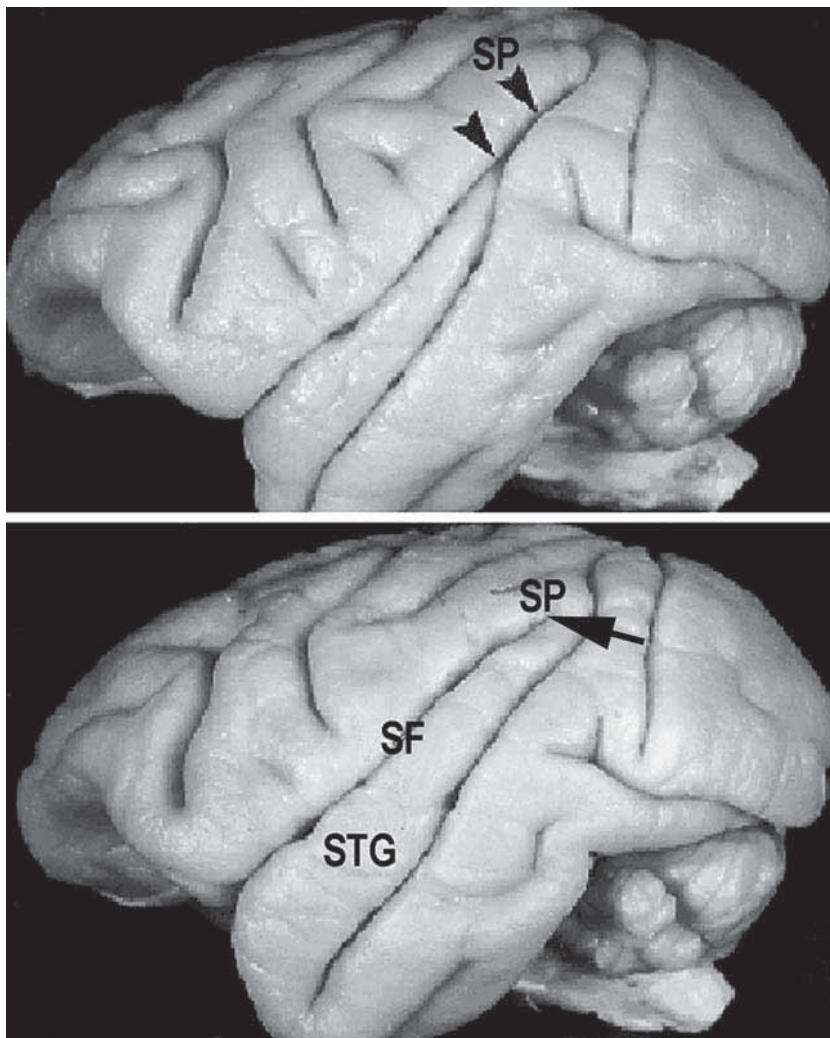
(Heilbroner & Holloway, 1988). These findings did not match with other studies that showed symmetry, not asymmetry, in macaques (Yeni-Komshian & Benson, 1976; Gannon et al., 2008). The 2008 study by Gannon et al. used perfusion fixed macaque brains and made direct surface measures of the sylvian fissure. It was found that the “true” sylvian point (posterior endpoint of the sylvian fissure) was often obscured at the surface by operculization of one or both of the inferior parietal and inferior temporal gyri. The result was a “false” sylvian point at the surface (see figure 2.3).

In order to simulate endocasts, where the “true” sylvian point was obscured such that a “false” sylvian point became evident, this was measured in the same series of brains from photographs of the lateral hemisphere (see figure 2.4).

There was no hemispheric asymmetry of the sylvian fissure evident whether the true or the false sylvian point was used as the posterior landmark (Gannon, Kheck, & Hof, 2008). The only reason that other studies may have determined leftward asymmetry of the sylvian fissure, in whole brains of the same or closely related species (as in the Gannon et al., 2008, study), and assuming that the “real” sylvian point was used, may be the difficulty of determining reliably the anterior landmark of the sylvian fissure. At this indicator, the inferior frontal and superior temporal gyri (IFG, STG) depart antero-superiorly and antero-inferiorly, respectively, to create a large V-shaped divergence (as can be seen in figures 2.3 and 2.4). Although these are perfusion fixed brains where an overall constant shrinkage is assumed, this anterior margin of the sylvian fissure may not look so unsullied in an immersion fixed brain after a prolonged postmortem period. Although the exact epicenter of the divergence may be difficult to determine in endocasts, it is not that easy in whole brains either, so application of a standardized assessment method is critical. The technique I have used (and compared across independent individuals) is to gently press the STG and IFG together and use the immediate point of touching as the landmark. It can be assumed that this would represent the (nonfixative shrunken) situation in life. If the anterior gap is wider on both sides as can be seen in figure 2.4, the more marked declination, prominent angulation, and straighter line at the STG takeoff margin can be used as an indicator. Either way, these measures should be conducted by several blinded individuals using agreed upon methods since, if differences in length of the sylvian fissure are in millimeters, which they often are, mistakes could easily be made.

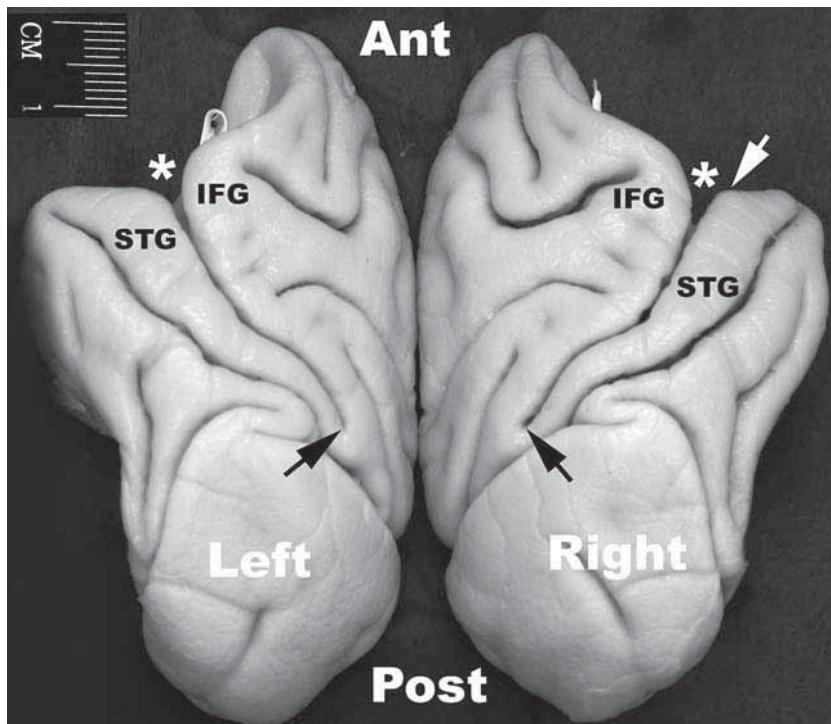
### **Cellular-Level Hemispheric Asymmetry of Wernicke’s Area Homologue in Primates**

The specific cellular (cytoarchitectural) component of the leftward asymmetrical planum temporale in humans (primarily area Tpt) has also been proposed to influence leftward asymmetry of the horizontal limb of the sylvian fissure (Galaburda, LeMay, et al., 1978; Habib & Galaburda, 1986). The homologous region of the left Tpt in macaques has been well described as being a part of the posterior parabelt region of the auditory association cortex (Hackett, Stepniewska, & Kaas, 1998; Kaas & Hackett,



**Figure 2.3**

Left hemispheres of two macaque brains. The top image shows how the “true” sylvian point (SP) may be masked by the middle temporal and inferior parietal gyri. This creates a second “false” sylvian point (left arrowhead) on the surface that would be seen on an endocast. The bottom image shows a “true” sylvian point (SP, black arrow) that clearly shows the posterior boundary of the sylvian fissure (SF) on the brain’s surface. STG, superior temporal gyrus.



**Figure 2.4**

Left and right hemispheres of a macaque brain laid flat on midsagittal surface with superior surfaces opposed. Black arrows show location of the “true” sylvian point exposed on the surface. White asterisks indicate the location of the anterior boundary of the sylvian fissure adjacent to the superior temporal gyrus (STG) and the inferior frontal gyrus (IFG). The white arrow shows the flattened part of the STG that forms more of an angled surface than the adjacent IFG. Ant, anterior; Post, posterior.

2000). However, these studies were purposefully broad and were not designed to focus on area Tpt or hemispheric asymmetry. A recent study focused on asymmetry of the cellular identity of area Tpt in macaques as a follow-up to previous work on gross anatomical asymmetry of its homologue, the planum temporale in great apes (Gannon et al., 1998, 2008). It was shown that the volume of the cytoarchitectural signature of area Tpt was significantly leftward asymmetrical. It was the first study to include area Tpt on the right hemisphere of macaques. Further, the intra- and interhemispheric profile of area Tpt topography was considerably more varied than had been shown previously on the left hemisphere (Gannon et al., 2008). These findings indicated that leftward asymmetry of auditory (or multisensory) association cortex

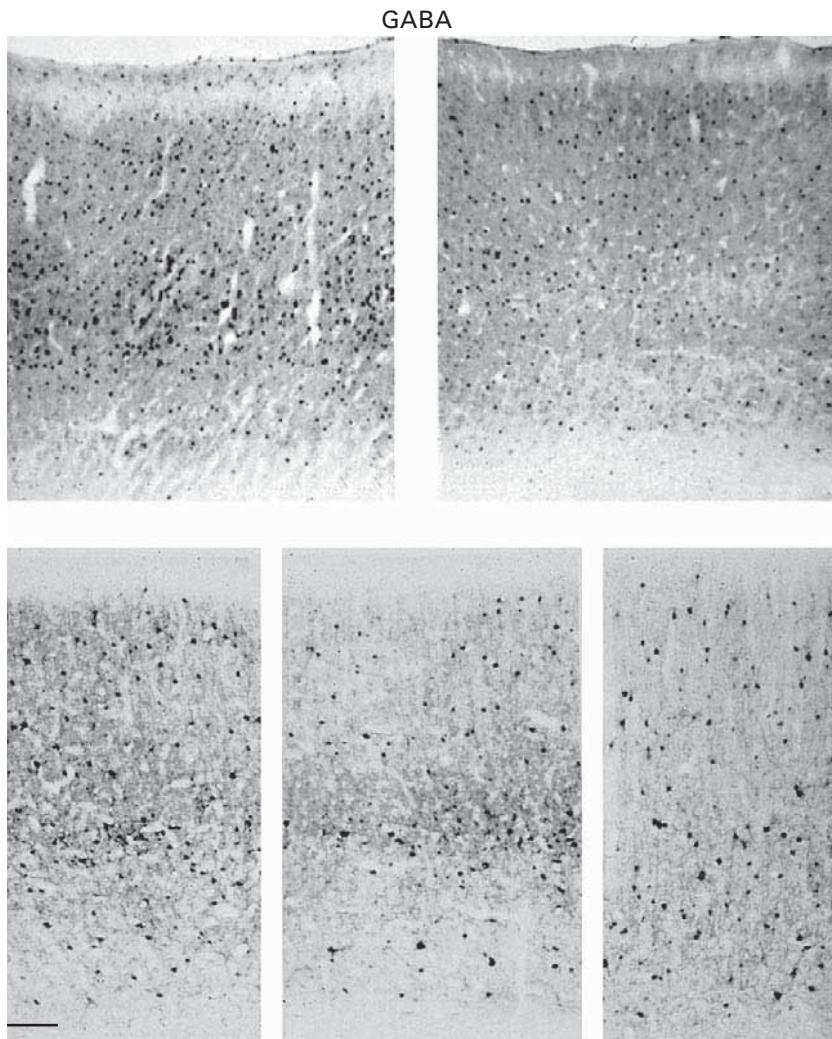
might have been in place in our common ancestor with Old World monkeys in Africa around 35 million years ago. Cytoarchitectural studies of area Tpt, similar to that done in humans (Galaburda, Sanides, & Geschwind, 1978) and now in macaques, have yet to be conducted in chimpanzees or other great apes. This would be important since assumptions of activation patterns in functional imaging studies would need to be informed by an understanding of location and topographic variation of areas such as Tpt that may play a more multimodal role in nonhuman primates than in humans.

### **Chemical and Functional Asymmetries of Wernicke's Area Homologue in Primates**

An inspirational line in an chapter by Albert Galaburda and coworkers, commented "the wealth of gross anatomical and functional lateralization data available for human language areas is not complemented by knowledge of whether neural substrates such as cellular and connectional architectures, neurons, synapses, receptors, enzymes or other molecules exist in one hemisphere but not the other" (Galaburda, Rosen, & Sherman, 1991). Studies have demonstrated cellular and neurochemical asymmetries in Broca's area. For example, using chemical and cellular approaches, significant leftward asymmetry in size and distribution of a group of acetylcholinesterase-rich layer 3 pyramidal neurons were shown in Brodmann's area 45, but not 44, both usually being in Broca's area (Garcia, Montiel, Villalon, Gatica, & Aboitiz, 2004; Hayes & Lewis, 1995).

Preliminary studies in my laboratory focused on expression of a range of neurochemical elements in area Tpt of the macaque brain. Since a leftward asymmetry of the cytoarchitectonic profile of this region had already been described, it was hypothesized that the neurochemical signature would mirror this and serve to indicate regional hemispheric functional specializations. As such, immunocytochemistry was used to determine whether the fundamental neurochemical signature of area Tpt differed across hemispheres. A range of classic neurochemicals such as GABA, calbindin, serotonin, and parvalbumin were chosen to represent a range of modulatory effects. Not surprisingly, marked hemispheric asymmetries were apparent in most of the neurochemical elements that were studied. For example, a dense population of GABA immunoreactive cells was present in layer IV of area Tpt on the left hemisphere (see figure 2.5, plate 2).

Similarly, there was a marked asymmetry of parvalbumin immunoreactive cells in area Tpt compared to a randomly selected control region in the inferior margins of the superior temporal gyrus (see figure 2.5/plate 2, lower panel). It is well-known that the distribution of GABA (inhibitory neurotransmitter) and parvalbumin (a calcium binding protein) is often similar, which suggests that GABAergic cells (a subpopulation of interneurons) express parvalbumin and that these components may act in a complementary fashion (Celio, 1986).



**Figure 2.5 (plate 2)**

(Top) Immunocytochemical labeling of GABA in area Tpt of left (a) and right (b) hemispheres of a macaque brain shows a striking asymmetrical distribution across cortical layers. In particular, a dense population of GABA immunoreactive cells is present on the left side. (Bottom) Immunocytochemical labeling of parvalbumin in area Tpt of left and right hemispheres of macaque shows a distinct asymmetrical distribution across cortical layers. In particular, a dense population of parvalbumin immunoreactive cells and processes were present on the left side layer II and layer V similar to GABA. Area Tpt on both sides is distinct from a random control (c) on the inferior wall of the right superior temporal gyrus (R-iSTG). WM, white matter.

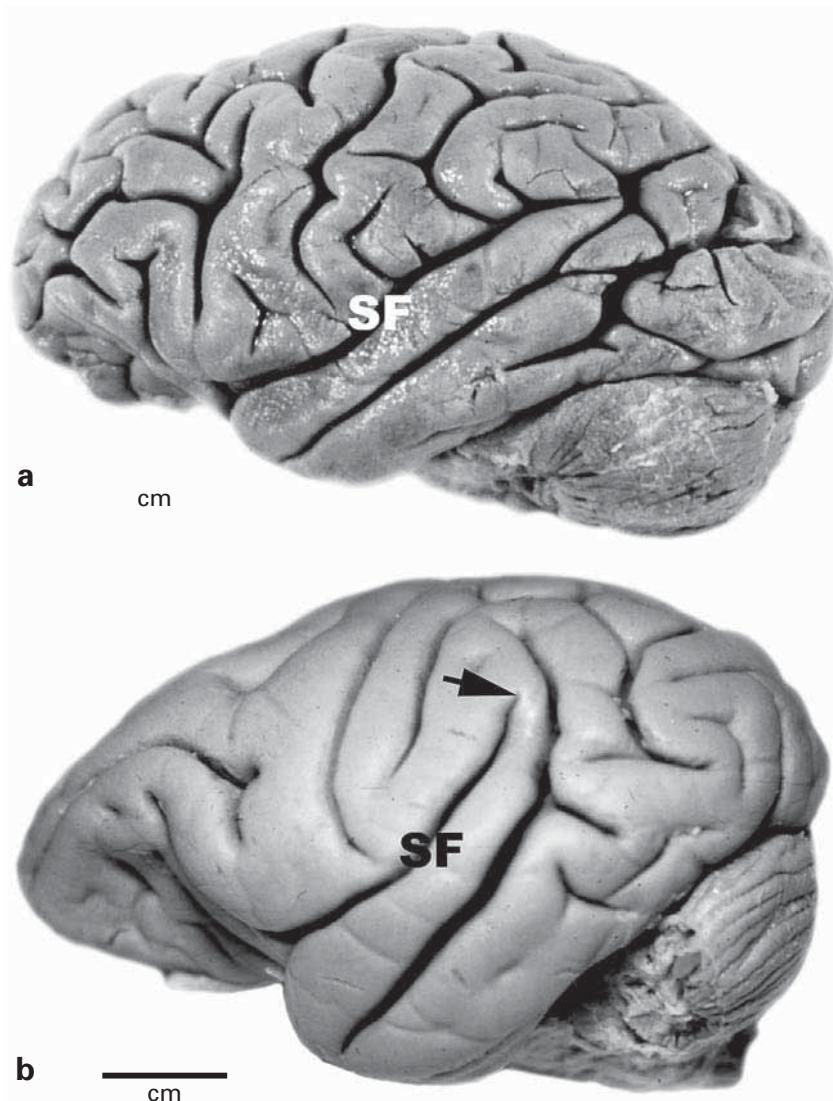
Although direct relation to “language” functions (homologous) in these regions is supported by hemispheric lateralization and distinct laminar distribution of neurochemical components, it is not possible to reliably assign specific functional roles. Instead, the combination of gross/macro anatomical, cytoarchitectonic, and chemoarchitectonic profiles offers support to other approaches such as functional imaging within a well-crafted tasking profile.

### **Gross Asymmetries of Brain “Language”: Areas in Apes**

In great apes there have been a number of different approaches used to measure brain asymmetries related to “language.” One study noted significant asymmetries across great apes, less so in gorillas, but particularly in orangutans (LeMay & Geschwind, 1975). It was claimed that this species would be a better model for the human condition. The reverse of this finding was noted by Gannon et al. (Gannon, Kheck, & Hof, 2000), where the planum temporale region of orangutans was observed to be indistinct compared to that of gorillas and chimpanzees. These workers proposed that this intermediary morphology fit with the longer evolutionary distance of the common ancestor with orangutans. The previous common ancestor shared with lesser apes lacked a clear gross anatomical signature, since the planum temporale was not present in gibbons or siamangs (Gannon et al., 2000; see figure 2.6). A similar study of humans, chimpanzees, and macaques showed significant leftward asymmetry of the sylvian fissure except in macaques (Yeni-Komshian & Benson, 1976).

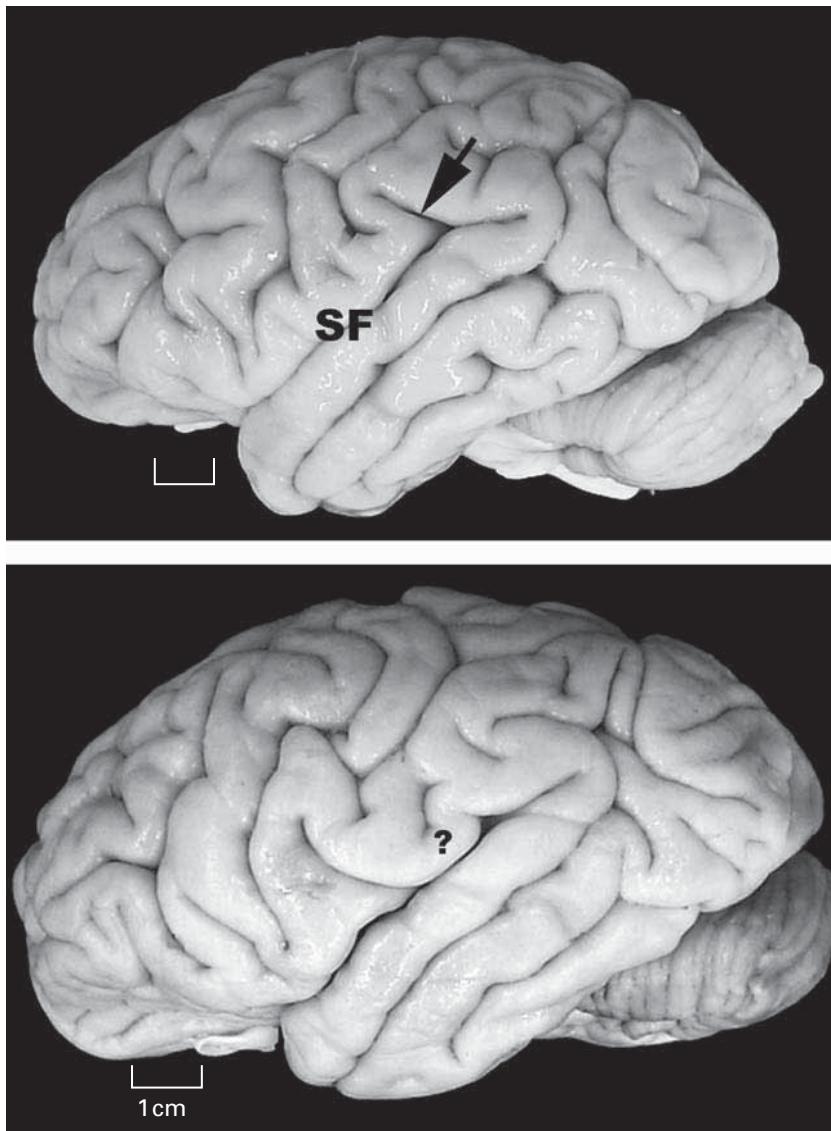
Measures of sylvian fissure length in great apes and humans fall into a new category of potential measurement error. As noted by Gannon et al. in a study of the planum parietale, the sylvian point, that is relatively easy to pinpoint in lesser apes and monkeys, is much more difficult to ascertain in great apes and humans (Gannon, Kheck, Braun, & Holloway, 2005). This is because the posterior margins of the sylvian fissure diverge into ascending and descending limbs (see figure 2.7). Decisions have to be made by the process of knowledge-based creative elimination by observation of critical landmarks and broad assessment of regional variation (Ide, Rodriguez, Zaidel, & Aboitiz, 1996; Steinmetz, Rademacher, Jäncke, Huang, Thron, & Zilles 1990).

In a recent study, this validated and accurate approach was used to determine expression of the posterior ascending limb of the sylvian fissure (palSF) in chimpanzees and orangutans. The posterior wall of the palSF includes the “planum parietale” that is similar in cellular profile to the “planum temporale” in humans (Gannon et al., 2005). The rightward asymmetry of the region is implicated with dyslexia in humans (Jancke, Schlaug, Huang, & Steinmetz, 1994). Even after multiple revisits to look at chimpanzee and orangutan brains, along with lengthy discussions across the table by two neuroscientists, a leading National Institutes of Health language research neurologist and an internationally renowned paleoneurologist, decisions did not come in easily. One of the reasons for this can be seen in figure 2.7. How would you place and



**Figure 2.6**

Left hemisphere of gorilla (a) and siamang (b) brains. The gorilla brain is essentially identical to the chimpanzee. The siamang brain is similar to the Old World monkey (see figures 2.3 and 2.4) with sulcal organization and a posterior termination of sylvian fissure (SF) at the sylvian point (arrow) with no bifurcation into ascending and descending limbs.



**Figure 2.7**

Left hemispheres of two chimpanzee brains. (a) shows a classic morphology of the sylvian fissure (SF) with an unambiguous posterior ascending limb (arrow) with the posterior descending limb to its right. In (b), this relationship is not as clear, and what's the sulcus to the left of the question mark? How would you make the determination?

measure the palSF or sylvian point in figure 2.7a versus 2.7b. Which of these is a relatively easy decision? Some example of the wide degree of variation across chimpanzees and orangutans can also be seen in figures 3 and 4 of a recent article (Gannon et al., 2005). However, decisions were made, and in this study significant rightward asymmetry of the palSF was shown to be present in chimpanzees ( $p = .04$ ). Considerable variation and a nonsignificant ( $p = .07$ ) rightward asymmetry was shown in a smaller sample of orangutans. These findings were similar to those shown for the planum temporale, which showed considerably more variation in orangutans compared to humans, chimpanzees, and gorillas (Gannon et al., 2000). The morphology that is seen in humans, chimpanzees, and gorillas is similar, but there is a huge rift between these and lesser apes (see figure 2.6). The whole sulcal pattern of gibbons and siamangs looks more like that of Old World monkeys, including termination of the sylvian fissure at a nonbifurcated sylvian point.

### Where Does This Leave Us?

That long and arduous but enjoyable research experience brings me to how alternative methods might be used to assess such gross and macromorphologies. One of the advantages of having a whole brain on the table, surrounded by cross-disciplinary experts, is that a depth of experience and an understanding of neuroanatomical variation can help guide the final decision toward accuracy and validity. A potential disadvantage is that this approach does not allow for blinding to eliminate potential bias. All investigators are fully aware upfront of the hypothesis and its implications and are experts to sidedness when important decisions of measured asymmetry are to be made.

This does not have to be the case if imaging techniques in live animals are used. For example, when using MRI, it is easy to randomly reverse all brains sections in an individual. These MRI measurers can also know the hypothesis and be brain region experts, but they are blinded to hemispheric side, so involuntary biases are eliminated. Unfortunately, many comparative neuroanatomy MRI studies are being published where random reversal blinding does not occur. I will not cite them here, but they are easy to find. Should they have been published in top-tier journals? Probably not, but editors are slowly becoming more aware of the issue, and some have made it a requirement, under the right circumstances, where hemispheric asymmetry is a major finding. MRI is a great technique, and it's definitely the future, but holding an ape brain in your hand and passing it around a table of experts takes some beating. Similarly, brains of wild caught specimens from a natural setting, which were shot out of the trees in the bad old days, like all museums did to add to their collections, can be found in the Smithsonian Institution. The advantage of these specimens is that they represent individuals; they were born and interacted with peers within a naturalistic, wild setting away from influences of an unnatural species, humans. However,

these 100-year-old fixed brains are very fragile and so can't be handled and manipulated. Thus, for example, to look at deep three-dimensional structures like Heschl's gyrus and the planum temporale within the sylvian fissure and much more, MRI is the only way it can be done (blinded to hemisphere, of course).

### **Other Approaches and Future Directions**

As discussed above, from the wide breadth of gross anatomical, microscopic, and neurochemical approaches and findings that are still coming in, the stage is being set to understand better the functional role of these brain language area homologues in monkeys and great apes. Data from all approaches should be aligned to create multi-factorial templates of neural organization and communication behaviors.

To date, there have been no definitive functional imaging studies of "language" functions in the brains of great apes. However, a recent study in macaques using functional MRI demonstrated a "monkey voice region" that showed a proclivity for species-specific vocalizations and the vocal identity of conspecifics (Petkov et al., 2008). This same group had also demonstrated multisensory phenomena in which both visual and tactile stimuli were integrated within the auditory cortex (Kayser, Petkov, Augath, & Logothetis, 2007; Kayser, Petkov, Lippert, & Logothetis, 2005; Kayser, Petkov, & Logothetis, 2008). Although these provocative studies and their findings were not directed primarily toward understanding the evolution of brain language areas, the demonstration of a multisensory capacity for what are usually considered auditory (only) regions is compelling for better understanding polymodal communication in primates. This can take us in the direction of evolutionary history.

Interestingly, another study in macaques using positron emission tomography (PET) showed "higher order" activation of homologues of Broca's and Wernicke's areas by species-specific vocalizations (Gil-da-Costa & Hauser, 2006; Gil-da-Costa et al., 2006). These examples alone demonstrate good support of the hypothesis that language areas have a long evolutionary history, at least in primates, and that the bauplan present in a series of common ancestors was customized within the boundaries of species-specific needs.

As the functional imaging approach moves along, it is imperative that the advanced cognitive repertoire of primates, particularly the great apes, is not underestimated. Clearly, lab-based functional imaging routines such as PET or MRI cannot capture subject blinded environmental and naturalistic behavioral context as readily as classic early playback studies. For example, without context, could functional imaging studies capture the neural activation equivalents of the behavioral studies conducted in vervets that showed appropriate response to predator calls (Seyfarth & Cheney, 2003)? Interestingly, a later review by the same group characterized perception of vocalizations in species such as vervets and baboons as a world of listeners, but not deliverers (Seyfarth, Cheney, & Marler, 1980). Similar to human speech, listeners acquire a rich

source of information that is simultaneously encoded for both semantic and emotional information to understand social events and beyond (Seyfarth & Cheney, 2003). Would higher order auditory (multisensory) association cortex be activated on the left-hemisphere homologue of Wernicke's area, or would highly intelligent monkeys choose to ignore it as they sit strapped in their PET or MRI laboratory chair with head stabilizer attached? They would probably know quite well that there is no way a (ghostly) martial eagle could come flying down or a leopard come prowling by. We probably cannot begin to imagine how sophisticated great apes like chimpanzees and bonobos would react to and process a task that is below their intellectual prowess. The nature of the tasking regime, designed to arrive at a meaningful outcome, would have to take such factors into account and become an appropriate stand-alone routine. As the old adage goes, "You cannot get your head into the mind of another species." However, with some creative collaboration between savvy field primatologists and comparative neurobiologists, links between brain and behavior might be made. Similarly, new age technologies that would allow us to record patterns of brain activation in a natural setting would allow more definitive observations in appropriate behavioral contexts.

### **Conclusions**

There is no such thing as a "transformation series" available in the monkey–ape–human endocast fossil record for the comparative neurobiologist to consult and compare data to. However, using Simpson's tool kit (described above) it is at least possible to be confident of homologous relationships (Simpson, 1961). Using and realizing these tools, researchers have amassed a wealth of evidence to support the hypothesis that the homologues of human brain language areas have been around for a long time. As such, we can be reasonably confident they were shared with the common ancestor of living Old World monkeys along with a shift to species such as *Propliopithecus* around 33 million years ago and beyond. What does this mean for future endeavors? Well, as data from the different approaches across species are amassed, a better understanding of species-specific needs and solutions may be translated to create a comparative evolutionary translation series. Maybe this will be the key to understanding better how a neural platform that was erected in the distant evolutionary past was so well designed that it was able to change and encompass the communicative needs of a broad spectrum of cognitive boundaries.

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### 3 Handedness and Cerebral Asymmetry: An Evolutionary Perspective

Michael C. Corballis

Until recently, cerebral asymmetries were widely considered to be uniquely human. In a book published in 1973, for example, the great Russian neuropsychologist A. R. Luria wrote the following:

With the appearance of *right-handedness* ..., and later with the appearance of another related process, namely *speech*, some degree of *lateralization of function* begins to take place, which has not been found in animals but which in man has been an important principle of the functional organization of the brain. (Luria, 1973, p. 77, his italics)

This was also the theme of my book, *The Lopsided Ape* (Corballis, 1991); the title referred, of course, to humans. Even more recently, Gazzaniga (2000) similarly suggested that cerebral asymmetries define humanness. In the subtitle to his review of split-brain studies, he asked "Does the corpus callosum enable the human condition?" implying that the corpus callosum allowed different functions to develop in the cerebral hemispheres in humans, while preserving mental unity. Genetic theorists have assumed a genetic mutation, unique to humans, that gave rise to both handedness and cerebral asymmetry for language functions (e.g., Annett, 2002; McManus, 2002), and Crow (2002) has gone so far as to suggest that this mutation was the speciation event that created *Homo sapiens* and other putatively human characteristics such as language, theory of mind, and a susceptibility to psychosis.

Contrary to these claims, evidence is accumulating that cerebral asymmetry is widespread in the animal kingdom. The edited volume by Rogers and Andrew (2002) covers asymmetries in invertebrates ranging from birds and fish to rodents and primates. In their Introduction to that volume, Rogers and Andrews write as follows:

Until recently, investigation of lateralization in species other than humans was neglected, largely because of the widespread notion that lateralization was unique to humans. Indeed, so long as lateralization was seen as intimately linked to tool use, consciousness and language, no other conclusion was possible. It is now obvious that this earlier assumption was incorrect. Some researchers, while recognizing the existence of lateralization in nonhuman species, then devel-

oped the idea that human uniqueness resided in the fact humans are more lateralized than all other species (Corballis, 1991). This too is incorrect, as many examples in various chapters of this book show. (p. 2)

This message was not universally heeded, and a sharp exchange between Crow (2004) and Rogers (2004) reveals the degree of dissent over the issue. Crow has nevertheless continued to insist on the uniqueness of human cerebral asymmetry (Chance & Crow, 2007; Crow, 2005).

Is there a middle ground? Clearly there are some asymmetries that are distinctively human, even if only by virtue of the fact that the functions that are represented asymmetrically in the brain are themselves distinctively human, if not uniquely so. In this chapter, then, I consider the issue from the opposite direction, beginning with two functions that are generally considered unique to our species. These functions are manual dexterity and language. Both are represented asymmetrically in the human brain. I then examine the possible evolutionary and genetic sources of these asymmetries.

### **Manual Dexterity**

The term “manual dexterity” captures both the ability to manipulate material objects with the hands and the fact that in the great majority of people one hand, usually the right, is dominant for such activities. Of course, many such activities are bimanual, but one hand usually plays the dominant or more manipulative role, while the other acts to hold or steady the object to be manipulated, as when one slices bread with a bread knife. Handedness is the most transparent of functional asymmetries, easily detectable in everyday activity. Around 90% of people are right-handed, whether defined in terms of a preference for the right hand (McManus, 1985b, 2002) or of greater skill or strength in that hand (Annett, 2002). Handedness clearly reflects a cerebral asymmetry, not an asymmetry of the hands themselves—although there may be slight peripheral asymmetries due to more frequent use of the dominant hand.

Humans also show a higher degree of dexterity, in the nonlateralized sense of the term, than do other species. Primates and some birds show skill in some manual activities, including the manufacture and use of simple tools, but they are far surpassed by humans. Consider, for example, such activities as writing, playing the piano, threading a needle, or even tying shoelaces—even if one discounts the cognitive component, these kinds of activity seem well beyond the capacity of other species. Dexterity, in both of its meanings, is at least a distinctive aspect of human behavior, if not a unique one.

A likely factor in the evolution of manual skill was bipedalism, the primary attribute distinguishing the hominins from the other great apes, and dating from 6 to 7 million years ago (e.g., Richmond & Jungers, 2008). Bipedalism would have freed the hands

from involvement in locomotion, allowing them to become more specialized for manipulation. Indeed, it is possible that manipulation, perhaps in the form of tool use, may have driven bipedalism itself. One argument against this is that the earliest record of stone tool manufacture dates from only 2.5 million years ago (Semaw et al., 1997), some 4 million years after the origins of bipedalism. It remains possible, though, that the early hominins fashioned tools from perishable materials, such as wooden sticks, or that bipedalism was driven by the use of the hands for other functions, such as transportation. Another possibility, considered below, is that the hands provided the primary means of intentional communication in the early hominins, and it was this that led to selection for bipedalism.

Handedness, in turn, may have been selected to enhance manipulation (including linguistic manipulation), with one hand taking the dominant manipulative or strength-demanding role and the other serving a holding or steadyng function. Thus, in lighting a match, one hand (usually the left) holds the matchbox while the other holds and moves the match; or in hammering a nail, one hand holds the nail while the other wields the hammer. This arrangement may permit the hemisphere controlling the dominant hand to develop the appropriate skill and is more efficient than having both hemispheres equally specialized for the same activities.

Perhaps the most fundamental of manual asymmetries is throwing. Individuals equally able to throw with each hand are extremely rare, and in the great majority of people the difference is marked. Although other primates can and do throw objects, they have none of the precision and force with which a skilled human can throw—although it has to be said that not all modern humans have developed or exploited that skill. Except for those who indulge in activities such as baseball or cricket, though, throwing may be something of a lost art in Western culture. The eighteenth-century explorer J. W. Vogel wrote that the Hottentots of southwestern Africa “know how to throw very accurately with stones.... It is also not rare for them to hit a target the size of a coin with a stone at 100 paces” (quoted in Isaac, 1992, p. 58). According to Isaac, Australian aborigines were also said to be able to throw stones with enough accuracy and force to bring down wallabies and flying birds, dislodge nuts from the baobab tree, and knock fledgling birds out of high nests.

### **Handedness in Other Species**

The strongest claims for handedness in chimpanzees, our closest nonhuman relatives, have come from William D. Hopkins and colleagues. Their studies show a population-level preference for the right hand in captive chimpanzees, at least for certain manipulative activities such as extracting peanut butter from a glass tube (Hopkins, 1996), using an anvil (Hopkins et al., 2007), engaging in gestural communication (Hopkins & Leavens, 1998), and throwing (Hopkins et al., 2005). The incidence of right-handedness in chimpanzees in these studies is typically around 65%, considerably

lower than the incidence of right-handedness in humans, which is around 90%. These figures may not be truly indicative, however, since within each species hand preference does vary with task, and the tasks themselves are somewhat species specific.

One activity common to tests on both species is throwing, and the proportion of chimpanzees throwing with the right hand is at least as high as that for other measures (Hopkins et al., 2005). In a sample of over a million people in the United States, the incidence of right-handed throwing was 89.9% for men and 92.4% for women (Gilbert & Wysocki, 1992), considerably higher than the values observed in a chimpanzee sample, where 53 animals were reported as right-handed, 16 as ambiguous, and 23 as left-handed (Hopkins et al., 2005). Of course, even throwing may not be strictly comparable in the two species. Humans have developed throwing to a more precise and intricate level, and many of the chimpanzees in the sample observed by Hopkins et al. did not throw at all and were excluded from the study.

Curiously, one study of 22 bonobos, who along with common chimpanzees are our closest living nonhuman relatives, revealed no evidence for species-level handedness (Harrison & Nystrom, 2008). Palmer (2002) has suggested that the findings of Hopkins and colleagues may be due to statistical artifacts and has shown the results to be marginal when assessed using funnel plots, which show scatter plots of right-hand use against sample size, although more recent studies do reveal significant species-level right-handedness using this technique (e.g., Hopkins et al., 2005).

Another difficulty is that observation of noncaptive animals in the wild suggests little or no population-level asymmetry in nonhuman primates, including chimpanzees. Sugiyama et al. (1993) examined handedness in chimpanzees for nut cracking, a lateralized task in which one hand manipulates the anvil and the other the hammer, but left-handers were as frequent as right-handers. McGrew and Marchant (2001) found no evidence for handedness across a variety of activities in chimpanzees observed in the wild and suggest that the bias in captive chimpanzees is a consequence of contact with right-handed humans. Hopkins et al. (2004) have disputed this, claiming that right-handedness occurs in three distinct populations of captive chimpanzees and is unrelated to the proportion of animals raised by humans. Yet a recent study of well-digging in wild chimpanzees again suggests a lack of any population bias in handedness (McGrew et al., 2007). To confound matters further, Corp and Byrne (2004) studied the dominant hand used by wild chimpanzees when eating *Saba florida* and found that females were predominantly right-handed and males predominantly left-handed.

Evidence from other primates is inconsistent. There have been claims that monkeys show a slight population-level preference for reaching with the left hand (MacNeilage et al., 1987). Subsequent evidence has been mixed (see commentaries to the article by MacNeilage et al., 1987), but, if true, the asymmetry may reflect a right-hemispheric bias for spatial perception—as also documented in humans (for a review, see

Corballis, 1991). At least one study has shown a slight *right*-hand advantage in a bimanual task in rhesus monkeys, but no bias in capuchins (Westergaard & Suomi, 1996). In a sample of baboons, too, nearly 80% were reported to prefer the right hand in making specific communicative gestures (Meguerditchian & Vauclair, 2006).

The clearest cases of limb asymmetry in nonhuman animals come not from primates but from birds. Most species of parrot show a strong preference for the left foot in picking up objects, and the proportion of left footers is close to 90%, comparable to the proportion of humans who are right-handed (Rogers, 1980). Given that the bill is the main manipulative organ in the parrot, the use of the left foot as the holding device could be regarded as the equivalent of the use of the left hand by right-handed humans. This result might be taken as evidence that manual specialization arises in species, like parrots, that use their limbs for manipulation, as proposed by Walker (1980). Consistent with this, Güntürkun et al. (1988) gave the task of scratching a piece of tape from their bills to pigeons, which do not use the feet in manipulative fashion, and found no preference for one or the other foot at either the individual or species level. Rogers and Workman (1993), though, found that 31 out of 38 chicks, given the same task, chose the right foot. Chicks make use of the feet in scratching the ground for food, whereas pigeons do not, suggesting to Rogers and Workman that involvement in feeding rather than manipulation *per se* may be the critical factor underlying limb preference in birds. This may generalize to other species. For example, Levermann et al. (2003) report that some 77% of walruses show a preference for the right flipper when feeding. The asymmetry may not always favor the right, though, since Sovrano (2007) reports a *left*-forelimb feeding bias in toads.

There may also be precursors to handedness in postural asymmetries. For example, horses tend to stand with the left foreleg in front of the right rather than vice versa, which has been taken as evidence that the right foreleg tends to be the weight-bearing one and, therefore, the stronger of the two (McGreevy & Rogers, 2005). Similar asymmetries are present in zebras and impalas (McGreevy et al., 2007). Horses also gallop asymmetrically, with one hind hoof striking the ground before the other. One study of two species of thoroughbred race horses, Arabians and American Quarter horses, showed that 90% led with the right hoof, and only 10% with the left hoof (Williams & Norris, 2007)—figures very close to those for hand and foot dominance in humans.

Perhaps the simplest conclusion to be drawn from these studies is that limb asymmetry can arise in vertebrates when it bestows a selective advantage. Humans are among the few species to have developed manipulative skills to a high level of sophistication. This led to an advantage in having the two hands differentially specialized, one for more operational actions and the other for holding actions. This does not explain why it is the right hand in particular, and therefore the left hemisphere, that plays the dominant role. With few exceptions, though, when manual differences arise

in other species, it is the right limb and left hemisphere that predominate, suggesting that the root cause of the bias lies deeper, perhaps at the molecular level (Corballis & Morgan, 1978). Of course, not all of us are right-handed; some 10% to 12% of the population are left-handed, and a small minority are ambidextrous. The reasons for this may be understood in terms of genetics.

### Genetic Theories

As mentioned earlier, genetic models of handedness have typically assumed that the responsible gene or genes are uniquely human, although one might equally assume that similar mechanisms apply to nonhuman asymmetries. One feature of these models is that they propose a genetic influence toward right-handedness but no such influence toward left-handedness—an idea first proposed by Annett (1972). In recent formulations, Annett (e.g., 2002) has proposed a single gene with two alleles, a right-shift allele, RS+, and an allele without directional specification, RS-. Most of the variation in handedness, though, is considered to be random, and the RS+ allele shifts a normal distribution of intermanual differences to the right. For individuals homozygous for the RS+ allele, designated RS++, the shift is about two standard deviations to the right of neutrality, for heterozygotes, designated RS+-, the shift is about one standard deviation to the right, and for those homozygous for the RS- allele, designated RS- -, the distribution is centered on the point of neutrality—that is, the direction of handedness is assigned at random, although there may be a slight culturally determined bias to right-handedness. Since the proportion of left-handers is slightly lower in women than in men, Annett (2002) proposes that the shifts are slightly larger in women. Left-handedness, then, arises through chance variation and is most likely in the RS- - genotype, who lack any genetic disposition to right-handedness.

A very similar model is proposed by McManus (1985b, 2002). Where Annett defines handedness in terms of performance differences between the hands and assumes a continuous distribution of intermanual differences, McManus assumes handedness to be a matter of preference rather than performance and to be dichotomous. Like Annett, he proposes a two-allele gene, with a dextral (D) allele specifying right-handedness and a chance (C) allele which does not specify the direction of handedness but leaves it to chance. He assumes all DD individuals to be right-handed, 75% of CD individuals to be right-handed and 25% left-handed, and CC individuals to be equally divided between left- and right-handers.

These two models, although different in spirit, make essentially identical predictions about the inheritance of handedness. The chance component explains why handedness does not “breed true.” For example, the children of left-handed parents are more often right-handed than left-handed, and some left-handers are born to right-handed parents. With appropriate choice of parameters, though, both theories

can account for the facts that the proportion of left-handers is higher in families with one left-handed parent than in families with two right-handed parents, and higher still in families with two left-handed parents.

A difficulty with genetic models proposing a single gene is that no such gene has yet been unambiguously identified. Crow (2002) argued that gene is located in the Xq21.3/Yp11.2 region of homology on the X and Y chromosomes and suggested protocadherinXY as a likely candidate, but a genome-wide screen has offered little support for X-linkage and suggests that the region 2p11.2–12 on chromosome 2 may be a more likely candidate (Francks et al., 2002). Although this failed to replicate in an independent sample, a later analysis revealed significant paternal linkage within this site (Francks et al., 2003), suggesting that imprinting may play a role. Still further investigation narrowed the locus to the leucine-rich repeat transmembrane neuronal 1 (LRRTM1) gene on chromosome 2p12, a maternally suppressed gene that appears to be associated paternally with handedness and schizophrenia (Francks et al., 2007). The effect was observed in a sample of dyslexic siblings but not in a set of twins, and the same haplotype was overtransmitted paternally in a large sample of individuals with schizophrenic and schizoaffective disorders, which are in turn known to be related to anomalies of handedness and cerebral asymmetry. The LRRTM1 gene is identical in human and chimpanzee. It seems unlikely, then, that LRRTM1 is the only gene involved in handedness and cerebral asymmetry—indeed it may have more to do with conditions such as dyslexia or schizophrenia, with only an indirect influence on laterality.

There are other reasons to suppose that several genes may be involved, perhaps with additive effects. Besides suggesting 2p12 as a candidate, linkage analyses have pointed to other regions of interest, including 17p11-q23 (Francks et al., 2003), 10q26 (Van Agtmael et al., 2002), and 12q21–23 (Warren et al., 2006). Inconsistencies between these reports might be due to differences in the way handedness is defined, differences in populations, or the vagaries of statistical analysis—or they may reflect weak determination of handedness from each of the several locations. Furthermore, if the models proposed by Annett and McManus are correct in the assumption that chance plays a major role, especially in the determination of left-handedness, the gene or genes will be difficult to detect using linkage analyses.

One difficulty with single-gene models is that they predict higher concordance of handedness between monozygotic (MZ) twins than between dizygotic (DZ) twins. As Collins (1970) long ago pointed out, this is not so. Laland (2008) cites a meta-analysis carried out by McManus (1985a) of 14 twin studies showing that the concordance among MZ twins is .771, and that among DZ twins .772—essentially identical. Because of the chance element, models such as those of McManus (2002) and Annett (2002) do not predict perfect concordance in handedness in MZ twins, and indeed MZ twins of opposite handedness—so-called “mirror twins,” like Tweedledum and

Tweedledee—comprise nearly a quarter of the MZ twin population. But these models still predict higher concordance between MZ than between DZ twins. McManus's genetic model, with the proportion of the D allele selected at .73, yields a concordance of .772 for DZ twins and .823 for MZ twins, and Annett's model, with the proportion of the RS+ allele set at .673, yields a concordance of .771 for DZ and .820 for MZ twins. These theoretical discrepancies between DZ and MZ are slight but sufficient to cast doubt on the single-gene models from which they were derived. The fact that concordance is essentially identical for MZ and DZ twins also rules out any special "mirroring" effect associated with the MZ twinning process.

### **Handedness as a Facultative Trait**

Another approach is to suppose that handedness is a facultative trait, with a gene or genes creating a population shift to right-handedness, and no genetic variation. Lack of genetic variation could explain why linkage analysis has so far failed to provide convincing evidence of a laterality gene. Crow (2007) has suggested that variation might be due to epigenetic factors, such as methylation of the DNA sequence, or variations in methylation, phosphorylation or acetylation of the histones that make up the chromosome, rather than variations in the DNA sequence itself. If true, the protocadherin region of the X and Y chromosomes may well be involved, as Crow (2002) had earlier suggested.

An alternative possibility is simply that variation is due to environmental factors. Laland (2008) has proposed that there is a universal genetic bias of 78% right-handedness, but this can be raised or lowered by parental (and other environmental) influences. With the further assumptions that having two right-handed parents raises the bias by 14% to 92%, while having two left-handed parents lowers it by the same amount to 64%, this theory then provides good fits to the familial data. Since variation is assumed to be environmental, the model explains why concordance between twins is the same for MZ as for DZ twins. The model need not assume a single gene. Instead, Laland suggests that right-handedness is driven by selective sweeps favoring right-handedness, and involving different genes. These selective sweeps, he suggests, may have raised the population-level incidence of handedness from some 56% in chimpanzees (Palmer, 2002), to 57% in Lower Pleistocene hominins, to 61% in Middle Pleistocene hominins (Toth, 1985), and to as much as 80% to 90% in the Late Pleistocene (Uomini, 2008).

Laland's theory probably makes the best sense of the facts as we know them. It can account for variations in handedness between species, the failure to find single clear genetic markers, and the equivalent concordance in MZ and DZ twins. Further, it does not require the assumption of a fortuitous mutation to explain human uniqueness, although it does allow that handedness can be more pronounced in humans than in other species. The theory is consistent with those proposed by Annett and McManus

in that the genetic influence is always toward right-handedness, so that left-handedness arises only through chance or environmental effects.

### Language

Language is widely considered uniquely human, at least with respect to the grammatical component (e.g., Chomsky, 1966; Hauser et al., 2002; Pinker, 1994), and is also the most obviously lateralized function in the human brain. Around 90% or more of people have speech represented predominantly in the left side of the brain; the dominance is somewhat more marked with respect to production than with respect to comprehension (Corballis, 1998). Signed languages are also represented predominantly in the left cerebral hemisphere (Corina, 1998; Hickok & Bellugi, 2000), although there may be more right-hemisphere involvement in sign language than in spoken language, especially in the coding of spatial relations (Emmorey et al., 2002). Broca's area, long recognized as critical to the production of speech, and located in the left hemisphere in the majority of people (Broca, 1861), is activated in signers while signing and in speakers while speaking (Horwitz et al., 2003).

Language therefore provides an example of a cerebral asymmetry that is indeed uniquely human, but that is because language itself is uniquely human. It is commonly assumed, though, that hemispheric specialization for language is related to right-handedness. In the majority of people, both imply a dominance of the left hemisphere, leading to the historical idea of the left hemisphere as the *major* hemisphere, the *leading* hemisphere, or the *dominant* hemisphere. This lopsided notion was largely discarded with the discovery of right-hemisphere specializations, especially in research on the split-brain initiated by Sperry (e.g., 1974, 1982; Sperry et al., 1979), but the association between right-handedness and left-cerebral specialization for language remains a prominent theme.

### Language and Gesture

The association between language and handedness is supported by evidence that language itself has strong connections to manual activity. Signed languages are, of course, carried out mostly with the hands, and although both hands are involved, one hand, usually the right, is generally considered dominant. Moreover, people typically gesture as they speak, and right-handers gesture more with the right than with the left hand (Kimura, 1973). However, more importantly, there is growing consensus that language itself evolved from manual gestures, not from vocal calls (e.g., Arbib, 2005; Armstrong et al., 1995; Armstrong & Wilcox, 2007; Corballis, 1991, 1992, 2002, 2003; Givón, 1995; Hewes, 1973; Pollick & de Waal, 2007; Rizzolatti & Arbib, 1998; Rizzolatti & Sinigaglia, 2008; Ruben, 2005; Tomasello, 2008—although for dissenting opinion, see Burling, 2005, and MacNeilage, 2008).

Potential insight into the gestural origins of language, and the relations between handedness and cerebral dominance for language, comes from so-called “mirror neurons,” first recorded in area F5 in the ventral premotor cortex of the monkey by Rizzolatti et al. (1996). They are activated both when the animal makes grasping movements and when it observes another individual making the same movements. Although these neurons responded to manual actions, whether produced or observed, area F5 is considered the homologue of Broca’s area in humans (Rizzolatti & Arbib, 1998), an area long associated with the production of speech (Broca, 1861). More precisely, Broca’s area in humans can be divided into Brodmann areas 44 and 45, with area 44 considered the true analogue of area F5. In humans, it is now evident that area 44 is involved not only in speech but also in motor functions unrelated to speech, including complex hand movements, as well as sensorimotor learning and integration (Binkofski & Buccino, 2004). Indeed it has been proposed that “Broca’s area” should now be regarded as a collective term, involving many different functions and no clearly demarcated subdivisions (Lindenbergh et al., 2007).

It has also become apparent that mirror neurons are part of a more general “mirror system” involving other regions of the brain as well as F5. In monkeys, the superior temporal sulcus (STS) also contains cells that respond to observed biological actions, including grasping actions (Perrett et al., 1989), although few, if any, respond when the animal itself performs an action. F5 and STS are connected to area PF in the inferior parietal lobule, where there are also neurons that respond to both the execution and perception of actions. These neurons are now known as “PF mirror neurons” (Rizzolatti et al., 2001). Other areas, such as the amygdala and orbitofrontal cortex, may also be part of the mirror system. Moreover, the extended mirror system in monkeys largely overlaps the homologues of the cortical circuits in humans that are involved in language, leading to the notion that language is just part of the mirror system itself (Fogassi & Ferrari, 2007; but see Grodzinsky, 2006, for some caveats). The question of how the primate mirror system might have evolved to accommodate the full complexity of human language is beyond the scope of this chapter (see Arbib, 2005, or Corballis, 2009, for possible accounts).

The discovery of the mirror system provides strong support for the idea that language evolved from manual gestures. One study shows, though, that some neurons in area F5 of the monkey respond to the *sounds* of manual actions, such as tearing paper or breaking peanuts (Kohler et al., 2002). Significantly, there was no response to monkey calls. This is consistent with evidence that vocalizations in nonhuman primates are controlled by the limbic system rather than by the neocortex (Ploog, 2002) and are therefore not part of the mirror system. Even in the chimpanzee, voluntary control of vocalization appears to be limited, at best (Goodall, 1986).

In humans, then, vocalization was incorporated into the mirror system and eventually replaced manual gesture as the primary medium for the expression of language

(Corballis, 2002, 2009), although speech is still generally accompanied by manual gestures (McNeill, 1985). This process appears to have been accompanied by lateralization of function. There is no evidence that the mirror system is lateralized in nonhuman primates, but Broca's area in humans is in the left hemispheres of the great majority of humans. Evidence from human studies also shows that the left frontal pole of the mirror system is active during the imitation of manual action (Iacoboni et al., 1999; Nishitani & Hari, 2000). Failures of voluntary action, or apraxia, typically result from left-hemisphere rather than right-hemisphere damage (Poizner et al., 1998), and of course right-handedness itself may be regarded as a left-hemisphere dominance for manual action.

What, if any, are the evolutionary precursors of this left-hemispheric dominance? One possibility is it arose from the left-hemispheric control of vocalization, which has been demonstrated in frogs (Bauer, 1993) and canaries (Halle et al., 2004; Nottebohm, 1977), and that incorporation of vocalization into the mirror system introduced a left-hemispheric bias for manual action (Corballis, 2003). The left-hemispheric dominance for vocalization, though, may depend on its functional nature. Hook-Costigan and Rogers (1998) found that marmosets opened the right side of the mouth wider when making social contact calls, again implying left-cerebral dominance, but the right side of the mouth wider when expressing fear, implying right-cerebral dominance for emotion. This finding mimics that found in humans, with the right side of the mouth more prominent for speech and the left for emotional expression (e.g., Graves & Goodglass, 1982; Graves & Potter, 1988). These asymmetries are also evident in 5- to 12-month-old human babies, who open the right side of the mouth wider when babbling, and the left side when smiling (Holowka & Petitto, 2002). The left side of the brain may therefore be dominant for vocalizations that are social, and therefore more "language"-like, while the right side is the more involved in emotional vocalization.

Asymmetries for vocalization apply to perception as well as to production. A left-hemispheric advantage for the perception of species-specific vocalizations has been demonstrated in mice (Ehert, 1987), rhesus monkeys (Hauser & Anderson, 1994; Poremba et al., 2004), and Japanese macaques (Heffner & Heffner, 1984). In chimpanzees, the left temporal planum is larger on the left than on the right (Gannon et al., 1998; Hopkins et al., 1998), an asymmetry that seems to be absent in rhesus monkeys and baboons (Wada et al., 1975) but is well documented in humans (Foundas et al., 1996; Geschwind & Levitsky, 1968; Jäncke & Steinmetz, 1993). These asymmetries may well be precursors to left-cerebral dominance for speech processing in humans.

One difficulty in attributing cerebral asymmetry for language to a prior left-hemispheric control of vocalization, though, is that language need not be vocal, and the asymmetry is present for signed languages as well as for spoken ones. Moreover, there

are reasons to believe that language bears little relation to animal calls. For example, Chomsky (1966) once wrote that language is based on “an entirely different principle” (p. 77) from animal communication. Even in nonhuman primates, vocalization seems to be largely under limbic rather than cortical control (Ploog, 2002) and relatively impervious to learning (Jarvis, 2006).

Rather than seek a single origin for cerebral asymmetry (pace Corballis, 2003), then, it may make better sense to suppose that cerebral asymmetries arise with increasing demand for neurological “space” as computational complexity increases. Another consideration may be the constraints imposed by the environment. In the natural environment, events are as likely to impinge from the right as from the left, and this would favor bilateral symmetry of bodily architecture, including sensory and motor apparatus as well as the mechanisms of sensorimotor learning (Corballis & Beale, 1970). Manual manipulation and productive language are actions *on* the environment rather than reactions *to* it, so the evolutionary pressure to bilateral symmetry is eased, allowing systematic asymmetry to evolve. The co-occurrence of left cerebral dominance for speech and manual praxis may then have arisen simply because both involve complex intentional action, and both are dependent on the mirror system. Both are, in effect, *gestural* systems.

### **Genetic Considerations**

The idea that language lateralization and handedness are related is also captured by the genetic models of Annett (2002) and McManus (2002), both of whom suggest that the lateralizing gene affects the representation of language as well as of manual control. Crow (2004) makes the same point, referring to what he calls the “Broca-Annett axiom” as the key to human uniqueness. Evidence suggests that handedness and cerebral dominance for language are indeed correlated, but not perfectly so. Studies based on the Wada test (Rasmussen & Milner 1977), electroconvulsive therapy (Warrington & Pratt 1973), and brain imaging (Knecht et al., 2000; Pujol et al., 1999) are reasonably consistent in showing that well over 90% of right-handers are left-cerebrally dominant for language, but so are some 70% of left-handers.

The imperfect relation between handedness and cerebral asymmetry does pose problems for the single-gene models, although it can be explained in part by the chance element in the models proposed by McManus and Annett. For convenience, I consider the problem in McManus’s terminology—similar arguments apply in Annett’s. In DD individuals, we suppose that all individuals are right-handed and left-cerebrally dominant for language. In CC individuals, we suppose that handedness and language dominance are determined randomly and independently, so that all four combinations of left- and right-handedness and left and right language dominance are equally represented. The issue then is how to treat the case of DC individuals. One possibility is that half are dominated by the D allele and half by the C

allele, which could provide a justification for McManus's assumption that 75% of DC individuals are right-handed and 25% left-handed. Those dominated by the D allele, like DD individuals, are all right-handed and left-cerebrally dominant for speech, while those dominated by the C allele, like CC individuals, have both asymmetries assigned randomly and independently. This version, though, predicts that left-handers should be evenly divided with respect to language dominance, whereas we have seen that some 70% of left-handers are left-cerebrally dominant.

A better fit is obtained by supposing that 75% biases toward right-handedness and left language dominance in DC individuals apply independently. Setting the proportion of the D allele to 0.75 results in a predicted incidence of 12.5% for both left-handedness and right-cerebral dominance. The model then results in the predicted combinations of handedness and language dominance shown in table 3.1, assuming a hypothetical population of 1,000. The percentage of left-handers predicted to be left-cerebrally dominant for language is 86/125, or 68.8%, which is close to the empirical value of around 70%, but the predicted percentage of right-handers left-cerebrally dominant for language is 789/875, or 90.17%, which is below the empirical estimates.

The basic problem here is that the percentage of those with left-cerebral dominance for language appears to be higher than the percentage of right-handers, in defiance of both McManus's and Annett's models. Of course, one might introduce further assumptions to enable better fits. For example, handedness might be more susceptible than language dominance to environmental influences, or one might assume a polygenic system, with different but perhaps overlapping genes involved in the two asymmetries. In these respects, then, Laland's (2008) account might be considered more satisfactory,

**Table 3.1**

Expected numbers of right- and left-handed individuals with left- and right-cerebral dominance for language in a hypothetical population of 1,000, according to McManus's model of handedness

		Language-dominant hemisphere	
		Left	Right
Right-handers	789	86	
Left-handers	86	39	

*Note.* The numbers are based on  $p(D) = .75$ , producing an incidence of left-handedness of 12.5%. All DD individuals are assumed to be right-handed and left-cerebrally dominant for language. In DC individuals, the proportions of right-handed and left-cerebrally dominant individuals are both .75, and are assumed to be uncorrelated. CC individuals are assumed to be equally divided among all combinations of right- and left-handedness and left- and right-cerebral dominance. D, dextral allele; C, chance allele.

if less specific, although it is difficult to understand how cerebral asymmetry could be as influenced by parental or other environmental effects as is handedness. One possibility, perhaps, is that the “default” bias toward both right-handedness and cerebral asymmetry for language is over 90% (perhaps even 100%), and not 78% as proposed by Laland, and that environmental influences can only serve to decrease this bias. Such influences would be more likely to affect handedness than cerebral dominance for language.

### The *FOXP2* Gene

One gene that might have a bearing on cerebral asymmetry for language, but not on handedness, is the forkhead box transcription factor *FOXP2*. A mutation of this gene in some members of an English family known as the KE family has resulted in a severe deficit in vocal articulation (Watkins et al., 2002) and perhaps some other aspects of spoken language—although this remains questionable (Vargha-Khadem et al., 2005). Moreover, the members of the family affected by the mutation show no activation in Broca’s area while covertly generating verbs and, indeed, show no consistent lateralization of activation (Liégeois et al., 2003). Their unaffected relatives show the expected lateralized activation in Broca’s area. This might be taken to mean that the *FOXP2* gene in humans normally plays a role in the lateralization of speech and in the introduction of vocal control into the mirror system (Corballis 2004). This role is disrupted in affected members of the KE family.

The *FOXP2* gene is highly conserved in mammals, differing in only three places from that in the mouse. Nevertheless it underwent two mutations since the split between the hominin and chimpanzee lines. According to one theoretical estimate, the more recent of these occurred “not less than” 100,000 years ago (Enard et al., 2002), although the error associated with this estimate makes it not unreasonable to suppose that it coincided with the emergence of *Homo sapiens* around 170,000 years ago. Contrary evidence, though, comes from a report that the mutation is also present in the DNA of a 45,000-year-old Neandertal fossil, suggesting that it goes back at least 300–400,000 years to the common ancestor of humans and Neandertals (Krause et al., 2007). This conclusion might itself be negated, though, if there were interbreeding between *sapiens* and Neandertals. Recent evidence suggests that microcephalin, a gene involved in regulating brain size, may have entered the human gene pool through interbreeding with Neandertals (Evans et al., 2006), so the reverse possibility of *FOXP2* entering the late Neandertal gene pool from *Homo sapiens* is not completely ruled out.

The role of *FOXP2* is not yet fully understood, and it is likely to be complex. It functions primarily as a regulator of embryogenesis and is expressed in other organs beside the brain, including the heart, lungs, and gut (Shu et al., 2001). The mutation that led to speech impediment in members of the KE family is not related to the

mutations that differentiate human *FOXP2* from that in the mouse or the chimpanzee, although any disruption of the gene may affect its role in vocalization. Although the data reported by Liégeois et al. (2003) suggest that *FOXP2* may also be involved in the lateralization of speech, it may not be the source of that lateralization, and its overall influence on the brain is bilateral (Vargha-Khadem et al., 2005). *FOXP2* may simply serve to introduce vocal control into an already lateralized system. According to one study, at least, the KE family show no deficits in skilled manual movements (Belton et al., 2004), and one study of 12 of the 15 affected members of the KE family showed all to be right-handed (Alcock et al., 2000). Although the *FOXP2* mutation removes lateralized activation of Broca's area, then, it appears to have no effect on handedness.

*FOXP2* is therefore not the lateralizing gene sought by Annett, McManus, Crow, and others, but it may well play a role in the development of speech—a function that is distinctively lateralized in our species. That role has yet to be fully articulated—a process that may itself require the cooperation of the *FOXP2* gene!

### Summary and Conclusions

Humans are the most manipulative creatures on the planet. It is true that spiders weave webs, birds build nests, beavers make dams, and some birds and primates make simple tools, but human manipulation has an open-ended quality unmatched by any other species. There seems to be no limit to human inventiveness, whether in the construction of mechanical devices or the generation of sentences—or of stories. The closest competitors may be New Caledonian crows, which construct implements from sticks and leaves for extracting food, and this activity may also be lateralized (Hunt et al., 2001). However, human manipulation far exceeds this, as is evident from the variety and complexity of manipulative implements contained in the average home. And the human ability to generate language may itself derive from the freedom and flexibility of the hands.

Manipulation also implies cognition—the ability to plan sequences of action, to reason, to imagine future consequences. In cerebral terms, the main requisite was probably not lateralization of function but rather the sheer size of the brain. From the emergence of the genus *Homo* some 2 million years ago, brain size effectively tripled relative to body size (Wood & Collard, 1999). The ensuing period marks the emergence of tool industries and, perhaps, the development of grammatical language. With increasing encephalization, lateralization may have been incorporated as an organizing principle, providing for more efficient programming through the allocation of different functions to the two cerebral hemispheres.

This is not to say that lateralization is uniquely human or even necessary for constructive processing. It may also feature in other manipulative species. As noted above,

tool manufacture in New Caledonian crows may be lateralized, and chimpanzees may show species-level right-handedness in a number of manipulative activities—although this remains somewhat controversial as we have seen. And lateralization need not arise solely in the context of manipulation. Many of the examples documented in the volume by Rogers and Andrew (2002) have to do with emotion or with spatial processing.

In all cases, moreover, lateralization appears to be a facultative trait rather than an obligate one, and it is relatively easily canceled or reversed. Ghirlanda and Vallortigara (2004) note that in animal studies the proportion of individuals that reverse the population-level bias ranges from about 10%, as in human handedness, to about 35%, as in claims of chimpanzee handedness. In humans, at least, there is no indication that those with reversed handedness or cerebral asymmetry are deficient in language or manual skill—although ambidexterity may be accompanied by slight deficits in some cognitive abilities (Corballis et al., 2008; Crow et al., 1998). The advantages of lateralization may be held in check by the perceptuomotor advantages of bilateral symmetry in a world without systematic left–right biases (Corballis, 2006).

Handedness, and more recently cerebral asymmetry, have long been topics of fascination, perhaps partly because they seem to defy the overall bilateral symmetry of living organisms, and partly because they are so evident in humans. There is no good reason to believe, though, that lateralization somehow defines the human condition, as suggested by authors such as Crow, Gazzaniga, Luria, and indeed myself. We humans are indeed distinctive among species in our ability to manipulate the physical and biological environment, including each other, and in most of us the cerebral mechanisms underlying this ability are lateralized. However, this lateralization is susceptible to variation, perhaps through environmental rather than genetic means, and the principles underlying it are almost certainly operative in many species besides humans.

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## **II Hemispheric Asymmetry in Nonmammalian Species**



## 4 Hemispheric Asymmetry of Songbirds

Isabelle George

One of the most intriguing puzzles in cognitive neuroscience is cerebral lateralization, namely, the phenomenon in which the two hemispheres of the brain specialize in different functions. Lateralization has many crucial facets: functional hemispheric differences in humans and other species, structural and biological differences that give rise to functional specialization, collaboration between the brain hemispheres, and implications for neurological and psychiatric disorders.

Until very recently, virtually all studies on cerebral lateralization have focused on humans and have mainly been confined to experimental psychology and neuropsychology. However, recent evidence in natural and seminatural settings has revealed a variety of left-right perceptual asymmetries among vertebrates (e.g., Vallortigara et al., 1999; Vallortigara, 2000; Rogers & Andrew, 2002). Such evidence is likely to force us to rethink some of the basic issues on the evolution of cerebral lateralization. Actually, the evidence available nowadays suggests that there is a common pattern of lateralization among vertebrates (e.g., Andrew, 2002; Rogers & Andrew, 2002; Güntürkün, 2003), and the overall similarities across species strongly support the hypothesis of an early common origin of lateralization in vertebrates.

A traditional hypothesis explaining why lateralization is so common among vertebrates is that functional lateralization would enhance cognitive capacity and efficiency of the brain, and this hypothesis has been recently supported by experimental evidence (e.g., Rogers et al., 2004). However, although such an increase in brain efficiency may explain individual lateralization, it cannot explain why most animals show left-right behavioral biases at the population level (meaning that most individuals show a similar direction of bias). A recent and interesting theory (see Ghirlanda & Vallortigara, 2004) currently proposes that there may be “social constraints” that force individuals to align their asymmetries with those of the other individuals of the group, and that population lateralization may have evolved under “social” selection pressures. This hypothesis offers a new way of looking at variations in lateralization in different species and tasks, and it raises numerous questions about the possible relationship between lateralization and social behaviors (such as, e.g., communicating

with others). Experimental evidence suggesting a relationship between lateralization and communication exists. For example, communicative gestures elicit a stronger degree of right-hand bias than noncommunicative actions in captive olive baboons (Meguerditchian & Vauclair, 2009). Moreover, there is growing evidence for a potential implication of lateralization in neurological and psychiatric disorders that sometimes involve severe impairment in social and/or language abilities. For example, atypical establishment of hemispheric specialization may be one cause of disordered language development in autism (Escalante-Mead et al., 2003), and, although atypical lateralization is not implicated in all cases of poor language development, it may act as a biological marker of persisting specific language impairment (Whitehouse & Bishop, 2008). In order to better understand the possible interactions between lateralization processes and the ability to communicate with others, a thorough understanding of the biological bases of lateralization appears of prime importance. Animal models can help us in this respect because they are a powerful tool for gaining detailed insights into the neuronal processes governing lateralized functions. Songbirds, in particular, form a unique model because they allow experimental investigation of the interplay of neurobiological substrate and the behavior that characterizes them, that is, song, which is a learned behavior whose critical function is to communicate with other birds. Birdsong is a behavior that can be easily recorded and quantified, that is controlled by a well-characterized and highly evolved network of interconnected brain regions, and, most importantly, whose development shows many parallels with that of human speech (e.g., Doupe & Kuhl, 1999; Jarvis, 2004). Moreover, social factors have been shown to play a major role in how both songbirds and humans produce, perceive, and learn their vocalizations (e.g., Goldstein et al., 2003; Kuhl, 2003; Vignal et al., 2004, 2005). Songbirds have thus become the best developed model to date to study language-like processes in the brain.

Now, it is commonly accepted that language functions are processed asymmetrically in the human brain, with the left hemisphere dealing predominantly with the semantic aspects, and the right one with the prosodic elements of speech (e.g., Buchanan et al., 2000). Thus, the discovery in the 1970s of a left bias for the production of song (Nottebohm, 1971) has stricken researchers as a reminiscence of this lateralization for speech. This discovery has boosted research on songbirds and has led to steady evidence of asymmetries in song behavior and its neural correlates. Of course, song is not the only system that is lateralized in songbirds. Examples of behavioral or neural lateralization include tool use in crows (which are songbirds; see, e.g., Hunt et al., 2001; Weir et al., 2004), lateralization of the magnetic compass in migratory birds (Wiltschko et al., 2002), lateralization in brain-hippocampal functions for learning-related plasticity and memory storage in various avian forms (e.g., Rogers, 1986; Andrew, 1991), and higher immediate early gene (IEG) expression in the left than in the right hemisphere during sexual imprinting (Lieshoff et al., 2004;

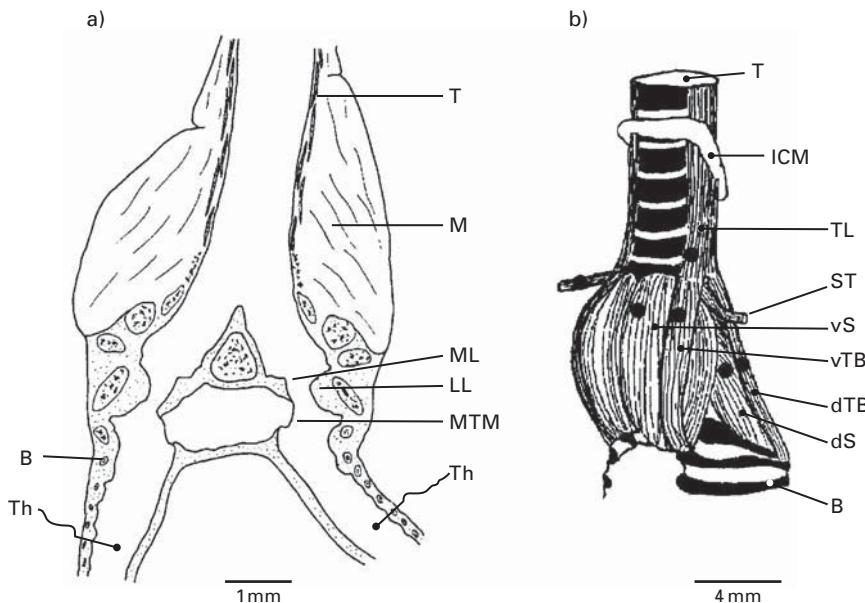
Sadananda & Bischof, 2004). However, we will here concentrate on hemispheric asymmetries related to song behavior, especially because of the parallels it shows with language. We will first review evidence of motor asymmetries in the production of song (which is the steadiest), both at the peripheral and central level, and then evidence of asymmetries in the perception of song (which is much less extensive than for song production). We will also briefly address the question of sex differences in song lateralization, for which only few data are available, before discussing why songbirds are a unique model that still has a lot to teach us about cerebral lateralization, especially in relation to communicative aspects of vocal behavior.

### Asymmetries in Song Production

Historically, studies on song lateralization have begun by investigating how song is produced and whether there were side differences in the production of song, at both the peripheral and central levels.

Birdsong, as speech, is produced by the coordinated action of vocal, supravocal, and respiratory muscles (Wild, 1997). However, unlike the larynx of humans, the sound source of songbirds (the syrinx) is a duplicated structure. The syrinx (see figure 4.1) is composed of modified cartilages at the cranial end of each primary bronchus and the caudal end of the trachea. Each bronchus contains medial and lateral labia, which vibrate when adducted into the respiratory airflow and provide the bird with two independently controlled sound sources, one in each bronchus (King, 1989; Suthers, 1990; Goller & Larsen, 2002).

At the central level, forebrain, thalamic, and brainstem nuclei responsible for song production, known collectively as the song system, are duplicated in both halves of the brain (Nottebohm et al., 1976; Wild, 1997; Wild et al., 2000; see figure 4.2). Thus, the projection from the main vocal center HVC (used as a formal name; see Reiner et al., 2004) to the robust nucleus of the arcopallium (RA) is unilateral and bilaterally symmetrical. RA forms part of the descending motor pathway in each hemisphere and sends independent output projections to the nucleus controlling the muscles of the vocal organ (the hypoglossal nucleus; nXIIts) and to brainstem nuclei that play an important role in vocal-respiratory control (Ashmore et al., 2008). It is important to note that, given that birds lack a corpus callosum, telencephalic nuclei are not connected across the midline, even by the anterior commissure, which is the only interhemispheric commissure present in the birds. However, projections influencing song system nuclei in the opposite hemisphere exist (Vates et al., 1997; Reinke & Wild, 1998; Striedter & Vu, 1998; see figure 4.2), and, based on their physiological and anatomical properties, these bilateral projections are well placed for mediating the coordination and synchronization observed during song production (Wild et al., 2000; Schmidt et al., 2004; Ashmore et al., 2008).

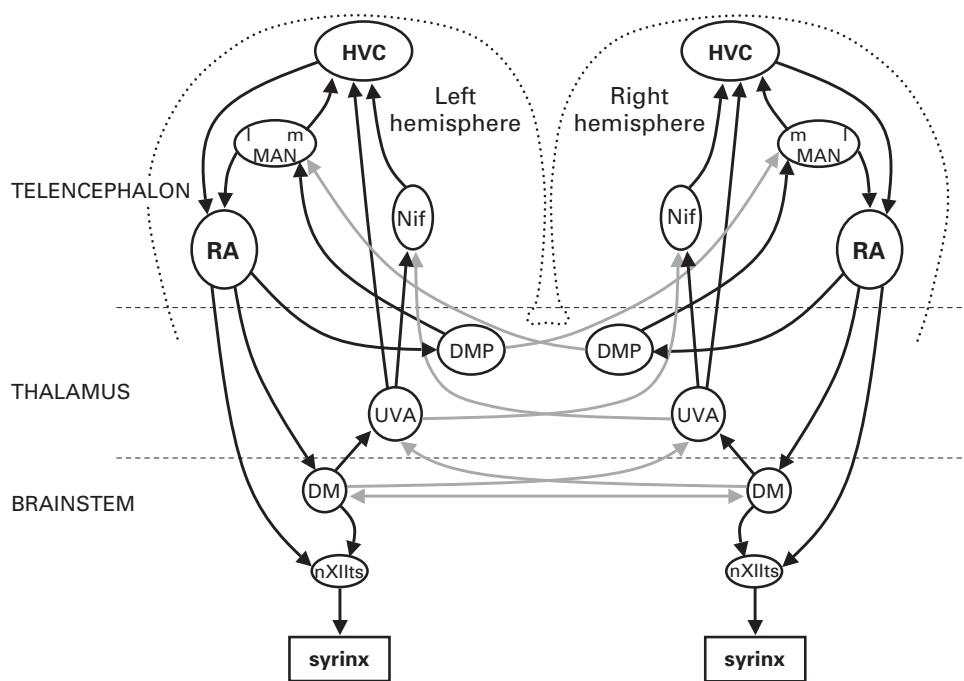


**Figure 4.1**

The oscine syrinx is a bipartite structure containing two sound sources. (a) Frontal section through a brown thrasher syrinx. Th, position of microbead thermistor to measure rate of airflow through each side of syrinx. See Suthers et al. (1994) for detailed methods and surgical procedures. (b) Ventrolateral external view of a thrasher syrinx depicting syringeal muscles. Black dots indicate for one side the approximate location where bipolar wire electrodes were placed. T, trachea; M, syringeal muscle; ML, medial labium; LL, lateral labium; MTM, medial tympaniform membrane; B, bronchus; ICM, membrane of the interclavicular air sac; TL, M. tracheolateralis; ST, M. sternotrachealis; vS, M. syringealis ventralis; vTB, M. tracheobronchialis ventralis; dTB, M. tracheobronchialis dorsalis; dS, M. syringealis dorsalis.

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The duplicated nature of the songbirds' vocal organ and its central control system offers a unique opportunity to study asymmetries in song production, and techniques for recording airflow through each side of the syrinx, together with syringeal and respiratory motor activity, during spontaneous song with both sides of the syrinx intact (Suthers, 1990) has allowed researchers to show that songbirds exploit their dual sound source to increase vocal virtuosity in multiple ways, including the production of two-voice elements, switching phonation between sides to produce abrupt frequency steps between notes, and taking advantage of lateralized functional specialization in the acoustic properties of each sound source (see Suthers & Goller, 1997; Suthers, 1999; Suthers & Zollinger, 2004; Zollinger et al., 2008). However, originally,

**Figure 4.2**

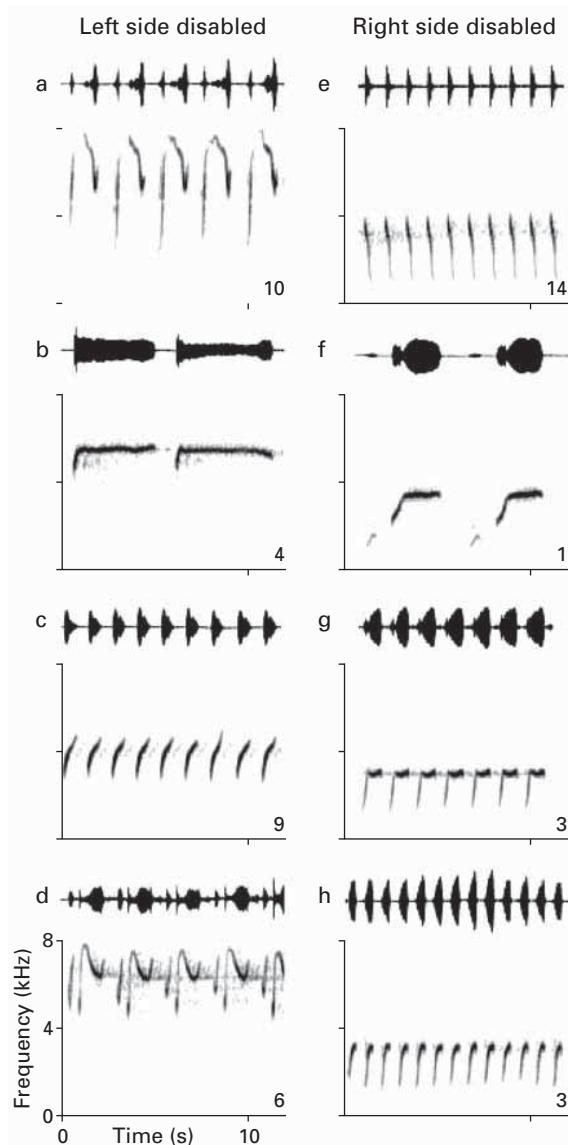
Schematic representation of some of the nuclei involved in song production and their projections. Projections are mainly ipsilateral (in black) but contralateral projections (in gray) exist. The connections shown in this figure represent major projections in the song system and have been compiled from different sources (Ashmore et al., 2008; Coleman & Vu, 2005; Schmidt et al., 2004; Striedter & Vu, 1998). Dorsal is up, and ventral is down. HVC = the formal name of this nucleus; MAN, magnocellular nucleus of the anterior nidopallium (l: lateral; m: medial); Nif, nucleus interfacialis of the nidopallium; RA, robust nucleus of the arcopallium; DMP, dorsomedial posterior nucleus of the thalamus; UVA, nucleus uvaformis; DM, dorsomedial nucleus of the intercollicular complex; nXIIts, tracheosyringeal part of the hypoglossal nucleus.

neural lateralization in song production has been mainly deduced from experiments that intended to induce inactivation of one syrinx half. Thus, by unilaterally blocking the syrinx of Wasserschlager canaries, a genetic strain that was bred by aviculturists for the low-pitched, liquid quality of its song, Nottebohm and Nottebohm (1976) demonstrated that about 85% or more of this bird's song is sung on the left side of its bipartite syrinx, making it one of the first and most robust nonhuman examples of a lateralized neural control of behavior. Yet, lateralized song production is not a universal trait of canaries. Indeed, in the common canary, which is an outbred strain that has not been subjected to as much artificial selection for either a particular song or appearance as the conspecific Wasserschlager strain, no clear unilateral dominance

has been observed. Thus, Suthers et al. (2004) investigated the contribution that each side of the syrinx makes to song by observing the effect of unilaterally occluding the left or right primary bronchus, followed by section of the ipsilateral branch of the tracheosyringeal nerve. In other birds with a bilaterally intact vocal system, they monitored airflow through each side of the syrinx, together with subsyringeal pressure, during spontaneous song. Their results showed a syringeal lateralization of frequency range (see figure 4.3) but also that both sides of the syrinx made a substantial contribution to song (two birds exhibited no lateral syringeal dominance and one showed a moderate right syringeal dominance).

On the whole, species for which song production has been shown to be asymmetrical, in the sense that the majority of syllables in their song are produced using the left side of the syrinx, as usually measured by the number of syllables lost or retained following unilateral syringeal denervation, include canary, chaffinch, white-throated sparrow, white-crowned sparrow, and java sparrow (Nottebohm, 1971, 1977; Lemon, 1973; Nottebohm & Nottebohm, 1976; Nottebohm et al., 1976; Seller, 1979; Hartley & Suthers, 1990; Suthers, 1997). In the zebra finch, which is a widely used species, functional and structural lateralization appear to be opposite. On the one hand, transection of the right tracheosyringeal nerve appears to produce consistent decreases in the fundamental frequency of male song, such that it converges to approximately 500 Hz (Williams et al., 1992; Floody & Arnold, 1997), and, on the other hand, one study found that left axotomy had little effect on syllable frequency or type (Williams et al., 1992), whereas another documented an increase in fundamental frequency and in variability of frequency modulation (Floody & Arnold, 1997). In fact, Goller and Cooper (2004) showed that lateralization of song production in zebra finches differs from that of other species in that there is almost continuous simultaneous production of independent sounds on both sides of the syrinx. However, they also observed that contact calls are generated with pronounced right-side dominance. Finally, with gray catbirds and brown thrashers, Suthers (1990) and Goller and Suthers (1996) found that neither side of the syrinx was dominant for syllabic production. In these mimic thrushes, different notes or syllables can be produced either on the left side or on the right side of the syrinx simultaneously, thus producing two harmonically unrelated voices, or on different sides in sequential fashion, the bird rapidly switching back and forth from one side to the other, even within the short time constraints of a single syllable. Frequently in these birds, and in northern cardinals, the left and right sides of the syrinx coordinate to produce a frequency-modulated syllable, in which lower frequency components are produced on the left side of the syrinx and higher frequency components on the right (Suthers et al., 1994; Suthers & Goller, 1996; reviewed in Suthers, 1997, and Suthers & Goller, 1997).

Overall, and as summarized by Suthers (1997), it thus appears that different species have adopted different motor strategies that use the left and right sides of the syrinx



**Figure 4.3**

Examples of syllables retained after disabling sound production on one side of the syrinx by occluding the bronchus and sectioning the ipsilateral tracheosyringeal nerve. (a-d) Syllables sung on right side, left side disabled. (e-h) Syllables sung on left side, right side disabled. The number identifying individual bird is in lower right corner of each spectrogram.

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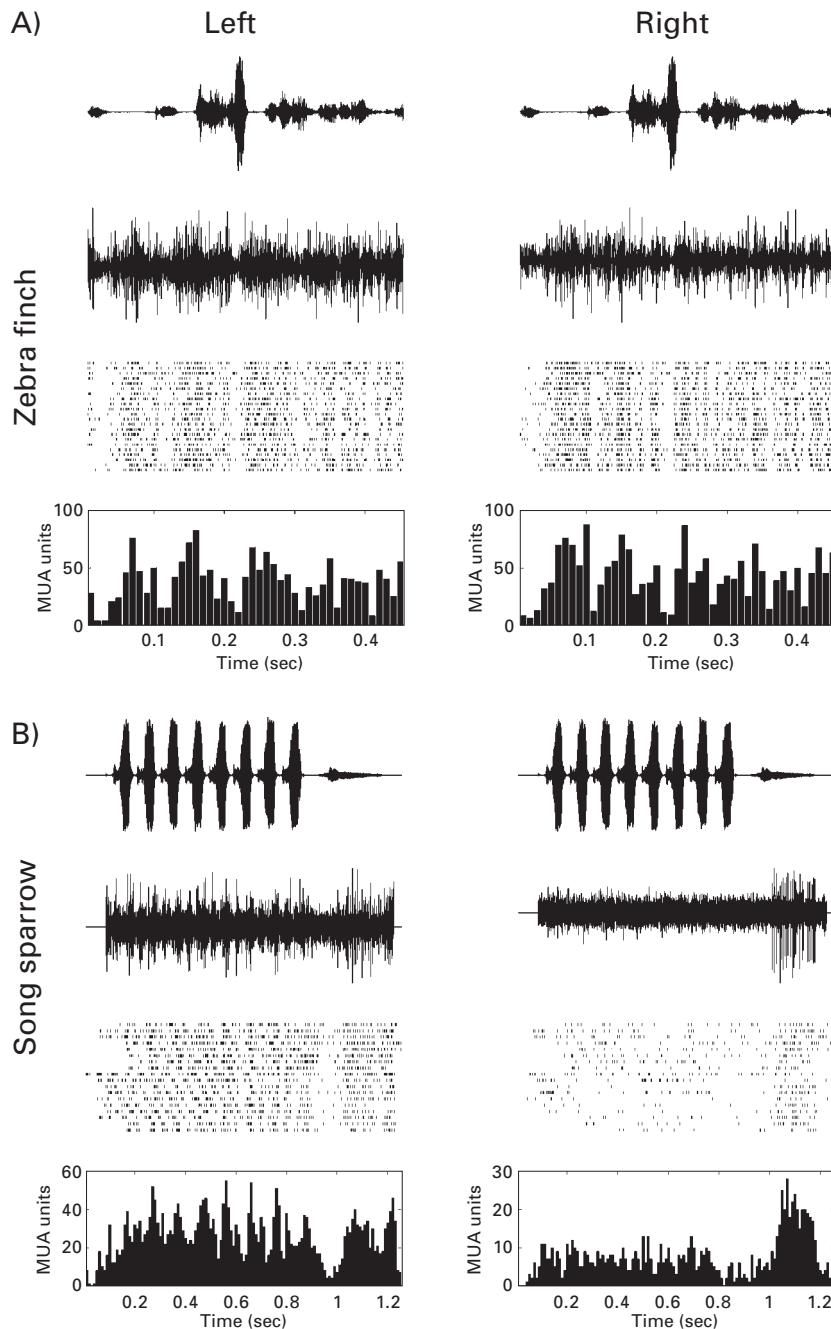
in patterns of unilateral, bilateral, alternating, or sequential phonation to achieve the differing temporal and spectral characteristics of their songs. As a result, the degree of song lateralization probably varies between species to form a continuum from unilateral dominance to bilateral equality. However, despite these variations, lateral specialization for different fundamental frequencies appears to be a widespread phenomenon among oscines (Suthers et al., 2004). Indeed, spectral diversity of song is enhanced by the fact that the left and right syrinxes have somewhat different vocal registers and generate syllables with fundamentals in different though overlapping frequency bands (Suthers, 1997). Thus, in the Wasserschlager and domestic canary strains (Nottebohm & Nottebohm, 1976; Halle et al., 2003; Suthers et al., 2004), brown thrasher and gray catbird (Suthers et al., 1994), brown-headed cowbird (Allan & Suthers, 1994), northern cardinal (Suthers & Goller, 1996), and northern mockingbird (Zollinger & Suthers, 2004), for example, the right syrinx covers a higher frequency range than the left, although in most species there is considerable overlap between sides. According to Suthers (1997), it is not clear whether these differences reflect lateral differences in motor control—for example, the firing rate or recruitment of motor neurons—or anatomical asymmetries in the vocal organ—for example, in the dimension or mass of sound-generating structures in the syrinx (Luine et al., 1980). However, the lateralization of song production is likely to be determined by both peripheral and central components (Goller & Suthers, 1995; Suthers et al., 2004).

At the central level, there is still little understanding of the differential contribution of each hemisphere to song production, and, here again, large variations appear between species. Thus, Nealen and Schmidt (2002) have shown that zebra finches and song sparrows exhibit different degrees of left-right laterality in HVC premotor activity (see figure 4.4). In the zebra finch, left and right activity for the production of

#### Figure 4.4

Zebra finches (A) and song sparrows (B) exhibit different degrees of left-right laterality in the main vocal area (HVC) premotor activity. Shown here for both species is HVC premotor activity from the left and right hemispheres over a short multisyllable sequence (upper amplitude trace in each panel, identical for left and right sides). Beneath the amplitude traces are single neural traces from both left and right HVC (offset in time to the song by the premotor latency). Successive repetitions were aligned at the start of each syllable and subjected to a thresholding spike-detection algorithm to produce spike raster plots. These raster plots depict neural activity over successive repetitions of these syllable sequences. From these spike rasters, cumulative activity histograms (lowest plots in each panel) depict overall left and right activity for the production of these syllable sequences. MUA, multiunit activity.

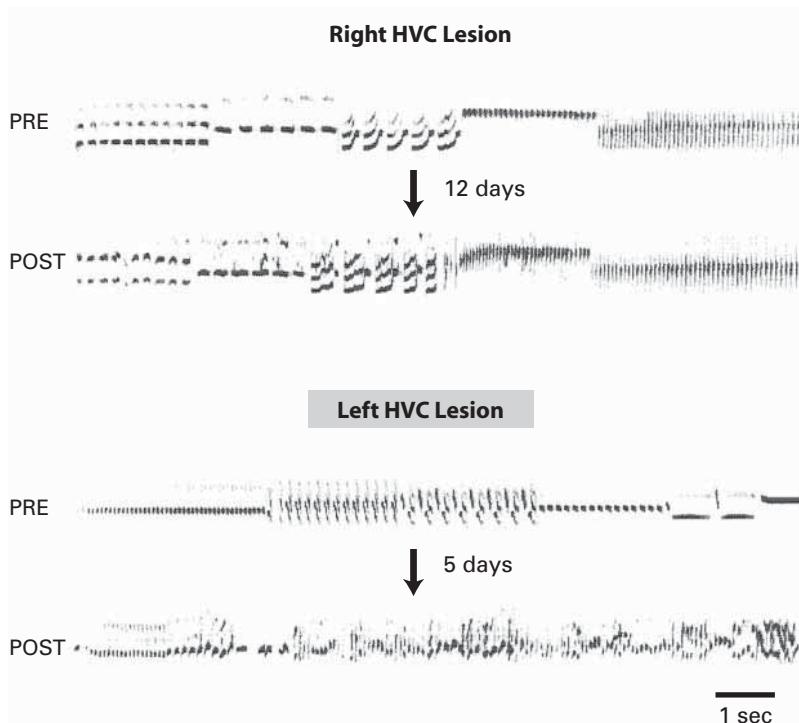
© 2002 Springer-Verlag. *Journal of Comparative Physiology A*, Comparative approaches to avian song system function: Insights into auditory and motor processing, 188, 2002, 929–941, Nealen, P. M., & Schmidt, M. F., figure 4. Reproduced with kind permission from Springer Science+Business Media.



syllables appears to be largely covarying, with similar modulation of activity between hemispheres, although, at a very fine scale, and according to the authors, hemispheric differences in the temporal pattern of neuronal firing do exist (see figure 4.4A). In marked contrast, left-right HVC premotor activity in the song sparrow can differ dramatically over the production of a given syllable sequence. Figure 4.4B shows the differences that can be observed in HVC activity between hemispheres. In this figure, one can see that left HVC recordings show elevated activity throughout the entire song segment, whereas activity in the right HVC is much more strongly modulated and most active during the last syllable only. These data suggest that laterality of HVC premotor activity in the song sparrow may be pronounced and they provide a rare instance of direct evidence of hemispheric differences in song-related neuronal activity at the level of the forebrain. Indeed, other studies have failed to find any hemispheric difference in the pattern of multiunit activity recorded in HVC and have concluded that, in zebra finches at least, hemispheric differences cannot be explained by comparing the slowly varying firing pattern in each hemisphere (Schmidt, 2003).

To date, whether lateralization of song production can be explained by studying the collective population pattern of individual identified neurons in each hemisphere thus remains an open question. However, there have been several studies where unilateral lesions of forebrain song structures, such as HVC, caused song deficits that were specific to the side in which the lesion was made (e.g., Nottebohm et al., 1976; Williams et al., 1992; Halle et al., 2003). The most dramatic example of such differential effects is once again the Wasserschlager canary (Nottebohm et al., 1976; Nottebohm, 1977), in which left-hemisphere lesions of HVC caused significant deterioration of the song, while right-hemisphere lesions produced much less pronounced song deficits (see figure 4.5). This lateralization of functions at the level of HVC paralleled what had been observed at the periphery (Nottebohm & Nottebohm, 1976; Hartley & Suthers, 1990). In the domestic canary, Halle et al. (2003), by lesioning either the left or right HVC, observed lateralization of both left and right vocal control pathways for particular features of the song. More precisely, their results showed a general right-side specialization for high frequencies and widest frequency bands and a general left-side specialization for the control of not only low frequency but also the number of different simple syllables, total repertoire size, and highest repetition rate, which correlated with lesion size. For these authors, however, this specialization reflected peripheral mechanisms and was due to asymmetry of the syrinx morphology, leading them to conclude for a lack of central lateralization. Finally, in zebra finches, parallel to the right-side dominance of the tracheosyringeal nerve, lesions of the HVC produced more substantial changes in the temporal patterning of song when they occurred on the right than the left side of the brain (Williams et al., 1992).

In conclusion, it appears that various species of songbirds show asymmetries in song production, although the degree and side of lateralization can vary greatly



**Figure 4.5**

Evidence for the differential contribution of the main vocal area (HVC) to song production. The top panel of the figure depicts song recorded from a Waterschlager canary before (PRE) and after (POST) HVC was lesioned in the right hemisphere. Right HVC lesions caused little effect on song structure. In contrast, lesioning HVC in the left hemisphere (bottom panel) caused nearly complete deterioration of the bird's song.

(Modified from figure 12 in Nottebohm et al., 1976.) © 2004 New York Academy of Sciences. *Annals of the New York Academy of Sciences*, Vol. 1016, 2004, 171–186. Reproduced with permission of Wiley Blackwell.

between species, and asymmetries globally appear to be clearer at the peripheral than at the central level. According to some authors, lateralization of song production would allow songbirds to make maximal use of the two independent sound sources of the syrinx for generation of spectrally and temporally complex acoustic signals (Suthers, 1997; Suthers & Goller, 1997). The evolutionary pressures leading to asymmetries in song production may therefore have been quite different from those leading to lateralization in the central control of human speech (Goller & Suthers, 1995, 1999). In this respect, studies on asymmetries in song perception might be more relevant to discussion of the origins of language lateralization.

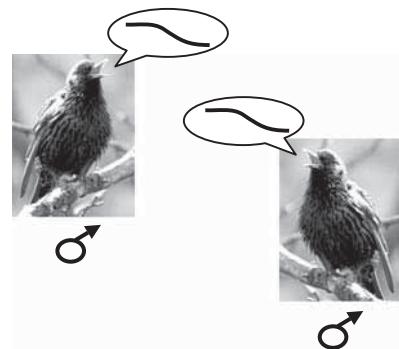
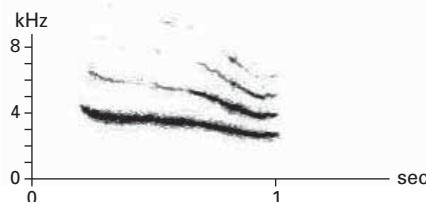
### Asymmetries in Song Perception

Studies on song lateralization have long focused on song production, and they have mainly investigated asymmetry at the peripheral level of the vocal system. Data on asymmetries in song perception are still sparse nowadays. Yet, hemispheric specialization for the perception and processing of species-specific communicative signals has been evidenced in other animal species. Thus, Hauser and Andersson (1994) have shown a right-ear/left-hemisphere bias for listening to species-specific vocalizations in adult rhesus monkeys. In mice, Ehret (1987) has shown a right-ear specialization for processing ultrasonic calls of the pups. In songbirds, initial studies suggesting hemispheric specialization for song perception were based on unilateral lesions of central structures combined with behavioral tests. Thus, Cynx et al. (1992), by lesioning a nucleus of the auditory thalamus (the nucleus ovoidalis) of either the right or left hemisphere of zebra finches, showed that the left hemisphere played a predominant role in discriminating the bird's own song from conspecific songs, while the right hemisphere was mainly involved in detecting subtle changes in the structure of songs. These results fit with the idea, coming mainly from studies on the avian visual system, of a predominant role of the left hemisphere in categorizing stimuli and of the right hemisphere in detail analysis (Rogers, 2000). Similarly, Okanoya et al. (2001) obtained results suggesting that, in Bengalese finches (*Lonchura striata var. domestica*), the HVC of the left hemisphere would play a predominant role not only in the production of song but also in the discrimination of species-specific songs. Yet, several anatomical and electrophysiological studies previously failed to find any evidence of structural or perceptual hemispheric differences in the songbird brain (McCasland, 1987; Sutter & Margoliash, 1994; Bernard & Ball, 1995). However, more recently, by recording neuronal responses to a variety of stimuli in the brain of adult male starlings, our team has provided clear evidence of hemispheric differences in song perception.

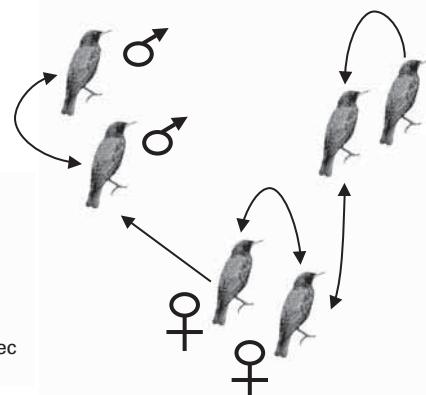
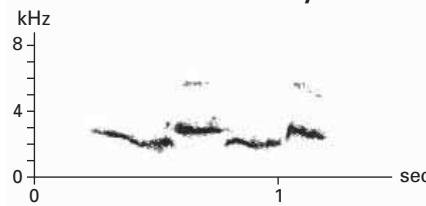
Starlings are a good model to study hemispheric specialization for the perception and processing of vocal signals because they use a complex song that allows several levels of discrimination. Thus, Hausberger (1997) has described three classes of songs in starlings (see figure 4.6). Classes I and II are whistles, and class III is warbling.

**Class I**

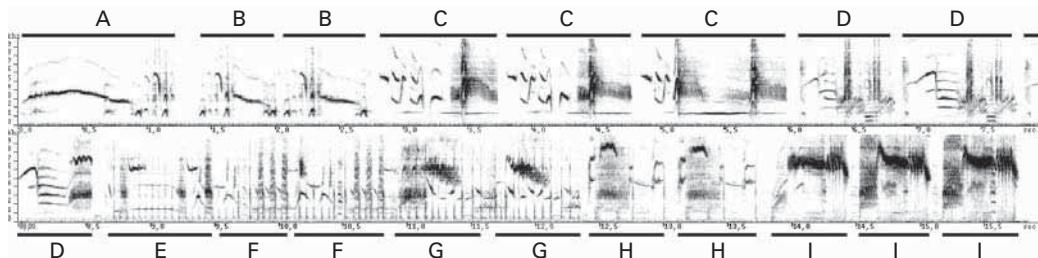
- Short, simple structures
- Local variation (dialects)
- Song matching

**Species- and population-specific identity****Class II**

- Short, simple structures
- Fast variations
- Song sharing

**Individual identity****Class III**

- Complex structures
- Breeding

**Figure 4.6**

Summary of the main characteristics of starling song (see explanations in the text).

Whistles show different levels of variations that allow species- and individual-specific recognition. Class I is made of whistles that are common to all male starlings, and class II of whistles that are specific to each individual. Warbling is a continuous song that is mainly composed of individual-specific motifs and that also contains some motifs that are common to all starlings. In order to test for brain lateralization in starlings, we recorded neural activity in response to all these classes of songs, at the level of the field L, which is the analogue of the primary auditory cortex of mammals, and of the HVC. In every case, birds heard their own songs, unfamiliar songs and familiar songs belonging to the three classes described above, and artificial nonspecific sounds (pure tones and white noise). Neuronal responses to these stimuli were recorded thanks to a systematic recording method that we have developed (George et al., 2003). This method allowed us to record a large number of neurons in the field L and HVC of both hemispheres in adult male starlings that were awake and restrained and then anesthetized. We thus could quantitatively describe the responses we obtained.

We first calculated the percentage of field L neurons that responded to at least one of the stimuli we used. These data showed that, when the birds were awake, there were significantly more responsive neurons in the right than in the left hemisphere. Interestingly, under anesthesia, this difference did not appear. The difference observed when the birds were awake reflected a systematically higher number of responsive neurons in the right than in the left hemisphere for all birds. Under anesthesia, this difference was reduced, or even reversed, in all birds (George et al., 2004).

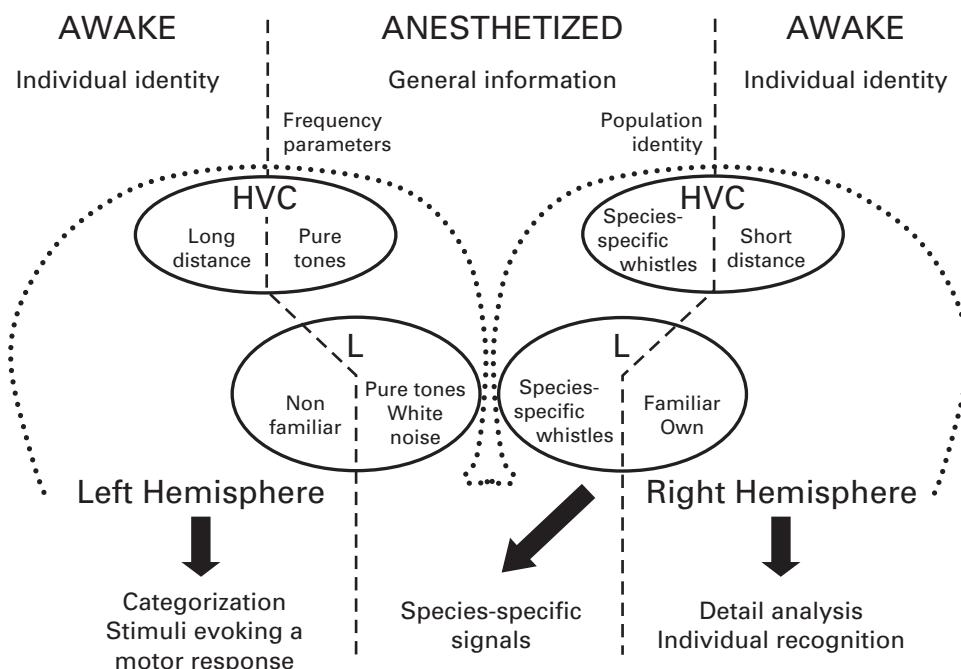
In the HVC, similar results were obtained. Again it appeared that there were significantly more responsive neurons in the right than in the left hemisphere when the birds were awake but not when they were anaesthetized (George et al., 2005). As in field L, the difference observed when the birds were awake reflected a systematically higher number of responsive neurons in the right than in the left hemisphere for all birds. However, under anesthesia, the overall absence of difference was mainly due to one individual and has thus to be interpreted with caution. Yet, there seemed to be a high interindividual variability that would deserve further investigation.

These results point to a relative predominance of the right hemisphere in waked birds, at the level of both field L and HVC. Furthermore, the analysis of the pattern of response to each stimulus according to the hemisphere and to the behavioral state of the birds revealed state-dependent hemispheric differences in the responses to the different classes of songs used by starlings. Thus, in field L, it appeared that responses to songs involved in individual recognition (i.e., class II and III songs) prevailed when the birds were awake. Responses to unfamiliar songs were mainly observed in the left hemisphere, whereas responses to familiar and bird's own songs predominated in the right hemisphere. As for responses to sounds corresponding to general or common information (that is species-specific class I songs and artificial nonspecific sounds),

they were mainly observed under anesthesia. Responses to artificial nonspecific sounds prevailed in the left hemisphere, and responses to class I songs, which are used in species-specific recognition, in the right hemisphere (George et al., 2004).

In the HVC, similar results were again obtained. Responses to songs involved in individual recognition, whether they were unfamiliar, familiar, or the bird's own songs, also prevailed when the birds were awake. Responses to class II songs were mainly observed in the left hemisphere, and responses to warbling in the right one. Both these types of songs are used in individual recognition, class II songs being rather used in long-distance interactions, and warbling in short-distance communication. Responses to sounds corresponding to general information were also mainly observed under anesthesia. Responses to one of the artificial nonspecific stimuli (a 500-Hz pure tone) prevailed in the left hemisphere, and responses to most class I songs in the right hemisphere (George et al., 2005).

Overall, our results showed a complex hemispheric specialization toward behaviorally relevant classes of stimuli, at the level of both field L and HVC (see figure 4.7 for



**Figure 4.7**

Summary of the pattern of responses to behaviorally relevant classes of sounds in the field L (L) and the main vocal area (HVC) of the left and right hemispheres of waked and anaesthetized male starlings (see explanations in the text). Dorsal is up and ventral is down.

a summary of the results). Under anesthesia, whatever the nucleus, it appeared that the number of responsive neurons was the same in both hemispheres. However, analysis of the responses to each class of stimuli showed a predominance of responses to artificial nonspecific sounds in the left hemisphere, and to class I songs, which are used in species-specific recognition, in the right hemisphere. These results suggest a specialization of the right hemisphere in processing species-specific signals, which, although the side of lateralization was not the same, is reminiscent of the functional specialization that has been observed in other animal species, such as, for example, rhesus monkeys (Hauser & Andersson, 1994) and mice (Ehret, 1987). When the birds were awake, we first observed a significantly higher number of responsive neurons in the right than in the left hemisphere. Given that responses to individual-specific songs prevailed when the birds were awake, this suggests an overall predominant role of the right hemisphere in individual recognition, which agrees with large evidence, in birds and mammals, of a dominant role of this hemisphere in conspecific recognition (Vallortigara & Andrew, 1994). Moreover, we observed a relative left bias in responses to unfamiliar individual-specific (i.e., class II and III) songs in the field L, and to all class II songs in the HVC. Class II songs are used in vocal interactions between social partners and are thought to evoke the listener's approach (Feare, 1984; Hausberger, 1991; Hausberger & Black, 1991; Hausberger et al., 1995). These results are therefore consistent with a prevailing role of the left hemisphere in categorization and in processing stimuli evoking a motor response, as has been proposed by several authors (Goldberg & Costa, 1981; Rogers, 2000). In the right hemisphere, we observed a relative predominance of responses to familiar and bird's own songs in the field L, and to warbling (i.e., class III songs) in the HVC. Warbling is a long and complex song that may be involved in female attraction (Verheyen, 1980; Adret-Hausberger et al., 1990; Eens et al., 1991). Again, our results are therefore in total accordance with a putative role of the right hemisphere in detail analysis and individual recognition (Vallortigara & Andrew, 1994; Andrew & Rogers, 2002; Vallortigara & Bisazza, 2002). To sum up, our work on brain lateralization of song perception in starlings, in addition to providing the first clear evidence of hemispheric specialization in a songbird, supports the idea suggested by other authors that the left hemisphere would play a prevailing role in categorization, in processing stimuli evoking a motor response, and in producing responses that require inhibition until a decision is made, whereas the right hemisphere would play a major role in detail analysis, in individual recognition, and in producing rapid responses (Goldberg & Costa, 1981; Andrew & Rogers, 2002; Vallortigara & Bisazza, 2002).

New evidence of hemispheric specialization in song perception has been very recently provided in other songbird species. Thus, taking advantage of functional magnetic resonance imaging, which was recently adapted to starlings (Van Meir et al., 2005) and zebra finches (e.g., Boumans et al., 2007; Voss et al., 2007), Poirier et al.

(2009) measured the blood-oxygen-level-dependent (BOLD) neural responses in anesthetized male zebra finches that were exposed to their own song (BOS), a conspecific song (CON) and a heterospecific song (HET). They discovered, at the level of the midbrain in the ascending auditory pathway, that the differential activations elicited by BOS versus CON on the one hand and CON vs. HET on the other hand were both significantly lateralized, to the right for BOS versus CON, and to the left for CON versus HET. According to them, the right lateralization they observed for BOS selectivity could be due to a right lateralization of the auditory feedback control system that is crucial to song learning and maintenance, suggesting an anatomofunctional convergence between birds and humans. Indeed, in humans, speech learning and maintenance are supposed to be supported by both a feed-forward and a feedback control, and recent studies suggest that the feed-forward control is lateralized to the left hemisphere while the auditory feedback control is, at least partially, lateralized to the right (Toyomura et al., 2007; Tourville et al., 2008).

In conclusion, multiple and consistent lateralization effects for sensory processing in songbirds echo the lateralization findings for perceptual processing in other taxa (e.g., Hauser & Andersson, 1994; Poremba et al., 2004; Taglialatela et al., 2008), including humans (reviewed in Zatorre, 2001), as well as robust lateralization findings in the vocal and visual system of songbirds in male song behavior (see, e.g., George et al., 2006, and this chapter for a review). Lateralization might therefore be a ubiquitous property of the vertebrate forebrain, especially in experience-dependent perceptual processing.

### Sex Differences

In humans, a powerful neuromodulatory action of estradiol on the dynamics of functional brain organization seems to exist in the female brain, and there has been evidence of a role for ovarian hormones in shaping laterality of speech perception in women (e.g., Wadnerkar et al., 2008). Thus, Weis et al. (2008) have, for example, shown that the inhibitory influence of left-hemispheric language areas on homotopic areas of the right hemisphere is strongest during the menses, resulting in a pronounced lateralization. During the follicular phase, due to rising estradiol levels, inhibition and thus functional cerebral asymmetries are reduced.

In songbirds, males and females do not appear to differ markedly, and lateralization has been observed in both sexes. For example, in an attempt to determine whether the visual stimulus of a courting male modifies song-induced expression of the IEG ZENK (*zif268*, *egr1*, *NGFI-A*, *Krox 24*) in the auditory forebrain of zebra finches, Avey et al. (2005) unexpectedly found a lateralization of Zenk response that was independent of sex, such that Zenk immunoreactivity was consistently higher in the left than in the right hemisphere and the majority of individual birds showed a left bias, sug-

gesting an overall specialization of the left auditory forebrain for song processing in females as well as in males.

More recently, Hauber et al. (2007), studying anaesthetized, nonbreeding, adult female zebra finches, found significantly greater normalized response strengths averaged for all the sounds they used (pure tones, white noise, and conspecific song) from right- than left-hemisphere units in two auditory forebrain regions (field L and the caudolateral mesopallium; CLM). In field L, the difference in responses between left and right hemispheres was only observed for the synthetic sounds while conspecific song responses were statistically identical in both sides, resulting in a differential response between song and other sounds that was actually greater in the left hemisphere. Further analysis indeed showed that only the left hemisphere displayed selectivity for conspecific song. In CLM, lateralization effect was only significant when all sounds were considered, and it was largest for white noise. This study thus also suggests a potential specialization of the left hemisphere for processing song in female zebra finches.

Finally, left-right differences in nXIIts volume, motoneuron number, and syrinx muscle fiber size (right > left) have been observed in both male and female zebra finches (Wade et al., 2002). However, these results were obtained in birds that had been killed before the males' songs had reached their mature form. In a previous study (Wade & Buhlman, 2000), in which birds were killed in adulthood, the same lateral biases were detected but those in the brains of adults (nXIIts volume and motoneuron number) were present only in males, who sing, and not in females, who do not. According to Wade and colleagues, it is therefore possible that lateralization exists in the motor nucleus of both males and females prior to sexual maturity but that it is not maintained in adult females, who do not use the structure to the same degree as males. The neural lateralization may thus diminish in females in adulthood but in males may facilitate or be a consequence of increased song production.

The tight link that seems to exist between vocal behavior and lateralization has been better studied in female canaries who, unlike female zebra finches, do sing when they are given testosterone. Thus, a left syringeal dominance in song production has been observed in testosterone-treated female canaries (Hartley et al., 1997). Moreover, in adult female canaries, the importance of the left hemisphere for controlling testosterone-induced song increases with singing experience (Greenspon & Stein, 1983), suggesting that the occurrence of left-lateralized control of vocal behavior may prove to be a characteristic typical of animals capable of vocal learning. Further studies, especially in species where both males and females sing, will be required to elucidate this point and to disentangle gender differences in lateralization from sexual dimorphism in vocal behavior. In starlings, preliminary results suggest that females, who do sing, might be less lateralized than males (George et al., unpublished data), and no left-right difference has been observed in their telencephalon and cerebellum volume (Van Meir et al., 2006).

## Conclusion and Perspectives

Hemispheric asymmetries are a widespread phenomenon in all vertebrate species, whether at the individual or population level, and one can thus find animal models for all types of asymmetries. Birdsong is the first system in which nonhuman lateralization was demonstrated, and it is still among the best characterized. The early discovery of a left bias in the neural control of song production (Nottebohm, 1971, 1977; Nottebohm et al., 1976) has even greatly contributed to establishing a connection between studies on birdsong and studies on human speech. Yet, today, a query on song lateralization on PubMed retrieves less than a hundred papers, dating from 1976 to 2008, which has to be compared to the almost 9,000 papers, dating from 1951 to 2009, that can be retrieved with a query on language lateralization. This shows that songbirds are an emerging model in the field of functional lateralization and that we undoubtedly still have a lot to learn from them.

Although the existence of motor asymmetries in song production of the Wasserschlager canary has been one of the first and most robust nonhuman examples of a lateralized neural control of behavior, we have seen that the degree and side of lateralization can vary greatly between species and that different species seem to have adopted different motor strategies that use the left and right sides of the syrinx in patterns of unilateral, bilateral, alternating, or sequential phonation to achieve the differing temporal and spectral characteristics of their songs (Suthers, 1997). Lateralization may thus have evolved, as suggested by some authors (Suthers, 1997; Suthers & Goller, 1997), to make maximal use of the bipartite structure of the syrinx, and its mostly unilateral central control, for generation of spectrally and temporally complex acoustic signals. The evolutionary pressures that have led to hemispheric asymmetries in song production may therefore have been quite different from those leading to the lateralized central control of human speech (Goller & Suthers, 1995).

In this respect, asymmetries in song perception, although much less investigated to date, may shed more light on the possible evolutionary origins of lateralization, especially in relation to language-like processes in the brain. Indeed, although evidence of hemispheric asymmetries in song perception is less steady than for song production, these asymmetries appear to show interesting parallels with asymmetries in speech processing. Thus, we have seen that starlings, which are highly social songbirds that have a sophisticated and plastic song, show a complex and state-dependent hemispheric specialization that is related to the social value of the acoustic signals (in terms of both familiarity and species-specific vs. individual recognition; see figure 4.7). The left hemisphere appears to be specialized in processing unfamiliar songs and simple, short whistles that are used in long-distance individual recognition (especially through vocal interactions such as “song matching”), while the right hemisphere appears to be specialized in processing familiar songs and complex, long vocalizations

that are used in individual recognition at short distance, especially between males and females. These results are in large accordance with other studies suggesting that the left hemisphere would be mainly involved in sustaining attention to stimuli for which a motor response is planned, and the right hemisphere in processing complex information (Goldberg & Costa, 1981), in diffuse attention (Andrew & Rogers, 2002), and in aggressive and sexual behaviors (Vallortigara & Bisazza, 2002). Interestingly, studies performed in our laboratory (UMR6552—Ethologie Animale et Humaine, Université Rennes 1—CNRS, Rennes, France) have also demonstrated hemispheric specializations related to familiarity and social or emotional valence of stimuli in other species such as horses and monkeys (Larose et al., 2006; De Boyer Des Roches et al., 2008; Baraud et al., 2009; de Latude et al., 2009). However, in starlings, we have also observed less pronounced hemispheric asymmetries for songs used in individual recognition (class II and III songs; see figure 4.6) than for nonspecific sounds and species-specific (class I) songs, which is particularly interesting. Indeed, one could imagine that the complexity of vocalizations bearing individual identity, which is especially clear in the case of warbling (or class III songs; see figure 4.6), could require a sophisticated processing involving both hemispheres, which could in turn explain why hemispheric differences, thought about in terms of complementary functional specializations, might have evolved. In this respect, parallels with language are highly informative. Indeed, in humans, it has been shown that, whereas the left hemisphere plays a predominant role in the detection of verbal components in speech, the right hemisphere plays a major role in the detection of emotional prosody and in the processing of pitch information (e.g., Wernicke, 1874; Ross, 1981; Buchanan et al., 2000). Assuming that these different types of information differ in their acoustic structure and thus in their processing requirements, Zatorre (2001) has suggested an interesting unifying hypothesis to explain complementary functional specializations of the two hemispheres. This hypothesis states that:

Whereas the analysis of speech requires good temporal resolution to process rapidly changing energy peaks (formants) that are characteristic of many speech consonants (see, for example, the work of Tallal et al., 1993), it can be argued that tonal processes instead require good frequency resolution. In a truly linear system, temporal and spectral resolution are inversely related, so that improving temporal resolution can only come at the expense of degrading spectral resolution and vice versa. This tradeoff naturally arises from a fundamental physical constraint in acoustic processing: better resolution in the frequency domain can be obtained only at the expense of sampling within a longer time window, hence degrading temporal resolution; conversely, high resolution in the temporal domain entails a degraded spectral representation. The auditory nervous system is, of course, a highly nonlinear and distributed system; yet, it may also respect this fundamental computational constraint, such that in the left auditory cortex the high temporal resolution needed to process speech imposes an upper limit on the ability to resolve spectral information, and vice versa for the right auditory cortex. To put it more simply, the hypothesis is that there may be a tradeoff in processing in temporal and spectral domains, and

that auditory cortical systems in the two hemispheres have evolved a complementary specialization, with the left having better temporal resolution, and the right better spectral resolution. (pp. 204–205)

This hypothesis has received experimental support from several human studies (see Zatorre, 2001, for references) and would definitely deserve further investigation in songbirds, especially as spectral and temporal features of songs naturally vary between species and as these features can also be experimentally manipulated with great ease.

In general, processing complex information involves fine, simultaneous analysis of a variety of parameters that often requires mutually exclusive specializations, and hemispheric specializations can in this respect be compared as a special case of cerebral functional localizations. Now, it is well established that cerebral functional organization is greatly dependent upon early sensory experience (for some reviews, see Singer, 1986; Frey, 2007; Petersen, 2007). Our studies on starlings have demonstrated experience-dependent neuronal specialization and functional organization in the primary auditory area (field L) of these birds, not only in relation to sensory experience (Cousillas et al., 2004) but also, and most importantly, in relation to social experience (Cousillas et al., 2006, 2008). One can thus wonder what role sensory and social experience may play in the development of hemispheric differences. Unfortunately, studies on songbirds are acutely lacking in this domain. Yet, songbirds constitute a particularly appropriate model that could certainly help us better address this issue, especially in relation to the communicative aspects of singing. Here again, parallels with human studies could be very informative. In humans, the recent discovery of early leftward asymmetries in the arcuate fasciculus and in the corticospinal tract have led some authors to suggest that early macroscopic geometry, microscopic organization, and maturation of the white matter bundles are related to the development of later functional lateralization (Dubois et al., 2009). However, to our view, although early anatomical asymmetries unquestionably provide a basis for the development of functional hemispheric specialization, early experience is likely to play a more crucial role in this development. Thus, although anatomical asymmetries seem to appear very early in life, functional lateralization appears much later in development. For example, it has been observed that the functional lateralization of linguistic neural networks involved in automatic word recognition and in phonological processing is not yet developed in linguistically competent children age 10 years (Spironelli & Angrilli, 2009). Moreover, there has been evidence of an influence of language on the functional organization of the brain. Thus, in adults, color categorical perception mainly takes place in the left hemisphere, whereas, in infants, it mainly takes place in the right hemisphere, and it appears that this hemispheric switch occurs when the words that distinguish the relevant category boundary are learned (Franklin et al., 2008). In view of growing evidence for a potential implication of lateralization, and especially

atypical establishment of hemispheric specialization, in neurological and psychiatric disorders that sometimes involve severe impairment in social and/or language abilities, it appears of prime importance to better understand how lateralization develops, especially in relation to sensory or social experience and to the development of the ability to communicate with others. We believe that studies of the development of hemispheric asymmetries of songbirds are very promising in this respect because, as we have seen, songbirds are a unique model allowing experimental investigation of the interplay of neurobiological substrate and behavior. The power and uniqueness of songbirds as a model to study functional lateralization in relation to communicative aspects of vocal behavior lies in the fact that song is a learned behavior whose critical function is to communicate with other birds. As such, song behavior is inevitably strongly experience dependent. Moreover, this behavior is controlled by a highly evolved and well-characterized network of brain regions that are duplicated in two hemispheres that are not directly connected, and it is strongly hormone dependent. Considering the fact that all these aspects of songs can be experimentally controlled and manipulated, which offers the possibility of compensating for the impossibility of experimentally controlling and manipulating language in human studies, there is no doubt that studies on hemispheric asymmetries of songbirds will long help us to better understand how the two halves of the brain process information, especially in relation to communicative behavior and its development, and also to the effects of not only experience but also gender and social factors.

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## 5 The Embryonic Development of Visual Asymmetry in the Pigeon

Onur Güntürkün and Martina Manns

"When 77 days old, he took the sucking bottle in his right hand, whether he was held on the right or left arm of his nurse, and he would not take it in his left hand until a week later although I tried to make him do so; so that his right hand was a week in advance to the left" wrote Charles Darwin about his son William, concluding that he would become right-handed. However, finally, "yet this infant afterwards proved to be left-handed, the tendency being no doubt inherited—his grandfather, mother, and another brother having been or being left-handed" (Darwin, 1905; cited according to McManus, 2002). For Charles Darwin, his contemporaries, and many recent researchers a genetic foundation of handedness and other cerebral asymmetries is a matter of fact. This view certainly is nourished by the presence of the striking population bias for handedness, which already existed from lower Pleistocene onwards (Toth, 1985). This assumption also gains strength from data that show that adopted children develop handedness patterns that resemble those of their biological and not their adoptive parents (Carter-Saltzman, 1980). In the meantime, several theoretical genetic models have been proposed to explain the cerebral lateralization pattern in the human population (Annett, 1985; McManus, 1985; Klar, 1999; Yeo et al., 1999). Only recently, two genes related to handedness have been identified (Francks et al., 2007; Sun et al., 2005; Sun & Walsh, 2006). Both are expressed within the early cerebral cortex and, hence, might be involved in the regulation of asymmetrical differentiation of cortical motor systems.

Nonetheless, neither genetic models nor single genes alone provide a clarification of the developmental mechanisms underlying asymmetry formation. Hence, they are not sufficient to explain deviations from expected patterns like discordance of cerebral asymmetries in twins. Cerebral lateralization displays a certain degree of plasticity, indicating that environmental factors before and/or after birth also play a role (Steinmetz et al., 1995; Eckert et al., 2002). Therefore, other researchers highlight the crucial influence of lateralized environmental experiences during embryonic (Previc, 1991) or postnatal (Michel & Harkins, 1986; Konishi et al., 1997) development. For example, Michel and Harkins (1986) propose that the neonatal rightward bias in the direction

of head orientation is the starting point in developing a stable hand preference since this turning bias influences the subsequent development of perceptual and motor preferences by increasing visual orientation to the right side.

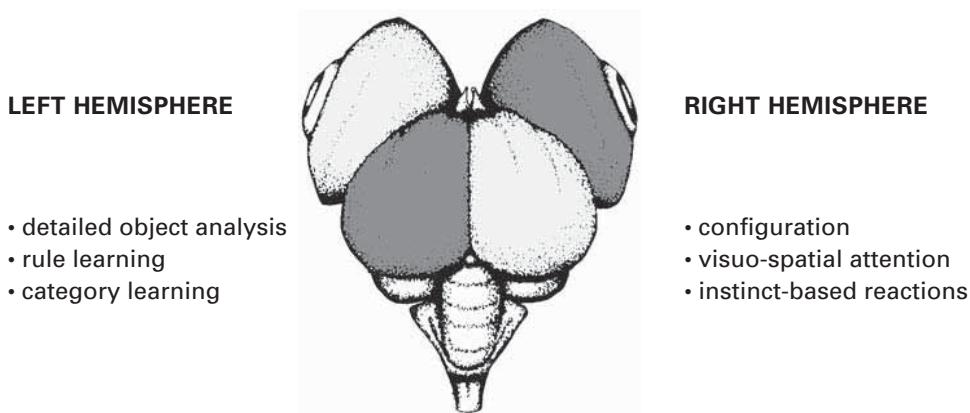
Presumably, both genetic and environmental factors are involved in the establishment of cerebral lateralization. However, their interplay, their relative importance, and the mediating neuronal processes are far from being clear. Today, a wide range of animal species from the entire animal kingdom are known to display left-right differences in neuronal structure and processing (Halpern et al., 2005; Vallortigara et al., 1999; Vallortigara & Rogers, 2005). Examples of functional asymmetries can be found in all vertebrate classes but also in octopuses (Byrne et al., 2006), fruit flies (Pascual et al. 2004), bees (Letzkus et al., 2006; Rogers & Vallortigara, 2008), and even in nematodes (Suzuki et al., 2008). These models allow experimental approaches to unraveling the ontogenetic mechanisms leading to a lateralized brain, and they may especially disentangle the interplay of genes and environment (Halpern et al., 2005).

New insights come also from the visual system of birds like chickens and pigeons, where a behavioral lateralization can be associated with morphological left-right differences at the individual as well as the population level. These models have elucidated important aspects of the relation between cognitive strategies and lateralization (Daisley et al., 2009; Rogers, 1996; Rogers et al., 2004). Here, we concentrate on data from research with pigeons, where we have started to understand the relevant developmental steps and cellular mechanisms that are necessary to generate neuronal asymmetries.

### The Model: Visual Lateralization of the Avian Brain

Birds like pigeons are virtually perfect models to investigate cerebral asymmetries. First of all, they possess high cognitive abilities (Jarvis et al., 2005; Kirsch et al., 2008), allowing researchers to test the interrelation between lateralization and cognition. Pigeons, for example, are able to memorize up to 725 different visual patterns (von Fersen & Delius, 1989) or learn to categorize images into “human” and “nonhuman” (Yamazaki et al., 2007), “human-made” and “natural” (Lubow, 1974), or “cubistic” and “impressionistic” painting (Watanabe et al., 1995). They can even rank patterns using transitive inferential logic (von Fersen et al., 1990; Siemann et al. 1996).

Since the optic nerves of birds cross almost completely (Weidner et al., 1985), it is very easy to test the cognitive functions of each hemisphere separately just by occluding one eye with an eye cap. Such monocular tests have demonstrated that the left and right halves of the brain analyze, to some extent, different aspects of visual stimuli and that the two hemispheres differently contribute to cognitive challenges (Güntürkün, 2002; Daisley et al., 2009; see figure 5.1). The left hemisphere is specialized for detailed



**Figure 5.1**

The left and right hemispheres of the avian brain analyze different aspects of visual stimuli. The brain of the pigeon is shown from above with the eyeballs attached. Note the large size of the eyes relative to the brain. The left eye and the contralateral right hemisphere are shown in light gray; the right eye and the left telencephalon are depicted in dark gray. Functional specializations of each hemisphere are shown on the corresponding side of the half brain.

object analysis and attends to local features of visual stimuli. This becomes especially apparent in studies with pigeons (e.g., Yamazaki et al., 2007), where visual stimuli were fragmented into smaller and smaller pieces. The left hemisphere is then clearly superior in identifying critical details in these tiny fragments. The generally better discrimination abilities of the right eye also become apparent in visual discrimination of grain versus grit in the chicken (Rogers et al., 2007), pigeon (Güntürkün & Kesch, 1987), quail (Valenti et al., 2003), and zebra finch (Alonso, 1998). Pigeons display superior left-hemispheric performance in the discrimination and memorization of two-dimensional artificial patterns (Güntürkün, 1985; von Fersen & Güntürkün, 1990), in the detection of geometrical optic illusions (Güntürkün, 1997b), in color reversal learning (Diekamp et al., 1999), and in categorization of the object category "human" (Yamazaki et al., 2007).

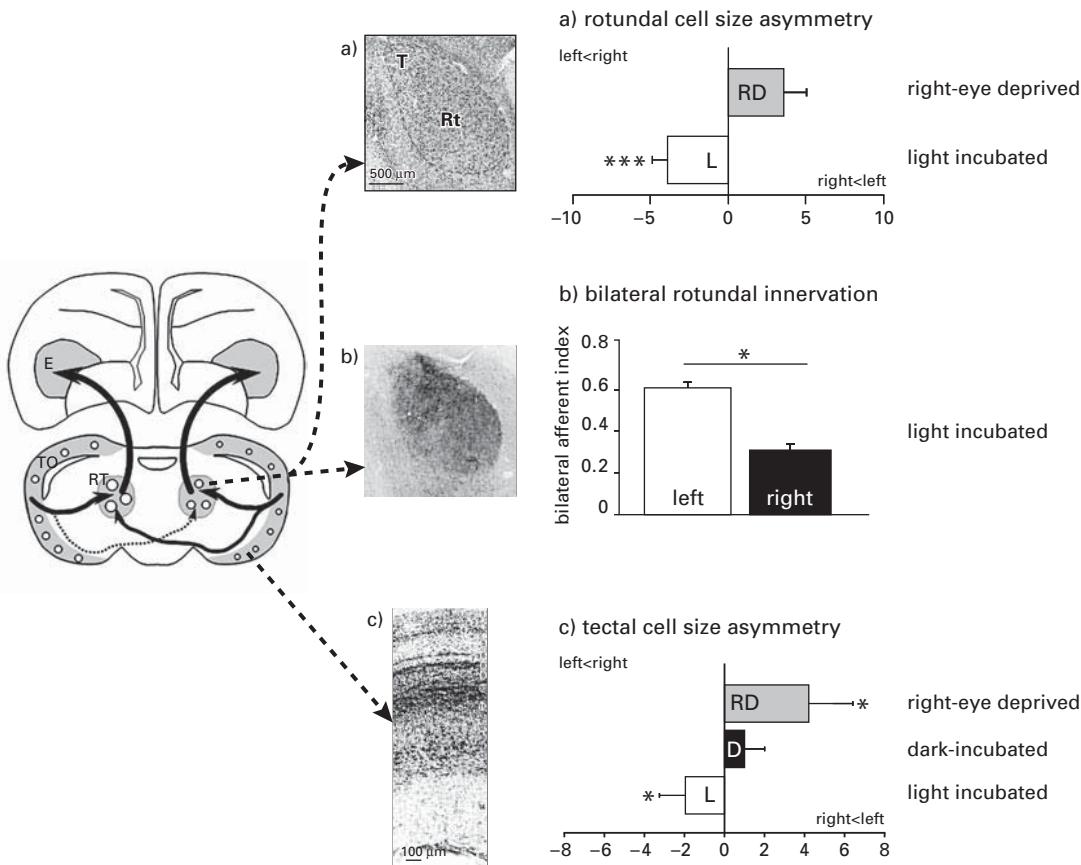
In contrast, the right hemisphere extracts relational configurations of visual stimuli and analyzes global aspects of the visual scenery as indicated in the chicken (Chiesa et al., 2006; Tommasi & Vallortigara 2001, 2004), pigeon (Kahn & Bingman, 2004), and marsh tit (Clayton & Krebs, 1994). This is presumably related to a right-hemispheric superiority in relational aspects of spatial cognition (Diekamp et al., 2005; Regolin, 2006). Comparable to the "pseudoneglect" of human subjects who primarily attend to objects in the left side of space (Jewell & McCourt, 2000), birds exhibit a left-side bias when tested on an adapted version of a cancellation task. Chicks or pigeons, which explore an area in front of them to sample grains, display a clear bias

into the left hemisphere, as evident in the pecking activity or the order in which pecks are placed in the left or right hemispace (Diekamp et al., 2005). Apart from spatial processing, the right hemisphere is in charge of species-typical or instinct-based reactions like novelty detection (Andrew et al., 2004), social discrimination and attack (Vallortigara & Andrew, 1994; Zucca & Sovrano, 2008), fear and escape responses (Dharmaretnam & Rogers, 2005; Koboroff et al., 2008), and sexual behavior (Bullock & Rogers, 1992; Gülbetekin et al., 2007).

### The Architecture: Asymmetrical Anatomy in Pigeons

The functional asymmetries in visual tasks can be related to structural left-right differences in the visual pathways. In the pigeon, a combination of anatomical, physiological, and behavioral studies demonstrate a tight relationship between structural and functional asymmetries (Güntürkün, 2002). The major visual pathway of pigeons is the tectofugal system. It corresponds to the mammalian extrageniculocortical pathway and very likely dominates frontal vision and, hence, visuomotor behavior in pigeons (Güntürkün, 2000). This system projects via the contralateral mesencephalic optic tectum and the diencephalic nucleus rotundus to the telencephalic entopallium (Bischof & Watanabe, 1997; Güntürkün, 2000; new nomenclature according to Reiner et al., 2004; see figure 5.2). The second ascending visual system is the thalamofugal pathway, which corresponds to the mammalian geniculocortical system. For two reasons we will concentrate on the tectofugal pathway in our review. First, it is by far the most important system as shown by a large number of lesion studies (e.g., Bessette & Hodos, 1989; Hodos & Bonbright, 1974; Hodos & Karten, 1974; Güntürkün & Hahmann, 1999; Riley et al., 1988). Second, the tecto- but not the thalamofugal pathway is characterized by anatomical left-right differences in the pigeon (Güntürkün, 2002).

Within the optic tectum, a majority of cells, including inhibitory GABAergic neurons, display larger cell bodies in the left tectum (Güntürkün, 1997a; Manns & Güntürkün, 2003; Skiba et al., 2002). Additionally, the tectorotundal projection is asymmetrically organized: While the majority of tectal efferents in both half brains ascend ipsilaterally onto the rotundus, a subpopulation projects to the contralateral side. Thus, each rotundus receives bilateral tectal input. However, more fibers cross from the right tectum to the left rotundus than vice versa (Güntürkün et al., 1993, 1998). The resulting stronger bilateral innervation of the left rotundus correlates with enlarged rotundal neurons on this side (Manns & Güntürkün, 1999b). In line with the stronger bilateral input, physiological and behavioral studies demonstrate enhanced bilateral processing in the left hemisphere (Folta et al., 2004; Valencia-Alfonso et al., 2009; Manns & Güntürkün, 2009). Thus, the ascending tectofugal pathway displays a neuronal organization that creates an asymmetrical representation of the visual scene at forebrain level. This lateralized bottom-up system is

**Figure 5.2**

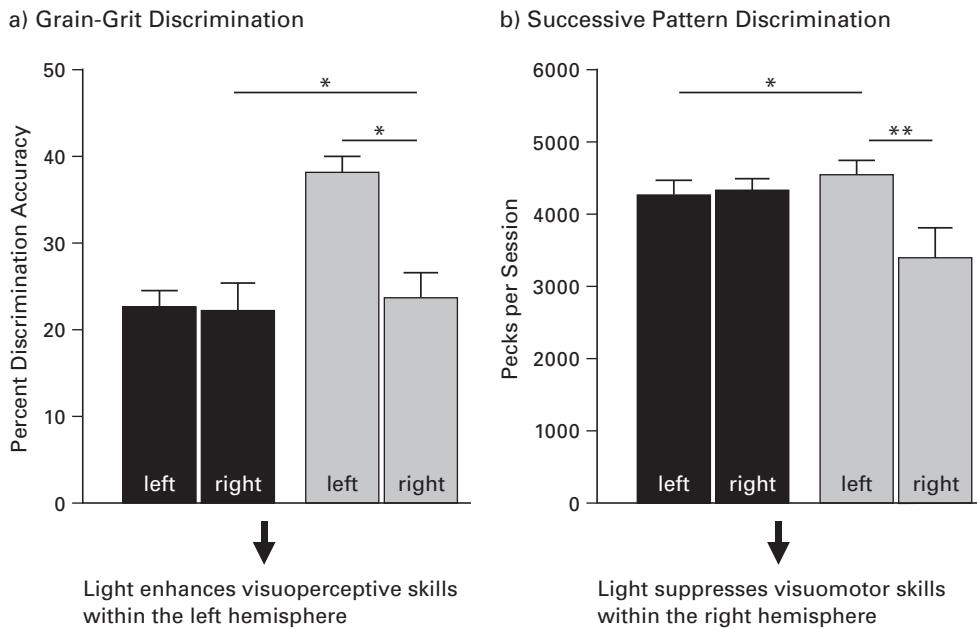
Structural asymmetries in the pigeon's tectofugal system (tectum opticum → nucleus rotundus → entopallium) with larger cells (a, c) and stronger bilateral input (b) on the left side. On the left side, a schematic overview of the tectofugal system is shown as seen in frontal plane. Insets a–c show Nissl-stained sections of the rotundus (a, b) and the tectum (c). (a) Cell-size asymmetries in the rotundus in light-incubated pigeons (natural condition) and in animals that were deprived of vision for ten days directly after hatching (right-eye deprived). The bars indicate the relative size of rotundal somata with a left and a right skew, indicating larger cells on the left and the right half brain, respectively. (b) Anterogradely traced tectal fibers that densely innervate the rotundus. The relative number of fibers from the ipsi- and the contralateral tectum are expressed as a bilaterality score. A score of -1 indicates a completely contralateral and 1 a completely ipsilateral innervation pattern. As depicted, the left rotundus is more bilaterally innervated than the right rotundus. (c) Cell-size asymmetries in the tectum with pigeons that were light-incubated (L), dark-incubated (D), or right-eye deprived for ten days after hatching (RD); (Güntürkün, 1997a; Güntürkün et al., 1998; Manns & Güntürkün, 1999a, 1999b; Skiba et al., 2002; \* $p < .05$ ; bars represent standard error).

controlled by telencephalic top-down projections. The impact of this system is also lateralized with a dominant role of the left forebrain (Valencia-Alfonso et al., 2009).

Taken together, the pigeons' tectofugal visual system shows morphological and physiological asymmetries along ascending and descending streams. In this chapter, we will not concentrate on the structural details but will focus instead on the chain of events which start to modulate these asymmetries during ontogeny. These events start during embryonic development and last into the posthatch phase to generate a lateralized functional architecture of the visual system that lasts for the entire lifetime of the animal.

### **The Source: Visual Lateralization Is Generated by Asymmetrical Visual Input during Ontogeny**

Inspection of fertilized eggs discloses a surprising observation. Avian embryos consistently tilt their heads in such a way that the right eye is close to the eggshell and the left eye is occluded by the body (Kuo, 1932). This positional asymmetry is likely related to an asymmetrical turning of the embryonic axis, which correlates with the asymmetrical placement of the internal organs and is controlled by left-/right-specific gene expression cascades (Collignon et al., 1996; Hamada et al., 2002; Raya & Belmonte, 2006). Since breeding birds regularly turn their eggs and therefore often leave their nests for short time periods, eggs are frequently exposed to light (Buschmann et al., 2006). This pattern guarantees that the embryos are repetitively stimulated by light. These light pulses have presumably long-lasting effects since light-induced cellular processes stay activated even when the parental birds turn back to their clutch and shut off the light input (Buschmann et al., 2006). As a consequence of the asymmetrical head position, light entering through the eggshell and the air sac membranes stimulates the right eye of the embryo while the left eye is visually deprived. Such asymmetrical stimulation induces asymmetrical differentiation processes within left- and right-hemispheric visual circuits, which ultimately establish the functional lateralization of the visual system. The critical impact of a biased visual stimulation is confirmed by experiments showing that bilateral light exposure, as well as incubation in complete darkness, prevents development of lateralized visual circuits (Deng & Rogers, 2002; Skiba et al., 2002; see figure 5.3). This means that normal rearing conditions correspond to a left-eye deprivation, resulting in a dominance of the right eye/left hemisphere for visual discrimination in most pigeons (Güntürkün et al., 2000). The crucial point is that this population bias is not genetically determined by factors within the nervous system. Instead, the asymmetrical action of the epigenetic factor light is the decisive event. However, the action of light goes always in the same direction only because of the invariantly lateralized, genetically determined body position.



**Figure 5.3**

Two behavioral paradigms reveal complementary aspects of visually guided behavior in pigeons. (a) Mean percentage of discrimination accuracies of dark- and light-incubated birds using their left or their right eye in a grain-grit discrimination task. Note that the asymmetry of the light-incubated animals is due to an increase of right-eye performance. (b) Mean pecks per session of dark- and light-incubated birds using their left or their right eye in a discrimination task. Note that the asymmetry of the light-incubated animals is due to a decrease of left-eye performance (Skiba et al., 2002; \* $p < .05$ ; \*\* $p < .01$ ; bars represent standard error).

However, induction during embryonic development is only the starting point for the asymmetry of the visual system. Pigeons are altricial birds, staying three weeks in the nest, where they are fed with crop milk by their parents. They hatch with closed eyes and a highly immature visual system (Bagnoli et al., 1987; Manns & Güntürkün, 1997; Manns, Freund, & Güntürkün, 2008). As a consequence of this prolonged visual developmental period, it is still possible to alter visual asymmetries after hatching (Manns & Güntürkün, 1999a, 1999b; Manns, Freund, & Güntürkün, 2008; Prior et al., 2004). For example, occlusion of the right eye for ten days reverses visual asymmetries by inducing a functional dominance of the left eye in visual discrimination. In parallel, cell-size asymmetries in the visual system are likewise modulated. Conversely, left-eye deprivation enhances the right-eye dominance (Manns & Güntürkün, 1999a, 1999b). This plasticity suggests that asymmetry formation in the pigeon's visual system is far from being completed at the time of hatching.

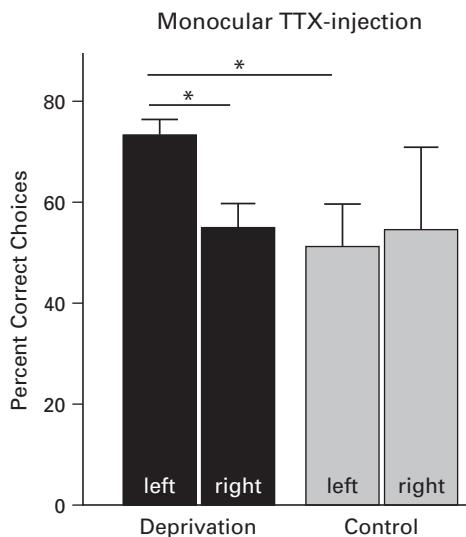
Accordingly, we can delineate two developmental phases that are critically involved in the establishment of lateralization: induction and stabilization. Asymmetries are *induced* during embryonic development by lateralized light input, and they are *stabilized* during posthatch development despite a usually symmetric stimulation by light. During this latter phase, the system is still sensitive to environmental influences. It is very likely that visual stimulation before or after hatching affects different neuronal processes in separable neuronal systems. During embryonic development, asymmetrical photic stimulation primarily influences differentiation of retinotectal connections, leading to hardwired structural left-right differences in the tectum. After hatching, effects onto nonretinorecipient components of the tectofugal systems might be more important for the determination of visual asymmetries (Manns and Güntürkün, 1999b). The interaction of these early and late mechanisms establishes visual asymmetries, which then exist for the entire lifetime of an individual (Manns & Güntürkün, 2009).

### **The Flowing Force: Asymmetry Formation Is Mediated by Activity-Dependent Processes**

Shortly before hatching, the retinotectal system of the pigeon embryo is still very immature. Retinal fibers have not completely invaded their tectal target layers (Bagnoli et al., 1987; Manns & Güntürkün, 1997), and specific cell types just start to differentiate (Manns & Güntürkün, 2003; Manns, Freund, & Güntürkün, 2008). Accordingly, the system is highly sensitive to visual input, and short periods of biased retinal activation are sufficient to initiate asymmetrical differentiation processes within the left and right tectum (Güntürkün, 1997a, 1997b).

Differences in retinal activity constitute the first step in the initiation of asymmetrical anatomical development. Transient reduction of retinal activity by just a single ocular injection of the sodium channel blocker tetrodotoxin (TTX) alters behavioral lateralization in adult pigeons (Prior et al., 2004; see figure 5.4). This observation shows that even a short period of asymmetrical retinal activity suffices to induce or modulate an asymmetrically wired system. Many effects of light-input-related retinal activity are mediated by neurotrophic factors, and the brain derived neurotrophic factor (BDNF), in particular, is a key player in activity-dependent development (Vicario-Abejón et al., 2002). Light stimulation adjusts the expression and the release of BDNF and hence regulates trophic support of target cells. In turn, BDNF affects synaptic transmission and controls sprouting, branching, and maintenance of axodendritic trees (Huang & Reichardt, 2001; Vicario-Abejón et al., 2002; Cohen-Cory & Lom, 2004). As a result, neurons differ in axodendritic complexity depending on the amount of available BDNF.

One indicator of neuronal complexity is the size of the neuronal cell body. Thus, it is conceivable that asymmetrical light effects on the developing retinotectal system



**Figure 5.4**

Mean discrimination success in a grit–grain discrimination task of dark-incubated pigeons when seeing with the left or right eye. Animals received a single tetrodotoxin (TTX; deprivation) or saline (control) injection into the right eye directly after hatching (Prior et al., 2004; \* $p < .05$ ; bars represent standard error).

are mediated by asymmetrical BDNF supply. BDNF and its high-affinity receptor TrkB are present in the developing retinotectal system (Theiss & Güntürkün, 2001), and the tectal TrkB signaling cascade is asymmetrically activated in response to embryonic light stimulation (Manns et al., 2005). The small G protein p21Ras is one critical molecular switch for relaying neurotrophic actions into morphological changes (Heumann et al. 2000). Indeed, Manns et al. (2005) revealed that the amount of p21Ras within the pigeon's optic tectum depends on photic stimulation. It is likely that asymmetries of p21Ras produce left–right differences during development by altering the morphology of chemically specified cellular intratectal populations (Manns & Güntürkün, 2005).

However, how exactly is the asymmetrical BDNF release translated into left–right differences of neuronal wiring? BDNF could do this via two different mechanisms. First, asymmetrical intraretinal BDNF expression could shape the tectofugal system by lateralized anterograde trophic support. In this case, BDNF would be produced within retinal ganglion cells and transported toward the tectum. Second, retinal activity differences could secondarily regulate intratectal BDNF release in an asymmetrical manner. This scenario assumes that the local release of BDNF from tectal cells is asymmetrically controlled by retinal output. To decide between these two options, Manns,

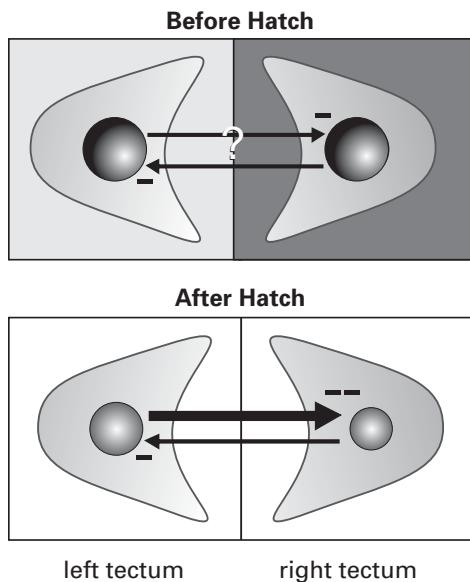
Freund, Leske, & Güntürkün (2008) injected BDNF into the right eye of dark-incubated pigeon embryos. Normally, these animals develop no visual lateralization. If intra-retinal BDNF is responsible for igniting visual asymmetry, this extra portion of neurotrophins should mimic light stimulation asymmetry in dark-incubated pigeon embryos and should result in a right-eye dominance of these animals. However, just the reverse was observed. Pigeons with BDNF injections into the right eye developed left-eye superiority in visual discrimination tasks. Thus, it is more likely that light differently activates tectal neurons, which in turn produce left-right differences in tectal BDNF release.

This finding makes one further aspect of the development of asymmetry very clear: Although the tectofugal system is primarily contralaterally organized, unilateral modulation of visual input affects neuronal circuits in both brain sides. This is only possible via interhemispheric interactions that modulate the ongoing plasticity within both sides of the visual system. This is exactly what we will outline in the next section.

### **The Bridge: Visual Lateralization Results from Bilateral Effects of Asymmetrical Visual Stimulation**

As outlined above, the consequences of asymmetrical light stimulation are not confined to the more strongly stimulated brain side. As shown in figure 5.3, light incubation differently affects visuomotor and visuoperceptual skills in both hemispheres (Skiba et al., 2002). Major effects of unilateral ocular manipulations by TTX or BDNF can even be manifested within the primarily unaffected brain side (Prior et al., 2004; Manns et al., 2008; Manns, Freund, Leske, & Güntürkün, 2008; see figure 5.4). This means that asymmetrical modulation of retinal input alters the balance of activity between left and right eye systems, thereby adjusting neural systems on either side.

Since GABAergic inhibition generally plays a critical role in the regulation of experience-dependent development (Berardi et al., 2000; Hensch, 2005), it is conceivable that especially inhibitory systems are involved in this interhemispheric regulation of development. Indeed, the mainly inhibitory intertectal interaction (Hardy et al., 1984; Robert & Cuénod, 1969) is asymmetrically organized with the left tectum inhibiting the right tectum to a larger extent than vice versa (Keyser et al., 2000). This means that activations of the left hemisphere possibly go along with a strong inhibition in the right tectum. This inhibitory mechanism could not only affect ongoing processes but could also decrease GABAergic cell growth in the right tectum. Indeed, GABAergic neurons become smaller in the right tectum of light-incubated pigeons (Manns & Güntürkün, 2003). The intertectal inhibition possibly constitutes a feedback loop, which preserves asymmetrical light effects within the posthatch period of symmetrical visual input (Manns & Güntürkün, 1999a; Manns, 2006; see figure 5.5). This action

**Figure 5.5**

Schematic model of the GABAergic tectal systems before and after hatch. Before hatch the right tectum is visually deprived. GABAergic neurons of both half brains do not differ in size. Presumably, the inhibitory intertectal interaction is also mostly symmetrically organized. Since this last point was never analyzed, we placed a question mark above the commissures. The asymmetrical light input ignites the development of morphological and physiological asymmetries in the pigeons' visual system. After hatch (lower part of the figure), both sides receive equal amounts of light. However, the asymmetrical changes that started before hatch now established a stronger inhibition from left to right, that secondarily reduces cell sizes of GABAergic neurons in the right tectum.

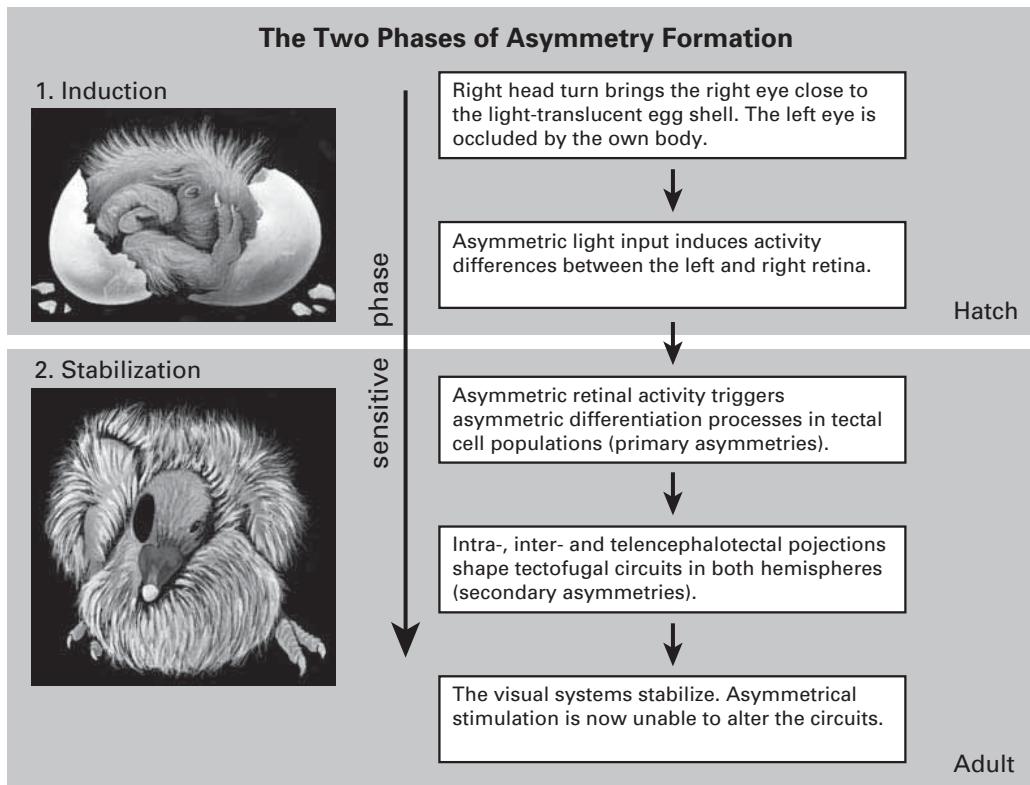
emerges as a secondary consequence of asymmetrical visual input since tectotectal neurons do not receive direct retinal input. The critical role of the tectotectal commissure in controlling asymmetrical interhemispheric processing presumably persists into adulthood (Keysers et al., 2000; Valencia-Alfonso et al., 2009; Manns & Güntürkün, 2009) since commissural transections result in a reversal of behavioral asymmetries (Güntürkün & Böhringer, 1987).

#### **Summary and Implications for the Study of Human Asymmetries**

The development of visual asymmetries in pigeons demonstrates that the establishment of a functional asymmetry can proceed along the same principles of synaptic plasticity that are already well-known from other sensory or motor systems. Avian

visual asymmetry results from an asymmetrical stimulation with light and hence from an epigenetic event during embryonic development (see figure 5.6). Thus, this lateralization is the result of an interaction between an epigenetic event (left-right differences of light stimulation) and a genetic factor (embryonic right turn of the head). Although this critical interaction takes place before hatch, the majority of events during the establishment of visual asymmetry happen after hatch—during a time when light input is symmetrical. Thus, the establishment of a visual asymmetry proceeds in at least two steps: first, the ignition of asymmetry by minute left-right differences of stimulation and, second, the establishment of morphological asymmetries that can take place without a biased input:

1. These developmental steps highlight two projection streams that interact to establish a lateralized functional architecture of the brain (Manns, 2006; Manns & Güntürkün, 2009). Comparable events may have relevance also in the mammalian and thus the human brain. Bottom-up projections: An asymmetrical environmental stimulation is able to induce the formation of structural and physiological left-right differences within the ascending sensory pathways. It is conceivable that such a critical role of a lateralized experience is not confined to sensory systems but also applies to the development of motor asymmetries as in the case of human handedness. For example, the ability of spinally controlled motor asymmetries to influence the cerebral cortex may represent a human corollary to the avian system (Hepper et al., 1991, 1998; Ververs et al., 1994; McCartney & Hepper, 1999). In this case, early spinal asymmetries could act as lateralized “precursors” of asymmetrical cortical motor functions (Hiscock & Kinsbourne, 1995). However, early motor asymmetries could even shape sensorimotor circuits of hand control in a lateralized way. As is the case in birds, humans have an early bias to turn the head to the right (Ververs et al., 1994). This right-turning bias not only persists into adulthood (Güntürkün, 2002) but also correlates with right-handedness (Ocklenburg & Güntürkün, 2009). This relation between head position and hand use could result from a higher probability of visuomotor coupling between gaze position and the right hand during early childhood. To test whether this link is causally related, Ocklenburg et al. (2009) studied children with slight torticollis that caused a subtle pathological tilt of the head to the left or to the right. Indeed, the head tilt had a strong effect on handedness. Thus, early biased sensory input or motor preference could modify lateralized systems of humans along similar pathways as outlined in this chapter for birds.
2. Interhemispheric projections: Unilateral modulations of visual experience affect development of neuronal circuits in both hemispheres. This requires interhemispheric mechanisms, which mediate the balance of left- and right-hemispheric developmental processes. This role is obtained by the mainly inhibitory commissures at brainstem level in the pigeon brain. These systems may also mediate the integration of sensory



**Figure 5.6**

Sequence of events that establish asymmetries in the pigeon's visual system. Two phases are distinguished. During the induction phase, the embryo assumes an asymmetrical position with respect to the egg with the head turned to the right. This brings the right eye close to the translucent shells, while the left eye is covered by the body. The resulting left-right-differences in visual input start the first step of the developing cerebral asymmetry. The second phase starts after hatch, when the young animal perceives light symmetrically. During this period, visual asymmetry is stabilized by the mechanisms listed on the right. The picture shows a ten-day-old pigeon chick with a cap on the right eye. This procedure is able to alter visual asymmetry within the first two weeks after hatch.

input from the left and right sensory half fields in the mature brain and, hence, regulate hemispheric-specific modes of processing (Manns & Güntürkün, 2009). Thus, brainstem or forebrain commissures are possibly critical for the development of cerebral asymmetries in birds and mammals (e.g., Cowell & Denenberg, 2002; Witelson & Nowakowski, 1991).

These systems may have differential developmental patterns, and their heterochronous maturation can cause instable developmental phases, during which functional asymmetries shift. This is shown in the young chicken (Andrew & Watkins, 2002) but is also observable in children that undergo a chaotic phase, during which hand preference swings (McManus, 2002)—exactly as observed by Charles Darwin about 150 years ago.

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### **III Neuroimaging and Hemispheric Asymmetry**



## 6 Structural Indices of Asymmetry

Katrin Amunts

### Brain Asymmetry versus Brain Symmetry

The realization that each of the two cerebral hemispheres is specialized with respect to function—for example, language—immediately raises questions regarding the structural correlates of such lateralization. The first attempts to analyze the underlying anatomical brain asymmetries of language go back to the middle of the nineteenth century (Broca, 1861; Cunningham, 1892; Eberstaller, 1890; Lichtheim, 1885b).

Structural indices of brain asymmetry include (1) macroscopic features such as volume, shape, and size of sulci, gyri, and cerebral lobes; (2) microstructural features such as number and density of nerve cells in a brain region, size, volume, surface, and cortical thickness of cytoarchitectonic areas including cellular indices (e.g., number of spines, degree of arborization of dendrites and axons); and (3) molecular aspects of brain organization and gene expression. Macroscopic features can be observed at brain autopsy or through the use of *in vivo* imaging techniques such as magnetic resonance imaging (MRI) and CT while microstructural analysis usually requires postmortem analyses and histological sections. Molecular aspects of brain organization can be studied both *in vivo* (e.g., receptor positron emission tomography; PET) and *in vitro* (e.g., immunohistochemistry, quantitative receptor autoradiography).

*In vivo* analyses of structural asymmetries have certain advantages. They make behavioral tests and functional imaging experiments possible. In these experiments, psychological paradigms are employed to activate certain brain regions, while anatomical MRI images of the brain can be investigated in parallel. However, the current spatial resolution of MRI images does not allow analyses at the cellular level, and thus the microstructural organization of the brain remains beyond spatial resolution of *in vivo* neuroimaging in most instances. The borders of cortical areas cannot be defined by macroanatomical landmarks, for example gyri and sulci in the vast majority of brain regions. Rather, they vary independently, and as a result, macroanatomical studies often do not enable the unambiguous identification of cytoarchitectonic areas underlying functional lateralization. Histological, postmortem analyses do reach the

cellular level. However, for these analyses, behavioral and psychological data on the same brain are not available (with few exceptions).

These methodical constraints have made the understanding of the interplay of structural and functional aspects of asymmetry in the human brain most challenging, leaving many important questions open. For example, how relevant are structural indices of asymmetry for the interhemispheric functional specialization, and with respect to neurological deficits in the lesioned brain? Do any (or all?) of them constitute the reason (or the result?) of a lateralized brain function? To what extent can structural asymmetry be modulated by extrinsic, environmental factors? Why do some patients develop severe aphasia after lesion of Broca's region whereas others do not, or do so to a lesser degree (Drai & Grodzinsky, 2006; Mohr et al., 1978)? How do structural indices change during ontogeny, aging, differences in the hormonal status, as a result of practice or regular training, or subsequent to brain injury?

An important aspect of brain organization and a confounding factor for the analysis of brain asymmetry is the intersubject variability in brain structure and function. Brains differ considerably with respect to their volume, sulcal pattern, shape, microstructure, and all other parameters and indices, which are potential correlates of functional lateralization. Subtle left-right differences in structural indices may have the same, or even smaller, magnitude than intersubject differences in this region (Amunts et al., 1999).

Finally, is brain symmetry instead of asymmetry the "natural" default mode? Is it appropriate to think about an asymmetrical brain, although major structural (and functional) indices are actually symmetric? Sensory input, for example from the retina, the cochlea, and the skin (pain, mechano-, and thermoreceptors) as well as from proprioceptors, olfactory and gustatory receptors reaches both hemispheres and is processed bilaterally, although parts of the fibers may cross the body or brain side. Handedness and hand preference may be interpreted as just a quantitative phenomenon, resulting in different performance and preference of the hands, rather than as the consequence of an asymmetrical structure of the motor cortex (White et al., 1997). The motor cortex can be identified in both hemispheres using the same cytoarchitectonic or electrophysiological criteria (Brodmann, 1909). Body and brain are strikingly symmetric in many other aspects (Corballis, 2008). Studies have shown that several structural indices do not differ between the hemispheres including brain regions involved in higher cognitive functions. In addition, no functional or cognitive disadvantage has been found in individuals with no lateralization (Hardyck et al., 1976; Toga & Thompson, 2003).

However, deviations from normal asymmetry or symmetry may be related to superior performances. An increased asymmetry of the planum temporale has been associated with perfect pitch in musicians (e.g., Schlaug et al., 1995), whereas more

symmetry in the depths of the central sulcus in professional keyboard players was associated with higher hand performance (Amunts et al., 1997). In addition, more symmetry in connectivity measured as interhemispheric transfer time in musicians has been related to superior performance (Patston et al., 2007). Thus, the functional significance of symmetry or asymmetry has to be addressed separately for each brain region and cannot be generalized.

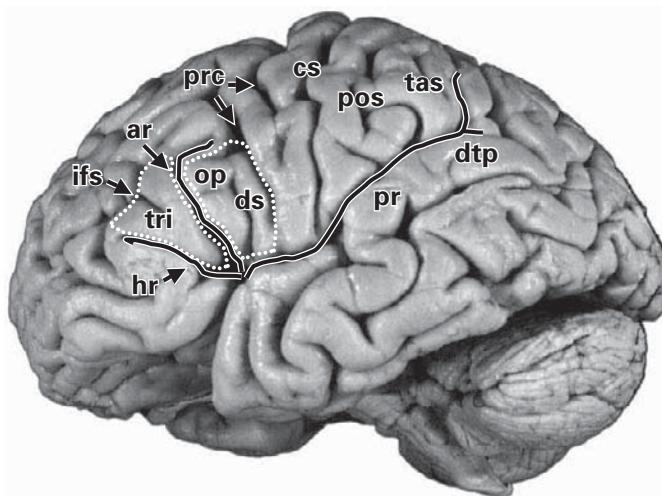
This chapter will discuss structural indices of (a)symmetry from the perspective of functional systems and will review examples of studies analyzing asymmetries observed in perisylvian regions as brain regions involved in language and auditory processing, the sensorimotor system, the limbic system, and brain areas involved in visuospatial processing, as well as analyses covering the whole brain including asymmetries of brain shape and gray matter. The focus will be on healthy human subjects. Recent brain mapping approaches will be considered, which can detect structural asymmetries in large samples, thus enabling researchers to identify even subtle factors modulating asymmetry.

### The Perisylvian Region: Language and Auditory System

Awareness that the brain is lateralized with respect to language goes back to the middle of the nineteenth century, when Broca and his predecessors Dax, Gall, and Bouillard developed the idea that disturbances of speech production result from lesions of the posterior part of the inferior frontal gyrus in the left hemisphere (Finger, 1996). Wernicke and Lichtheim proposed the first process model of language. They emphasized the role of the posterior language region for language comprehension (Wernicke's region) and that of the anterior language region (Broca's region) for language production (Lichtheim, 1885a). The primary auditory cortex, which receives auditory information, occupies the Heschl gyrus, which is located on the dorsal surface of the superior temporal gyurs. All three regions are located in the vicinity of the sylvian fissure. This fissure and its surrounding tissue therefore deserved particular attention with respect to its asymmetry.

### The Sylvian Fissure

This structure can be subdivided into several segments (see figure 6.1)—a stem with two anterior rami (the ascending and horizontal), a posterior ramus (i.e., the segment between the ascending ramus and the terminal ascending segment), a terminal ascending segment, and a descending terminal portion (Ono et al., 1990). Some investigators subdivide the sylvian fissure into a main horizontal segment with anterior and posterior portions, and four branches, that is, anterior ascending, anterior horizontal, posterior ascending, and posterior descending (Jäncke & Steinmetz, 2004; Steinmetz, Fürst, & Freund, 1990; Witelson & Kigar, 1992).



**Figure 6.1**

Morphology of the sylvian fissure. Lateral view of a postmortem brain: ar, ascending ramus; hr, horizontal ramus; pr, posterior ramus; tas, terminal ascending segment; dtp, descending terminal portion of the sylvian fissure; ds, diagonal sulcus; prc, precentral sulcus; cs, central sulcus; pos, postcentral sulcus; ifs, inferior frontal sulcus (Ono et al., 1990). Rami belonging to the sylvian fissure are labeled in black. The terminal ascending segment is sometimes called posterior ascending ramus, the descending terminal portion can also be found as posterior descending ramus, which is less stable than the posterior ascending ramus (Witelson & Kigar, 1992). Tri, pars triangularis and op, pars opercularis of the inferior frontal gyrus; both *paries* constitute the anterior language region, the Broca region.

Eberstaller and Cunningham found interhemispheric differences in the length and angulation of the sylvian fissure, with the left being longer and running more horizontal than the right (Cunningham, 1892; Eberstaller, 1890). CT and MRI enabled the measurement of asymmetries of the sylvian fissure in healthy human subjects and the quantification of differences in sulcal pattern. Although the morphology of the sylvian fissure is highly variable (Ono et al., 1990), two subtypes can be distinguished according to the length of the posterior horizontal portion and the size of the two posterior rami: (1) a subtype with a long horizontal part of the fissure, more frequently found in the left hemisphere, and (2) a subtype with a smaller posterior horizontal part, more frequently found in the right hemisphere (Ide et al., 1996; Jäncke & Steinmetz, 2004; Steinmetz, Rademacher, et al., 1990).

LeMay and Culebras showed that the end of the sylvian fissure was already higher on the right than on the left in fetal brains, indicating that asymmetry of the sylvian fissure already exists at early stages of ontogeny (LeMay & Culebras, 1972). A higher

end in the left than right hemisphere was also found in great apes (Zilles et al., 1996).

Several studies related structural asymmetry of the sylvian fissure to functional aspects of lateralization: Witelson and Kigar found that men with consistent right-hand preference had longer horizontal segments in both hemispheres than men without this preference (Witelson & Kigar, 1992). This study was performed on a sample of brains coming from 67 patients with cancer. Another study associated the length of the sylvian fissure of the right hemisphere with the error rate for detecting briefly presented consonant–vowel–consonant trigrams to the left or right visual half-field (Heillige et al., 1998).

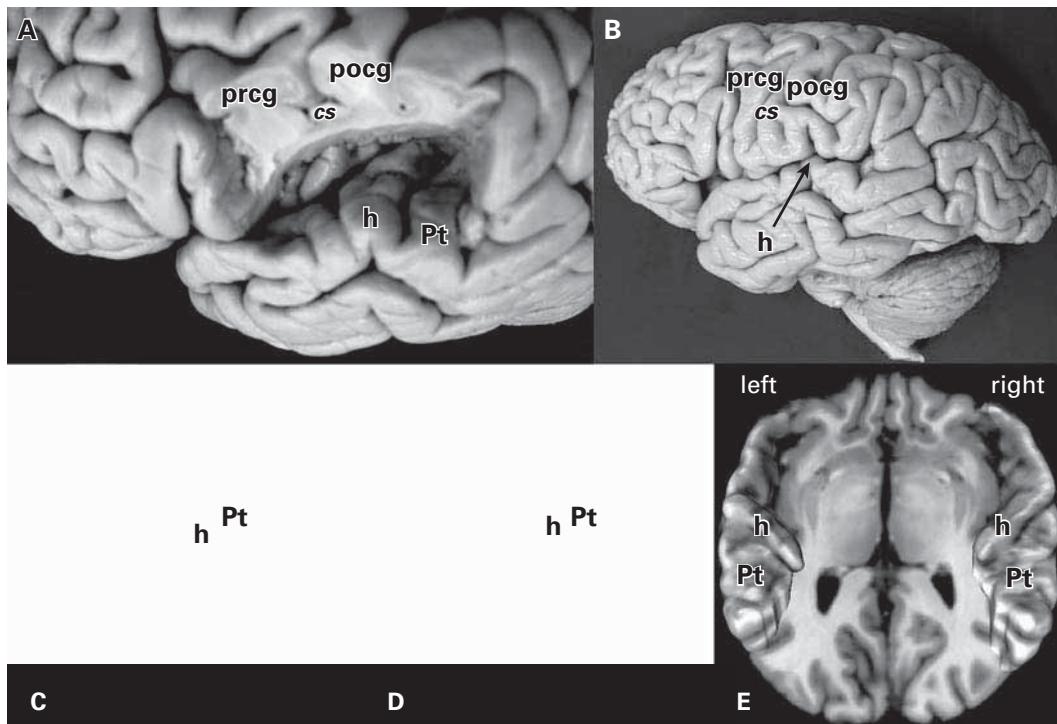
### **Heschl Gyrus and Primary Auditory Cortex**

The Heschl gyrus with the primary auditory cortex was found to be larger in the left than in the right hemisphere (Rademacher et al., 1993), which was interpreted to result from larger amounts of white matter underlying the gyrus (Galaburda & Geschwind, 1981; Penhune et al., 1996). The volume of the primary auditory cortex (area 41; Brodmann, 1909) or area Te1 (Morosan et al., 2001; Rademacher et al., 2001), which occupies the Heschl gyrus, was not found to be asymmetrical (Morosan et al., 2001). The distance between cell columns of multiple areas of the auditory cortex, with exception of primary auditory cortex, was remarkably larger in the left than in the right hemispheres, as demonstrated in Golgi-impregnated sections, suggesting more space for neuropil in the left than in the right hemisphere (Seldon, 1981a; Seldon, 1981b). An *in vivo* MRI morphometry study reported more white substance in the left primary auditory cortex as compared to the right site, whereas the gray matter did not differ significantly (Penhune et al., 1996). As compared to the interhemispheric differences in the planum temporale, these indicators of asymmetry are rather subtle.

### **The Planum Temporale and Superior Temporal Gyrus**

The planum temporale with its continuation to the lateral surface of the superior temporal gyrus, and probably the ventral parts of the angular and supramarginal gyri, is a landmark of Wernicke's region. The planum is located posterior to Heschl's gyrus within auditory cortex (see figure 6.2). Pfeifer (1911) and von Economo and Horn (1930) were among the first to observe that the left planum temporale was often larger than the right. Although the last two studies did not find such asymmetry in apes, later observations seemed to come to different results (for a review, see Chance & Crow, 2007).

Geschwind and Levitzky later put forward a hypothesis about an association between the structural asymmetry of the planum temporale and lateralization of function (Geschwind & Levitsky, 1968). Subsequently, several studies (postmortem and in



**Figure 6.2**

Anatomy of the planum temporale in a postmortem brain (A, B) and in magnetic resonance images of the T1-weighted, single subject template of the MNI (Collins et al., 1994; Evans et al., 1992; Holmes et al., 1998) (C–E). E shows a surface reconstruction of the planum temporale in combination with horizontal sections through the single subject template. h, Heschl gyrus; Pt, planum temporale; prcg, precentral gyrus; pocg, postcentral gyrus; cs, central sulcus.

vivo) revealed a pronounced leftward asymmetry with respect to the length, the area, and the volume of the planum (Geschwind & Levitsky, 1968; Shapleske et al., 1999; Steinmetz, 1996). The hypothesis of Geschwind and Levitzky stimulated studies to directly correlate the asymmetry of the planum temporale with measures of functional asymmetry such as handedness and auditory lateralization (Jäncke & Steinmetz, 1993; Steinmetz et al., 1991; Steinmetz et al., 1995; Steinmetz, 1996). A reduced leftward (but not inverted) asymmetry of the planum temporale was found in healthy left-handers as compared to right-handers (Jäncke & Steinmetz, 2004; Steinmetz, 1996). This result may underlie differences in language dominance between left- and right-handers. Right-handers more often have a strong left-hemispheric dominance than left-handers, who show a right-hemispheric dominance: Approximately 97% of right-

handed subjects show a left-hemispheric dominance for language, while 3% of them demonstrate a right-hemispheric or bilateral representation; this relationship degrades to 70% to 30% in left-handers (Coren, 1992).

The list of studies reporting left-right differences in the morphology of the planum temporale can be extended by microstructural studies of this region. The planum largely corresponds to cytoarchitectonic area 42 (Brodmann, 1909) or TB (von Economo & Koskinas, 1925). One of the first postmortem studies showed that the size of area TB was greater on the left than on the right (von Economo & Horn, 1930). The same was true for area Tpt, which occupies parts of the planum temporale and the superior temporal gyrus (Galaburda et al., 1978). Left and right Tpt also differed with respect to choline acetyltransferase activity, which was higher in the left than in the right hemisphere as shown in a sample of four human brains (Amaducci et al., 1981). Additional interhemispheric differences were found in area 22, more laterally located in the superior temporal gyrus, where clusters of neurons were spaced further apart than corresponding clusters in the right hemisphere; notably, the same parameter of the primary auditory cortex did not reveal interhemispheric differences (Buxhoeveden et al., 2001; Hutsler & Galuske, 2003). Galuske and colleagues have studied the distribution of lipophilic tract tracers to label axons and dendrites on area 22 and reported that the interpatch spacing was greater in the left than in the right hemisphere, whereas the size of the patches appeared to be similar (Galuske et al., 2000; Hutsler & Galuske, 2003). These data extend and supplement an earlier Golgi study of the dendritic structure of the superior temporal gyrus, which showed a slight advantage of the left as compared to the right hemisphere for all dendritic measures in a relatively large sample of 20 postmortem brains (Jacobs, Schall, & Scheibel, 1993).

The asymmetry of the planum temporale is not a constant throughout life but can be modulated by environmental and/or genetic factors. A morphometric study has analyzed the planum temporale in a sample of professional musicians and controls (Schlaug et al., 1995). The asymmetry in the size of the planum temporale was estimated by measuring the curved length of the planum in MRI sections. The size of the planum was compared between musicians with perfect pitch (those who may identify or sing any musical tone without any reference tone), those without perfect pitch, and nonmusician controls. It was found that the musicians with perfect pitch had an asymmetry that was twice as great as in nonmusicians and musicians without perfect pitch. The increased asymmetry was related to a smaller right (rather than larger left) planum temporale in the musicians with perfect pitch as compared to musicians without perfect pitch and controls (Keenan et al., 2001). Thus, exaggerated asymmetry of the planum temporale was associated with increased abilities to process certain auditory information.

In contrast, reduced asymmetry of the cortical surface area of the planum temporale was reported in brains of patients with schizophrenia (Chance et al., 2008).

Structural asymmetries may change during normal aging as well—a study employing voxel-based morphometry identified areas of relative accelerated loss of gray matter concentration in the left planum temporale (not in the right); Heschl's gyri, in contrast, showed a symmetric loss (Good et al., 2001).

Interhemispheric asymmetries, with the left planum being larger than the right, were recognizable by 31 weeks of gestation, as shown in a postmortem study with a sample of 207 fetal brains (Chi et al., 1977). Combined genetic–MRI studies suggest that heredity plays a central role in shaping the perisylvian cortex; gray matter volumes seem to be highly heritable (Posthuma et al., 2002; Thompson et al., 2001) whereas gyral and sulcal patterns appear much less heritable (Lohmann et al., 2008).

### **Broca's Region**

Areas 44 and 45 are key regions of the anterior language region, Broca's region. They occupy the pars opercularis and pars triangularis, respectively (see figure 6.1). The volumes of left area 44 were greater than those of the right hemisphere as shown in two postmortem studies (Amunts et al., 1999; Galaburda, 1980). The volumes of area 45 did not differ significantly between the hemispheres (Amunts et al., 1999), although for six of the ten subjects (including all females), the volume of area 45 was greater in the left hemisphere than the right (Amunts et al., 1999; Uylings et al., 2006). Both areas, 44 and 45, were asymmetrical with respect to the laminar distribution of cell bodies, that is, cytoarchitecture as estimated by multivariate analysis of cytoarchitectonic features, collected from serial histological sections through both areas (Amunts & Zilles, 2001). Additional differences between left and right areas 45 were found in the size of pyramidal cells in layer III, which were larger in the left than in the right hemisphere (Hayes & Lewis, 1996). A significant leftward asymmetry has been found in the total neuron number in area 44 of males (Uylings et al., 2006). Although the total number of neurons in left area 45 was larger in all five female subjects, this asymmetry did not reach significance. In the male subjects, no significant asymmetry difference in total neuron number was found in area 45 either (Uylings et al., 2006).

Interestingly, significant interhemispheric differences in cytoarchitecture are already present in 1-year-old infants (Amunts et al., 2003). Asymmetry tends to increase with age, which is significant for area 45 but not for area 44. An adult-like, left-larger-than-right asymmetry in the volume fraction of cell bodies was reached at an age of approximately 5 years in area 45, and 11 years in area 44. The authors discussed whether and how far this rather late maturation, when compared to that of motor cortex, is the microstructural basis for the development of language abilities and the influence of language practice on cytoarchitecture during childhood. The results supplement earlier data on interhemispheric asymmetry on a cellular level (Hayes & Lewis, 1995; Jacobs, Batal, et al., 1993). Assuming that area 44 is more involved in

syntactic processes and area 45 more involved in semantic processes, the data on the developmental aspects of interhemispheric asymmetry fit with behavioral findings showing that adult-like syntactic processes are observable only around the age of 10 years, whereas adult-like semantic processes are established much earlier (Friederici & Kotz, 2003).

Cytoarchitectonic mapping of areas 44 and 45 revealed a considerable intersubject variability of the extent of both areas, and the location of their borders with respect to surrounding sulci and gyri (Amunts et al., 1999). This variability is additive to intersubject variability in the sulcal pattern (Keller et al., 2007; Ono et al., 1990; Tomaiuolo et al., 1999). Intersubject variability in the anatomy of this region combined with the loose association of cytoarchitectonic borders with sulcal landmarks may contribute to the conflicting results of macroscopical indices of brain asymmetry of this region. Wada and colleagues measured the surface of the pars opercularis and the posterior portion of the pars triangularis in 100 adult and 100 infant postmortem brains (Wada et al., 1975). They reported a rightward asymmetry of this region, particularly in the adults. However, the authors were aware that consideration of the intrasulcal portion may yield different results. They noted that "We suspect that, in spite of our measurement, the total cortical surface area of the operculum could be larger on the left in most brains" (Wada et al., 1975, p. 245). The consideration of the surface, and not the deep portion of the cortex, represents a serious limitation when one considers that about two thirds of the cortex is buried in the depths of the sulci (Zilles et al., 1988). Falzi et al. analyzed the asymmetry of the pars opercularis and pars triangularis and determined the area on the lateral convexity and the full intrasulcal area (Falzi et al., 1982). They did not find an asymmetry for the surface of the gyrus but did find a significant leftward asymmetry for the intrasulcal anatomy of the gyrus. A similar (leftward) asymmetry was found in the pars triangularis (Albanese et al., 1989; Foundas et al., 1995). Another morphometric study reported that the entire inferior frontal gyrus was not asymmetrical (Harasty et al., 1997). Statistically significant leftward asymmetry in the volume of the pars opercularis has been reported in an MRI study (Keller et al., 2007). Another study found a significant leftward volume asymmetry of the pars opercularis in right-handed subjects, and a rightward asymmetry in left-handers (Foundas et al., 1998), which was not revealed in an earlier study of this group (Foundas et al., 1995). Nine of ten patients who had undergone selective hemispheric anesthesia to determine language lateralization showed a leftward asymmetry of the pars triangularis (Foundas et al., 1996). Other studies did not reveal a significant leftward asymmetry in volume, surface area, or cortical thickness of the pars opercularis (Good et al., 2001). For a review of asymmetry in Broca's region, see Keller et al. (2009).

Interhemispheric differences in the inferior frontal cortex are supplemented by white matter asymmetries. The uncinate fascicle, a major fiber tract that is assumed

to connect the inferior frontal cortex with anterior temporal cortex, was asymmetrical in brains of both males and females; it was 27% larger and contained 33% more fibers in the right than in the left hemisphere (Highley et al., 2002).

It has to be noted, however, that intersubject variability of interhemispheric differences may be considerable, both with respect to the degree and the direction of asymmetry (Amunts et al., 1999; Amunts et al., 2003; Galaburda, 1980; Galaburda et al., 1987). Moreover, certain changes in structural asymmetry are related to neurological and psychiatric diseases. As discussed before, the planum temporale was shown to be more asymmetrical in musicians with an absolute pitch—that is, with a higher performance—than in musicians without absolute pitch and controls (Schlaug et al., 1995). Does this mean that higher structural asymmetry is, in general, superior as compared to more symmetry? This is not the case as illustrated in a cytoarchitectonic study. Histological sections through areas 44 and 45 of the brain of a language genius, who knew more than 60 languages, were compared with those from 11 control brains (Amunts et al., 2004). Multivariate analysis of cytoarchitectonic features was employed to quantify left-right differences in all brains. Area 44 was more asymmetrical than any other of the control brains, whereas area 45 was more symmetrical than any other brain. That is, asymmetry was extreme in this particular brain, and it was different with respect to the direction in the two neighboring areas. Therefore, altered levels of asymmetry may accompany superior performance, but the direction of this alteration, that is, more asymmetry, or more symmetry, depends on the context. Higher asymmetry (or symmetry) per se is not an indicator of a modified-improved function.

### Somatosensory and Motor Regions

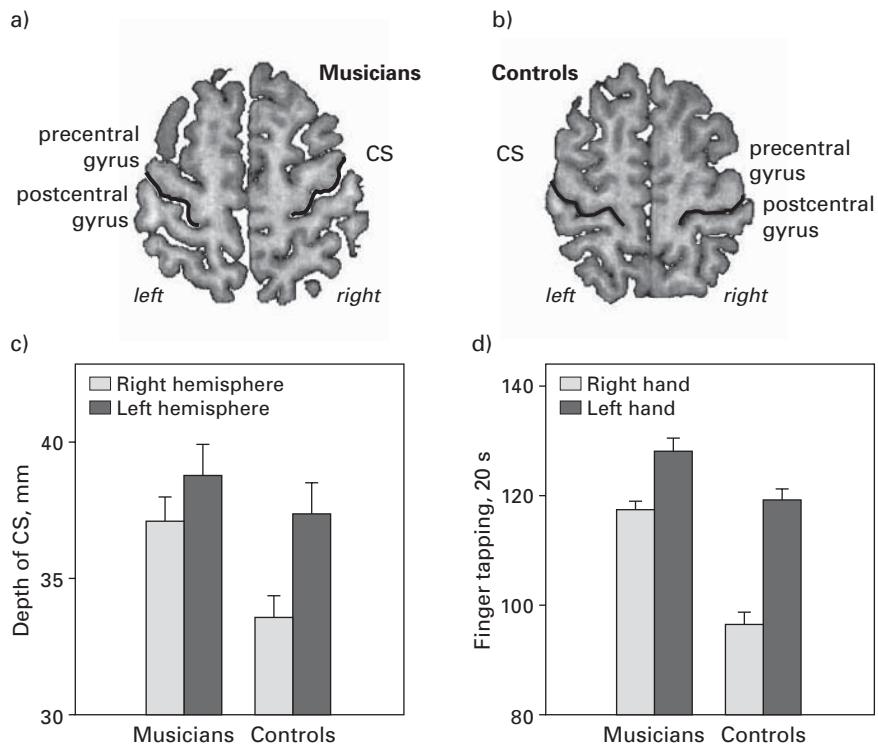
Interhemispheric asymmetry has been found in several components of the motor and sensory systems—for example, the caudate nucleus (Watkins et al., 2001), the cerebellum (Snyder et al., 1995), and the sensory and motor cortices. The central sulcus has frequently been the focus of attention as a potential anatomical correlate of handedness. About 90% of humans are right-handed, preferring the right hand for skilled and unskilled activities; the remaining 10% are left-handed (Gilbert & Wysocki, 1992). A major part of the population is mixed-handed (Annett, 1994), favoring the right hand for some actions and the left hand for others. The proportion of consistent right-handed, mixed-handed, and left-handed subjects is approximately 64%, 33%, and 4%, respectively (Annett, 1996). The left motor cortex controls the right hand, and right motor cortex, the left hand. Fibers originating in the primary motor cortex cross the midline in the brainstem at the level of the pyramids. Primary motor cortex occupies the precentral gyrus—the anterior wall of the central sulcus up to the postcentral gyrus, where somatosensory cortex is located. In light of this strong correspondence between macroanatomy and microstructure, many researchers have been attracted to

the central sulcus, as it enables the study of interhemispheric differences in the somatosensory and motor systems. It was hypothesized that the preferred hand has a larger cortical region at its disposal than the nonpreferred hand and that this functional anatomy is reflected in the shape of the central sulcus.

However, investigations of asymmetries in the central sulcus obtained different results. Although some researchers reported that the central sulcus was deeper and larger in the right hemisphere than in the left in both males and females (Davatzikos & Bryan, 2002), others found a deeper central sulcus in the left, dominant hemisphere in right-handers. For example, the depth of the central sulcus was measured in horizontal MRI sections of right-handed males (Amunts et al., 1996). The leftward asymmetry was most pronounced in the most dorsal portion of the sections (see figure 6.3). The direction of asymmetry tended to be inverse in consistent left-handers and had an intermediate position in mixed-handed males; the effect was found in males, not in females (Amunts, Jäncke, et al., 2000). Similar data were provided by White et al. in a sample of postmortem brains with unknown handedness (White et al., 1994). A later study of the same group, however, reported symmetry instead of asymmetry in central sulcus depth (White et al., 1997). The above-mentioned studies differ with respect to age distribution, methods, and parameters applied to estimate central sulcus (a)symmetry, as well as regarding the samples used. Sample composition may play a role in the estimation of intersubject variability in the anatomy of the central sulcus (Cykowski et al., 2008; Fesl et al., 2003; Ono et al., 1990). Taken together, such differences may explain the above-mentioned inconsistencies.

Studies of the underlying white matter have also reached different results—White et al. reported that the pyramidal tract seemed to be symmetrical (White et al., 1997), while an earlier study found priority for pyramidal tract fibers coming from the left hemisphere (Yakovlev & Rakic, 1966). Nathan and colleagues reported asymmetry in the size of the lateral and anterior corticospinal tract (Nathan et al., 1990). They found that the right corticospinal tract was larger, which is consistent with the size left-larger-than-right difference in cortex. The anterior corticospinal tract was larger on the right side. It is largely uncrossed, which suggests that the originating cortex is larger on the right than on the left side.

Results from a series of recent studies support the existence of structural leftward asymmetry in the region around the central sulcus: Leftward asymmetry was found in the lower central and precentral sulci in right-handed subjects, through voxel-based morphometry (Hervé et al., 2006). Another study of the central sulcus (Cykowski et al., 2008) applied a novel method combining automated sulcus reconstruction, surface parameterization, and an observer-independent depth measurement. The asymmetry in males was maximal in the more dorsally located regions, in accordance with the studies of Amunts et al. (1996; Amunts, Jäncke, et al., 2000). It can be hypothesized that this asymmetry results from increase in connectivity of left-hemispheric neural



**Figure 6.3**

Comparison of the depth of the central sulcus (CS) in musicians (keyboard players and nonmusician controls). The depths of the CS, that is, the intrasulcal length of the posterior bank of the precentral gyrus, was measured in horizontal sections from  $z = 69$  to  $z = 35$  (Talairach & Tournoux, 1988) in both hemispheres (Amunts et al., 1997). MRI data sets of 21 professional musicians (keyboard players) and 30 controls (all males) were analyzed. The depth of the CS is labeled on two exemplary sections from an MRI data set of a brain of a musician (a) and a control brain (b) at  $z = 54$ . The motor cortex is located at the precentral gyrus; the somatosensory cortex is located at the postcentral gyrus. The analyses revealed that asymmetry in CS depths was maximal in the dorsal portion of horizontal sections ( $z = 65$  to  $z = 54$ ). (c) This region was further analyzed using an analysis of variance. The comparison of left and right depths of the CS showed a higher degree of symmetry in musicians than in controls. The right CS was significantly deeper in musicians than in controls, while there was no significant between-groups difference in this measure for the left hemisphere. That is, greater symmetry of CS depths in musicians was mainly due to deeper CS in the hemisphere controlling the nondominant, left hand. This result cannot be explained by a simple scaling effect, since absolute brain volumes did not show a significant difference:  $1,500 \text{ cm}^3$  ( $SD = 89$ ) for musicians versus  $1,517 \text{ cm}^3$  ( $SD = 129$ ) for right-handed controls ( $p > .05$ ). The tapping scores as a measure of hand performance show a similar pattern of asymmetry. (d) Results of the statistical analysis of the tapping test, which was performed for 20 seconds. Less anatomical asymmetry with deeper sulci in musicians was accompanied by less asymmetrical and superior hand performance in musicians. The reduced hand skill asymmetry in musicians was due to superior performance of the nondominant hand. Tapping data thus paralleled those of CS depths. Furthermore, significant correlations were found between the sulcal depths and the time at which musical training had begun—the earlier the training started, the deeper the right and left sulcus.

circuits and/or in cortex dedicated to the coordination of the dominant limb, which coincides with the left-larger-than-right asymmetry of neuropil in the left hemisphere of a postmortem sample (Amunts et al., 1996). These data are discussed in the context of more and/or larger dendritic and axonal surfaces and, thus, of increased volume compartment for intracortical connections in the hemisphere contralateral to the preferred hand (Amunts et al., 1996). Further support comes from a recent study (Luders et al., 2006) that shows that cortical thickness in the left superior precentral gyrus is up to 15% greater than the right-sided homologue in 60 right-handed individuals.

The study of Cykowski et al. (2008) also revealed a significant correlation between the degree of asymmetry in the depth of the central sulcus and age (age range 21–89 years). Interestingly, no similar correlation was found for the female subgroup, which further supports the notion about gender differences during development and aging. Extrinsic and/or intrinsic factors may underlie this focal leftward asymmetry near the somatotopic distribution of the proximal upper limb in male subjects.

An *in vivo* MRI morphometry study found that right-handed male professional keyboard players reveal less asymmetry (i.e., more symmetry) in the central sulcus than do matched controls (Amunts et al., 1997). This finding was interpreted as emanating from lifelong bimanual coordination in the male musician group in terms of “training-induced plasticity.” Similar to the correlation of sulcal asymmetry and age in males (Cykowski et al., 2008), the loss of regional leftward asymmetry was especially notable in the superior extent of the somatotopic upper limb representation. Furthermore, the depth of the central sulcus in keyboard players was negatively correlated with the age at which the musicians began bimanual training (Amunts et al., 1997). This convergence of findings suggests that the anatomy of the central sulcus and its asymmetry, at least in its superior extent of the male brains, are part of a lifelong remodeling process of the sulcus.

### **The Limbic System**

Indices of brain asymmetry have been reported with respect to different structures, for example, the hippocampus, the cingulate gyrus, the amygdala, and the habenula. These structures received particular attention in studies analyzing the biological underpinnings of neurological and psychiatric diseases, since several of these (schizophrenia, autism, corticobasal degeneration, etc.) are accompanied by changes in asymmetry (for reviews, see Shenton et al., 2001). Many of the patient-control studies investigating structural asymmetry employed MRI in combination with *in vivo* brain morphometry.

#### **Hippocampus and Amygdala**

Several studies have analyzed the asymmetry of the hippocampus with respect to volume and surface. For example, rightward asymmetry was found in an MRI data set

of 61 healthy volunteers (ages 6–82). After normalizing intersubject variation in head size, no statistically significant differences were found among different age and gender groups (Li et al., 2007). Some studies support the notion of a rightward asymmetry in hippocampal and amygdalar volume (Niemann et al., 2000; Szabo et al., 2001), whereas others do not (Bhatia et al., 1993). As well, a study based on a deformable hippocampal model and principal-components analysis reported a leftward asymmetry in volume in healthy controls (Kim et al., 2005), while another study found no significant interhemispheric differences (Narr et al., 2004).

Methodical constraints pertaining to spatial resolution may be a factor underlying such contradictory results. The hippocampus is not easy to distinguish from neighboring structures, for example, the amygdala (Shenton et al., 2001). Substructures of the hippocampus such as different parts of the cornu ammonis and the subiculum cannot be distinguished in routine MRI scans with 1-mm isotropic resolution. This difficulty may result in the inclusion of different portions of the hippocampus into morphometry. The anterior and posterior borders do not appear precisely enough in routine MRI images of 1-mm resolution, and formal criteria for the definition of the hippocampus (e.g., “beneath the amygdala as the anterior recess of the temporal horn ascended laterally”; Szabo et al., 2001, p. 2454) are not uniform across *in vivo* MRI studies and differ with respect to the true border as seen in histological sections. If, for example, the extent of the fascia dentata is taken as an indicator of the rostral border, the rostral extent would be underestimated by several millimeters (Amunts et al., 2005). Only a few studies have analyzed hippocampal volume in histological sections, where its different parts can clearly be separated and the borders defined unambiguously. One of them has measured the volume of the hippocampus in histological sections of ten postmortem brains; volumetric differences between the hemispheres did not reach significance, although there was a tendency of a left-larger-than-right asymmetry (Amunts et al., 2005). This is consistent with an earlier postmortem observation (Duvernoy & Bourgouin, 1998).

Experiments that investigate temporal changes of hippocampal asymmetry in healthy controls have shown that it tends to decrease over time; this pattern is distinct from the one in Alzheimer disease, where asymmetry tends to increase over time (Shi et al., 2007). That is, different age distributions in the above-mentioned studies may alter the results on volumetric asymmetry and contribute to the divergence of results as well. An interaction of age and asymmetry has also been found in other brain regions, for example, the anterior insula, anterior cingulate cortex (Kovalev et al., 2003). Handedness seems to be a factor modulating interhemispheric asymmetry with left-handers showing no significant asymmetry with respect to hippocampal and amygdalar volumes (Szabo et al., 2001).

Asymmetry has also been investigated with respect to the molecular organization of the brain and limbic structures, in particular. No interhemispheric difference was

found in the serotonergic 5-HT<sub>1A</sub> receptor binding in the hippocampus, amygdala, and insula in a receptor PET study of 34 healthy subjects (Fink et al., 2009). In contrast, asymmetries in different muscarinic receptor binding sites of acetylcholine were investigated in the hippocampus of female rats by *in vitro* autoradiography. Binding of different radioligands was higher on the right than the left side of CA1, CA3, and dentate gyrus in almost every brain, confirming hemispheric asymmetry at the neurochemical level (Wolff et al., 2008).

### Cingulate Cortex

The cingulate cortex also shows signs of interhemispheric asymmetry. In a recent study, T1-weighted MRI scans were collected in 68 healthy subjects and a group of patients with schizophrenia (Wang et al., 2007). The volume, surface area, and thickness of the cortical mantle were assessed within the anterior and posterior segments of the cingulate gyrus, excluding the paracingulate gyrus, and related to measures of psychopathology and illness duration. Across both groups, there was significant leftward asymmetry in the thickness of the anterior segment and significant leftward asymmetry in the surface area of the posterior segment (Wang et al., 2007). Another study analyzed the surface area of an anterior and a posterior cingulate region; a rightward asymmetry was reported for the anterior cingulate region, which was more frequently found in females than in males (Pujol et al., 2002). The posterior cingulate region did not differ between the hemispheres. Subjects with a larger right anterior region described themselves as experiencing greater worry about possible problems, fearfulness in the face of uncertainty, shyness with strangers, and fatigability. Thus, differences in asymmetry of the anterior cingulate region seem to correspond with the behavioral style, that is, temperamental disposition to fear and anticipatory worry in males and in females.

Intersubject variability in the location of the cingulate and paracingulate sulci was analyzed in a large sample of MRI scans of 247 healthy young subjects (Paus et al., 1996). The paracingulate sulcus was found more frequently in the left than in the right hemisphere (Paus et al., 1996). This feature was discussed in the context of the participation of the left anterior cingulate cortex in language processing. A subsequent functional MRI experiment showed that the activation during a word generation task rarely extended into the cingulate sulcus when a prominent paracingulate sulcus was present; it reached into the cingulate if no paracingulate was present (Crosson et al., 1999). Using optimized voxel-based morphometry (VBM), the presence and extension of the paracingulate sulcus was quantified in male and female left- and right-handers, considering that handedness can be a factor influencing sulcal asymmetry. The sulcus occurred more often and was more pronounced in the left than in the right anterior cingulate region, although hemispheric differences were less pronounced in male left- and female right-handers. The authors argue that the discrepancies between groups

seem to stem from variations of cingulate morphology in the left rather than the right hemisphere (Huster et al., 2007).

### Prefrontal Cortex

Evidence has been provided that asymmetry of the prefrontal cortex is associated with affective behavior and dysbehavior. Its relationship with aspects of the adolescents' brain structure was investigated in a sample of 137 early adolescents (Whittle et al., 2008). Affective behavior was assessed during observations of parent–child interactions. The authors found male-specific associations between the volume of prefrontal structures and affective behavior, with decreased leftward anterior paralimbic cortex volume asymmetry associated with increased duration of aggressive behavior, and decreased leftward orbitofrontal cortex volume asymmetry associated with increased reciprocity of dysphoric behavior (Whittle et al., 2008).

Further evidence with respect to interhemispheric differences of prefrontal cortex was obtained in a postmortem study. The neuronal density, size, and shape was analyzed in Brodmann's areas 9 and 10 in ten brains of patients with schizophrenia and ten control brains (Cullen et al., 2006). The left hemispheres showed a larger density of neurons in the left as compared to the right hemisphere, whereas the schizophrenia patients' brains showed the reversed pattern; pyramidal neurons of layer III were larger on the left and more spherical than the right side in controls' brains, whereas such parameters did not differ between each other in brains of patients with schizophrenia (Cullen et al., 2006).

### Brain Areas Involved in Visuospatial Processing

Gender differences in the hemispheric specialization of several visual and spatial processes have recently been shown. For example, about one third of the population is left-eye dominant, preferring to use the left eye rather than the right one for monocular tasks (Bourassa et al., 1996; McManus et al., 1999). Later studies tested whether and which parts of the visual system are asymmetrical on a structural level and how this asymmetry is related to visuospatial function.

### Occipital Cortex

Hasnain and colleagues (2006) analyzed the spatial covariance between human occipital sulci and functionally defined visual areas, defined through retinotopic mapping. Sulcus–function covariance was stronger in the left occipital lobe than in the right occipital lobe. The left calcarine fissure demonstrated strong covariance with functional areas in both hemispheres, suggesting that it serves as a developmental “anchor” for functional areas in the occipital cortex. These findings support the hypothesis that the degree of hemispheric lateralization of function is reflected in the strength of correspondence between cortical surface anatomy and function (Hasnain et al., 2006).

A recent cytoarchitectonic study analyzed volumes and cortical thickness of area 17 (striate cortex), area 18 (Amunts, Malikovic, et al., 2000), and the cytoarchitectonic correlate (area hOc5) of human V5/MT (Malikovic et al., 2007) in a postmortem sample of 5 male and 5 female brains (Amunts et al., 2007). Genders differed in the interhemispheric asymmetry of hOc5 volumes, and in the right-hemispheric volumetric ratio of hOc5 to area 17, an area that projects to hOc5/V5/MT+. The volumetric asymmetry was accompanied by asymmetry in the surface area of hOc5, but not in its cortical thickness. Males therefore seem to have a potential for more space in which to process additional information, a finding consistent with superior male processing in particular visuospatial tasks, such as mental rotation. Gender differences in hOc5 exist without any differences in volume fractions of cell bodies, implying that, overall, the visual neural circuitry is similar in males and females.

Volumetric analyses in a sample of postmortem fetal brains in the Yakovlev Collection showed that male striate-extrastriate cortices were far more asymmetrical than they were in female brains (de Lacoste et al., 1991). Another study revealed a significant right-larger-than-left volumetric asymmetry of the human striate cortex but failed to demonstrate a significant gender difference (Murphy et al., 1996).

### Parietal Cortex

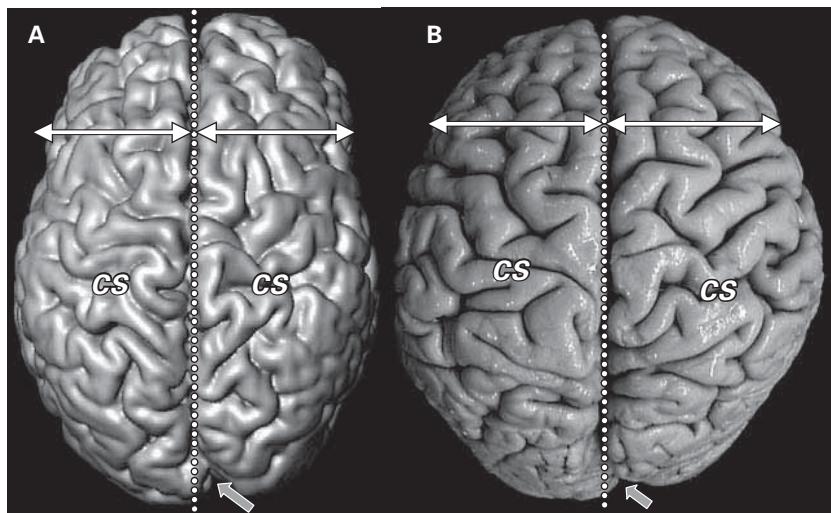
The posterior wall of the ascending ramus of the sylvian fissure, the planum parietale, would be a structural marker of the lateralization of visuospatial functions to the right hemisphere (Jäncke et al., 1994). This conclusion was reached on the basis of measurements of planum parietale in MRI images in a sample of 106 right-handers and 35 left-handers. Cytoarchitectonically, this region encompasses Brodmann area 40 (i.e., PFop, PFt, PF, PFm, and PFcm; Caspers et al., 2006) and parts of area 39 (PGa and PGp according to Caspers et al., 2006). Cytoarchitectonic asymmetry has been described only for area PEG, located in the intraparietal sulcus and, to a lesser extent, at the angular gyrus (Eidelberg & Galaburda, 1984). Areas PGa and PGp, also located at the angular gyrus and corresponding approximately to Brodmann area 39, approached a rightward asymmetry in volume both in female and male postmortem brains; this difference, however, did not reach significance (Caspers et al., 2008). A volumetric asymmetry of the more anteriorly located areas corresponding to area 40 of Brodmann of the PF group as defined by Caspers et al. has not been found in either of the two cytoarchitectonic studies.

### Whole Brain Indices of Asymmetry

Numerous structural MRI and CT studies have reported whole brain indices of asymmetries. Among the first prominent observations were right frontal and occipital petalias, or protrusions of the surface of one hemisphere relative to the other. Using CT, it was shown that the left occipital pole is frequently wider and protrudes further

posteriorly than the right whereas the right frontal cortex often measures wider than the left (LeMay & Kido, 1978). This pattern is characteristic for male right-handers (Kertesz et al., 1990; LeMay & Kido, 1978). More recent methods of analysis of brain shape, for example, deformation based asymmetry introduced by Lancaster and colleagues, enable researchers to analyze the petalias in more detail and to quantify their extent (Good et al., 2001; Hervé et al., 2006; Lancaster et al., 2003; Watkins et al., 2001). Petalias as impressions on the inner skull represent a negative of the outer shape of the brain. Asymmetries like these can also be found in nonhuman primates as demonstrated in endocasts (Zilles et al., 1996). They suggest, therefore, a phylogenetic origin of lateralization.

The Yakovlevian (anticlockwise) torque of the brain includes the above-described features and the frequent extension of the left occipital lobe across the midline to the right site (see figure 6.4). This torque has practical consequences for imaging studies, which often align brains into some reference space. For example, the Talairach space and the reference space of the MNI (Montreal Neurological Institute) are organized in such a way that positions in the left hemisphere are indicated by negative



**Figure 6.4**

Yakovlevian (anticlockwise) torque of the brain (Kertesz et al., 1990; LeMay & Kido, 1978). (A) Dorsal view of a three-dimensional-reconstructed human brain—the left occipital pole protrudes across the midline (dotted line) to the right site (gray arrows). The right frontal cortex measures wider (white arrows) than the left (lengths of right and left white arrows are similar). (B) Post-mortem brain with the typical protrusion of the occipital pole but without a rightward asymmetry of the frontal lobe. CS, central sulcus.

*x*-coordinates, whereas those of the right hemisphere are indicated by positive *x*-coordinates (Evans et al., 1992; Talairach & Tournoux, 1988). Because of the Yakovlevian torque, parts of the left occipital lobe and their activation may appear in the space of the right hemisphere (Amunts, Malikovic, et al., 2000).

Chance and colleagues distinguish two components of brain torque—(1) a horizontal shift of one hemisphere with respect to the other (the greater asymmetrical protrusion of one hemisphere beyond the other) and (2) a differential distribution of tissue within each hemisphere along the anteroposterior axis (“volume torque”; Chance et al., 2005). Crow has proposed a four-quadrant model of the brain that takes as its inspiration the macroscopic asymmetry of the (human) cerebral hemispheres in order to model language (Chance & Crow, 2007; Crow, 2000).

Sulcal comparisons across a sample of MRI data sets of 19 pairs of monozygotic twins suggested that the left posterior lateral hemispheric surface may be the least variable brain region. Posterior sulci were defined as those sulci which were located posterior to the central sulcus. Methodologically, these results were obtained by the representation of sulci as three-dimensional polygonal lines, which are extracted automatically from MRI data sets (Lohmann et al., 1999).

Analyses of asymmetry in large populations have become feasible with the development of brain atlases (Mazziotta et al., 1995; Toga et al., 2006), tools for registration of individual MRI data sets to a common reference space, and tools for automated analysis of volume of tissue compartments, surface, and cortical thickness within this space (Ashburner & Friston, 2000; Gaser et al., 1999; Lancaster et al., 2003; Lerch et al., 2006; Lohmann & von Cramon, 2000; Luders et al., 2006; Narr et al., 2007; Pieperhoff et al., 2008; Thompson et al., 1998; van Essen et al., 2001). Automated analysis of the whole brain supplements studies that are based on manual segmentation. One of its advantages is the possibility to consider large cohorts and thus identify factors such as age, gender, hormonal effects, environmental factors including functional adaptation, disease modulating brain asymmetry, and combinations thereof. Another aspect is that no a priori definition of a region of interest is necessary.

Luders and coworkers analyzed gray matter asymmetries in a sample of 60 male and female professional musicians with and without absolute pitch using VBM (Luders et al., 2004). They found that male musicians with absolute pitch were more leftward lateralized in the anterior region of the planum temporale than male non-absolute-pitch musicians, which was in agreement with an earlier study based on a region-of-interest approach (Schlaug et al., 1995). A second confirmation of an earlier study based on manual delineation of the central sulcus was the finding of significantly increased leftward asymmetry in males in a region posterior to the central sulcus as compared to females (Amunts, Jäncke, et al., 2000). In addition, rightward gray matter asymmetries in the frontal and prefrontal cortex and parts of the temporal

lobes were found in the musician sample which were not previously detected (Luders et al., 2004).

In addition to the above-mentioned studies investigating aspects of macro- and microstructural organization of interhemispheric asymmetry, it has been found that molecular organization differs between the hemispheres as well. One of the transmitters for which differences in the binding between the hemispheres have been demonstrated is serotonin. A PET study was performed, and the concentration of binding of the 5-HT<sub>1A</sub> receptor in 34 right-handed males and females was measured in 14 auditory, language, and limbic areas (Fink et al., 2009). Higher binding in the right hemisphere was found in the superior and middle frontal gyri, the triangular and orbital parts of the inferior frontal gyrus, the supramarginal gyrus, the superior gyrus of the temporal pole, and the middle temporal gyrus. Heschl's gyrus, the superior temporal gyrus, and the Rolandic operculum showed significantly higher receptor binding in the left hemisphere. The data suggested that the asymmetrical receptor binding differed between genders in the triangular part of the inferior frontal gyrus (Fink et al., 2009), a region that is involved in language processing and that shows both microstructural and macrostructural interhemispheric differences, interacting with gender (see the section on Broca's region). This study is one example of many studies that demonstrate interhemispheric asymmetry in the distribution of receptors or their subunits of transmitter receptors, for example, glutamate (Shinohara et al., 2008), dopamine (Cannon et al., 2008; Vernaleken et al., 2008), and acetylcholine (Wolff et al., 2008).

## Conclusions

In summary, we can say the following with respect to structural indices of asymmetry:

- Structural asymmetry can be found in language and motor areas, as well as in many (all?) other brain regions (e.g., visual cortex, parietal cortex, hippocampus).
- The degree of asymmetry differs with respect to brain region, handedness, gender, and disease.
- Asymmetry interferes with extrinsic and genetic factors, and it changes during development and aging.
- Asymmetry develops in early stages of evolution and during ontogeny.
- Anatomical asymmetry and lateralization interact.

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## 7 Asymmetry of White Matter Pathways

Marco Catani, Stephanie Forkel, and Michel Thiebaut de Schotten

Here are eight instances in which the lesion was in the posterior third of the third frontal convolution. This number seems to me to be sufficient to give strong presumptions. And the most remarkable thing is that in all the patients the lesion was on the left side. I do not dare draw conclusions from this.

—Paul Broca (1863)

With these words, from a short report of a series of patients with acquired speech deficits, begins the modern period of the study of cerebral asymmetry. Despite Broca's reticence to draw any conclusion from his clinical-anatomical observation, his words clearly allude to a concept that has stood the test of time: the asymmetrical distribution of functions in the human brain. In later writings, Broca not only vehemently defended his idea of left lateralization of speech but initiated the discussion on the anatomical correlates of cerebral dominance (Finger, 1994). This became an intensely growing field of research where anatomists focused their attention on either macroscopic (e.g., volume of gyri) or microscopic (e.g., cytoarchitectonic) differences between the two hemispheres. However, a handful of researchers faithful to their belief on the importance of brain connections have tried to explain cerebral dominance in terms of white matter asymmetry. Their efforts have often been limited to mere speculation, for the availability of reliable methods to trace connections in the human brain being lacking for decades. Recent developments in magnetic resonance imaging (MRI) have introduced new methods, based on diffusion imaging tractography that can reconstruct white matter trajectories in the living human brain (Basser et al., 2000; Le Bihan, 2003). The resultant influx of information on human connectional anatomy derived from tractography is likely to fill the gap on our anatomical knowledge of human brain connections and reinvigorate models of cognition based on asymmetrical distribution of large-scale networks (Catani & Mesulam, 2008).

An overview of the hodological (pathway-based) approach to cerebral dominance and its historical context, with a special focus on the perisylvian networks, constitutes

the subject matter of this chapter. We first focus on the nineteenth-century postmortem studies of white matter tracts and the models of brain function and cerebral dominance based on those anatomical findings. We then survey twentieth-century studies derived from blunt dissections and neuroimaging and highlight their advantages and limitations. Finally, we present preliminary contributions from diffusion imaging tractography to the anatomy of the perisylvian networks, its heterogeneity in the normal population, and possible functional and behavioral correlates of different patterns of lateralization. Other tracts such as the uncinate, the cingulum, and the corticospinal and cerebellar tracts will also be discussed. One outcome of this review will be to underline the merits of the hodological approach to cerebral dominance and its modern pursuit with diffusion imaging tractography.

### **Early Hodological Approaches to Higher Cognitive Functions and Cerebral Dominance**

The seventeenth century was a time of great accomplishments in the brain sciences, where anatomists called for a more realistic model of brain function than one tied to the pineal gland and spirits flowing from the ventricles into the hollow nerves (Smith, 2007). For the first time, distinct anatomical features of the brain surface were highlighted (e.g., lateral fissure as the most prominent cleft of the cerebral hemisphere) and the anatomy of previously unknown structures described in some details (e.g., corpus striatus). Others, such as Nicolaus Steno (1669), began to draw attention to the complexity of the fiber system:

We need only view a dissection of that large mass, the brain, to have ground to bewail our ignorance. On the very surface you see varieties which deserve your admiration: but when you look into its inner substance you are utterly in the dark, being able to say nothing more than that there are two substances, one greyish and the other white, which last is continuous with the nerves distributed all over the body. [...] If this substance is everywhere fibrous, as it appears in many places to be, you must own that these fibres are disposed in the most artful manner; since all the diversity of our sensations and motions depend upon them. We admire the contrivance of the fibres of every muscle, and ought still more to admire their disposition in the brain, where an infinite number of them contained in a very small space, do each execute their particular offices without confusion or disorder. (Translated in Stirling, 1902, p. 32)

Despite these early anatomical achievements and insightful writings, new findings on the anatomy of white matter and novel ideas about the functional correlates of brain connections were not forthcoming. Throughout the eighteenth century, the development of physiological methods to study the nervous tissue allowed the formulation of theories of nerve conduction as scientists moved away from “fluidist” or “vibratory” explanations and began to experiment with electricity. This was an important development, although it resulted in the shifting of attention from human to animal anatomy and from the central nervous system to peripheral nerves.

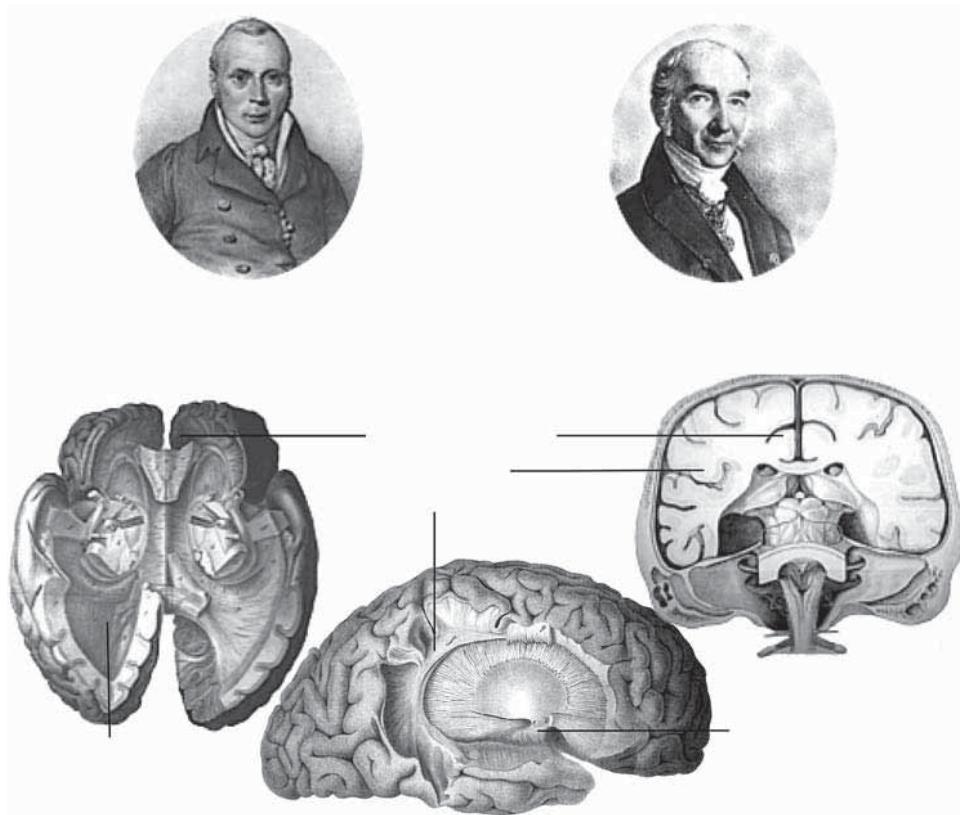
The emergence of the hodological theme as a central component of neurological and psychiatric thinking took place in the nineteenth century and can be attributed to the confluence of two developments: the extension of neuroanatomical research from a description of surface morphology to the dissections of the subcortical tracts, and the spread of “associationist” models of cognitive functions from the realm of psychology to that of neurology and psychiatry (Catani & Mesulam, 2008). An obvious conduit for this convergence was the identification of white matter pathways. Below, we review the pioneering anatomical work of Johann Christian Reil and Karl Friedrich Burdach, which led to the discovery of most association tracts of the human brain. We then introduce the work of Theodor Hermann Meynert and his associationist school, which had a profound influence across countries, continents, and centuries. In the final section of this first part, we discuss the disconnection paradigm derived from associationist theory and Hugo Liepmann’s model of cerebral dominance based on the asymmetry of large-scale sensory-motor networks for praxis.

### **The Discovery of the Association White Matter Tracts**

The first development pivotal to the emergence of the hodological approach to brain function was the identification of the association tracts connecting distant regions within the same cerebral hemisphere. Several anatomists made important contributions to this field, but Johann Christian Reil and Karl Friedrich Burdach (see figure 7.1) stand out for the originality of their findings and the far-reaching influence of their writings.

In 1788 Johann Christian Reil became professor at the University of Halle and director of the Clinical Institute at the age of 29 (Scharf, 1960). In 1795 he founded the first physiology journal in Germany, the *Archiv für die Physiologie*, which he used as a vehicle for many publications about anatomy and physiology, including his own description of cortical and subcortical brain structures (Reil, 1809a, 1812b). His anatomical discoveries derived from the development of a method based on the soaking of the brain in alcohol (initially he used brandy) that made it more suitable for dissection (Reil, 1808). This method allowed him to reveal the course of the white matter bundles running beneath the major convolutions of the human brain (see figure 7.1). Among the tracts that he identified were the medial curving fibers within the cingulate gyrus (i.e., *Bedeckte Bänder* or *Längenbänder*; Reil, 1812b) and the lateral arching connections coursing beneath the perisylvian fronto-parieto-temporal gyri that he described as the unnamed white matter substance (i.e., *Ungenannte Marksubstanz*; Reil, 1812a). Other tracts that he identified on the most ventral part of the brain are the hooked-shaped fibers behind the insula (i.e., *Hakenförmiges Markbuendel*; Reil, 1809b) and a longitudinal bundle between the occipital and temporal lobes (i.e., *Stratum von Längenfasern*; Reil, 1812b).

Reil illustrated and commented on the presence of these tracts on both hemispheres and their possible role:

**Figure 7.1**

Johann Christian Reil and Karl Friedrich Burdach described for the first time the association tracts of the human brain. Here the original drawings from their work are shown (the figures on the left and in the middle are from Reil).

**Table 7.1**

Nomenclatures for the association tracts

Reil (1809b, 1812a, 1812b)	Burdach (1822)	<i>Nomina Anatomica</i> (1989)
<i>Ungenannte Marksubstanz</i>	<i>Bogenbündel (arcuatus)</i>	Arcuate fasciculus
<i>Hakenförmiges Markbündel</i>	<i>Hakenbündel (unciformes)</i>	Uncinate fasciculus
<i>Stratum von Längenfasern</i>	<i>Längenbündel (longitudinalis inferior)</i>	Inferior longitudinal fasciculus
<i>Bedeckte Bänder</i>	<i>Zwingen (cingula)</i>	Cingulum

Each hemisphere is an independent organ and forms a closed loop in its own; both loops flow into each other through the mentioned structures [arcuate and uncinate]. (Reil, 1809b)

Reil's findings were confirmed a decade later by Karl Friedrich Burdach. Burdach was conferred doctor in medicine at Leipzig in 1799 and received a professorship for anatomy, physiology, and forensic medicine in Dorpat in 1811 (Meyer, 1970). Here he commenced his anatomical dissections of the brain that he continued after moving to Königsberg as director of the Anatomical Institute. His studies culminated in the *Vom Baue und Leben des Gehirns*. This is a three-volume textbook containing confirmatory dissections of Reil's findings and his own original descriptions of some previously unidentified tracts (Burdach, 1822), including the fibers connecting the occipital to the frontal lobe, later identified as part of the inferior fronto-occipital fasciculus (Curran, 1909). He also used Latin names for the major tracts, which became widely adopted and still remain almost unchanged in the current international anatomical nomenclature (see table 7.1; Commitee, 1989).

Both Reil and Burdach were fascinated by Schelling's natural philosophy, which inspired their functional interpretations and speculative reflections (Meyer, 1970). However their functional inferences were either dismissive of the role of the association tracts (e.g., Reil) or based on erroneous physiological speculations (e.g., Burdach):

The core [of the brain] is constituted by the organizations of the crus cerebri [*Hirnschenkel*] and the corpus callosum [*Balken*]. These together with the gyri and the grey matter seem to be the fundamental component of the brain, everything else seems to be just connection and transduction apparatus. (Reil, 1809c)

Fantasy is warm and lively; organically linked to blood circulation and can therefore be excited by the fast change of blood, resulting in a stronger tension in the brain. Reason in contrast is cold and cautious; any tempestuous movement is hostile to it [...]. The longitudinal system [association fibers] is more closely linked to the blood vessels [...] its alert activation causes more blood to be drawn to the vascular plexus [...]. The transverse [commissural] system on the contrary is in no special relation to the vascular system. (Burdach, 1826)

This theoretical vacuum left the field open to the triumph of cortical localizationist theories and the fierce antilocalizationist opposition based on holistic stances. One would have to wait until the second half of the century for the emergence of the hodological theme following the spread of "associationist" models of cognitive functions from the realm of psychology to that of neurology and psychiatry (James, 1890; Meynert, 1885; Wundt, 1904). According to the associationist doctrine, the formation of concepts, the recall of memories, the naming of objects, and even the spontaneous and voluntary initiation of movement, required the associative convergence (or integration) of information from multiple sources. The association tracts seemed to be the ideal anatomical substrate for such a theory.

### Meynert's Associationist Theory of Brain Function

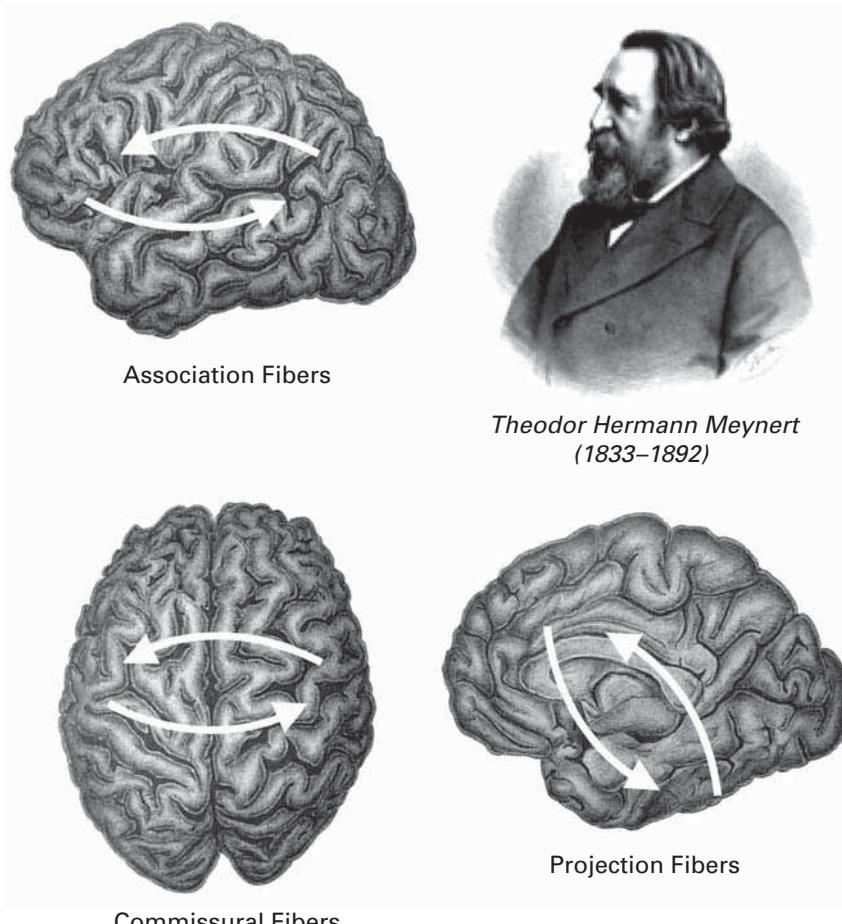
The idea of association has roots in Aristotle's writing and has been passed down the centuries from Epicurus through Hobbes to Hartley (Glassman & Buckingham, 2007). However, the credit for the formulation of an associationist theory grounded on anatomy falls to a psychiatrist known by his contemporaries as the great brain-anatomist, Theodor Meynert, Professor of Nervous Diseases and Director of the Psychiatric Clinic in Vienna. He took an original position with regard to the explanation of brain function and mental disorders (Catani & ffytche, 2005). He first rejected contemporary theories of predisposition, which became in psychiatry the theory of moral insanity:

As regards to the theory of predisposition, and more particularly the doctrine of hereditary, which has been carried to the extreme of assuming the existence of innate idea, and which in clinical medicine, has led to the erroneous theory of moral insanity, I have deemed it necessary to criticise, in its proper connections, Darwin's theory of the inheritance of acquired faculties, as has been done before me by other German authors, among them DuBois-Reymond and Weissman. It is taking altogether too simple a view of things, to regard morality as one of man's talents, and as a definite psychical property which is present in some persons and lacking in others. (Meynert, 1885, preface, viii)

Thus, "dissatisfied with the statistical method, which laid inordinate stress upon hereditary predisposition to disease," Meynert resolved for an anatomical approach to mental disorders:

In view of the necessity of starting from anatomical facts, I have endeavored, in every case, not only to give due weight to the structure of the brain as the fundamental basis for the various forms of disease, but have endeavored, with the same end in view, to insist upon and to explain every visible symptom exhibited by the patient. (Meynert, 1885, preface, vii)

Meynert's ambitious clinical research program aimed to establish the anatomical bases not only of mental disorders but also of specific symptoms; the success of its realization depending entirely on the deep anatomical knowledge of the human brain. In 1884 he published in German *Psychiatry—Clinical Treatise on Diseases of the Fore-Brain based upon a study of its structure, functions, and nutrition*, impelled by the conviction of a need for a "scientific" treatise on mental disease. The title is a direct attack on the "science of psychiatry [that] has been too largely subjective" and refers "to the fundamental studies [of structure] indispensable to an understanding of the clinical manifestations of mental disease" (Meynert, 1885, p. vi). The first volume of the *Treatise*, which Sachs translated and published in English the year after (Meynert, 1885), contains Meynert's description and classification of the main white matter tracts of the brain (see figure 7.2). Before him, other anatomists such as Vieussens, Vicq d'Azyr, Reil, Burdach, and Gall had described differences in origin, course, and termination of fibers, but Meynert was the first to put forward an orderly classification



**Figure 7.2**

Theodore Hermann Meynert and his classification of white matter in association, commissural, and projection fibers.

(Drawings of the brain are from Catani and ffytche, 2005, and were originally produced by Luca Santaniccha)

of white matter fibers into three groups. The first group consisted of *projection* fibers, the ascending or descending pathways arising and terminating in the cortex, the second of *commissural* fibers, which connect cortex in both hemispheres, and the third of *association* fibers, which connect cortical regions within a hemisphere. He further subdivided the association tracts (or “*fibrae propriae*”) into two groups, the *short U-shaped fibers* and the *long association bundles*, according to their cortical projections and the length of their subcortical course:

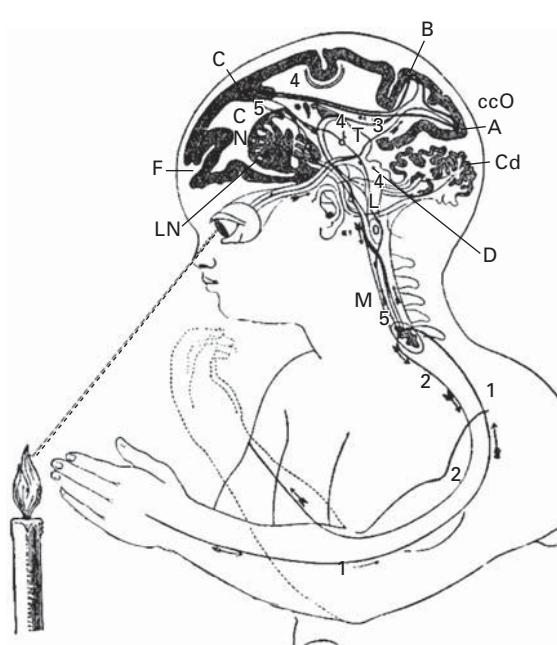
The U-shaped bundles of the cortex do not necessarily extend simply from one convolution to one next adjoining, but they may skip one, two, three, or an entire series of convolutions, and may thus join convolutions which are united among themselves to a convolution lying at some distance from these. The shortest *fibrae propriae* lie nearest to the cortex; the longest at the greatest depth, and are separated from the cortex by other intervening *fibrae propriae*, the length of which increases gradatim from the surface inward. (Meynert, 1885, p. 39)

Once he had laid down the anatomical foundations of the model Meynert defined a specific role for each group of connections.

First Meynert extended Bell’s division of the sensory ascending (centrifugal) and motor descending (centripetal) tracts of the spinal cord to the brain, thus considering the projection fibers, the major communication system between specialized cortical regions and peripheral sensory organs and muscles. Then he added a layer of complexity to the model by introducing the association fiber system:

In examining the structure of the hemispheres, and remembering that different, distinctly limited and functionally separated portions of the cortex receive impressions from the various senses, we may naturally infer that the association-bundles, the *fibrae propriae* of the cortex, which form anatomical connections between the different cortical regions, effect the physiological associations of the images which are stored in these various parts. (Meynert, 1885, p. 153)

Thus, in this model, the cortex, through its projection and association connection system, becomes a place not only for sensation and motor response but also for higher cognitive functions and complex behaviors such as “logical functions” (e.g., *Schlussprocess*, induction), “recollection,” “learning,” and “initiation of conscious movement” (see figure 7.3). Meynert was an outstanding anatomist of international repute who attracted young doctors eager to learn anatomy from all over Europe and North America. Among them were Carl Wernicke, Sergei Korsakoff, Auguste-Henri Forel, Paul Flechsig, Bernard Sachs, and Sigmund Freud. Although Meynert used his neuroanatomical findings to develop a theory of psychological function, which had profound influence on the early development of psychiatry, it was one of his most talented students, Carl Wernicke, who brought the associationist model to the clinic by applying the disconnection paradigm to explain neurological and psychiatric disorders.

**Figure Legend**

- A. Part of the visual cortex;
- B. Part of the cortical centre for cutaneous sensation;
- C. A centre in the cortex for sensations of innervation;
- Cd. Cerebellum;
- CN. Caudate nucleus;
- D. Mesencephalon;
- F. Frontal cortex;
- L. Pons Variolii;
- LN. Nucleus lenticularis;
- M. Medulla spinalis, terminating with a cross-section of the cervical spinal cord;
- ccO. Occipital cortex;
- T. Thalamus opticus

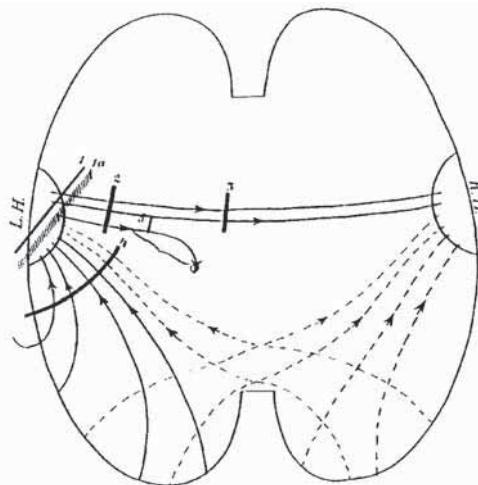
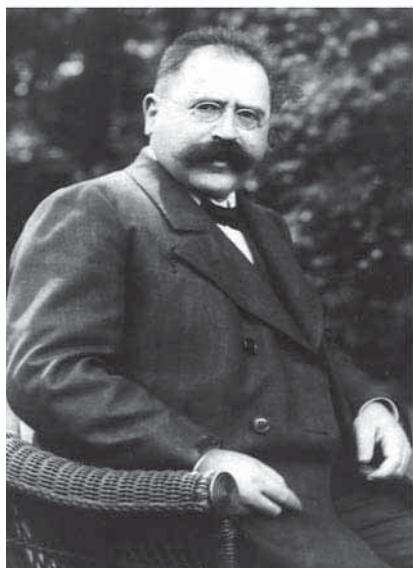
**Figure 7.3**

Diagram from Meynert's (1885) textbook used to explain the formation of conscious movements in a child's brain. Below is the Meynert's original explanation of the figure: "Let us suppose a flame to have injured the hand of a child, and that the latter withdrew the hand from the flame. This movement (the withdrawal of the hand) will be effected, without the intervention of the conscious impulses, by an impulse conveyed from the injured part by the centripetal tract 1, and transmitted through a spinal-cord centre along the path 2, which withdraws the hand from the flame. [...] The following records of this act will be transmitted to the cortex through the agency of the projection-systems: first, the visual image of the flame from the eye along the tract 3A; secondly, a painful sensation from the injured part along the tract 4B. Thirdly [...] the innervation-sensation C acts through the centrifugally-conducting tract 5 upon the central origin of those anterior roots which, through reflex excitation, protected the arm against the flame. Since the centre C is connected with the association bundle CB, CA, and the latter with one another by the bundle BA, the child need not actually burn its hand again before guarding against the flame; but the memory of the flame and of its effect (through association with the centre in which the painful sensation has been rooted), will suffice, through the one or the other of these associations, to initiate a movement which will put the arm beyond the reach of the flame."

**Disconnection Syndromes and Early Hodological Theories of Hemispheric Dominance**

Carl Wernicke (1848–1904) was born in Tarnowitz, which was in those days a town in Prussian Upper Silesia but is now in Poland. He read medicine in Breslau (Wroclaw) where he undertook most of his studies except for a six-month period in Vienna with Meynert (Keyser, 1994). Wernicke was greatly influenced by his teacher's associationist theory, and in his M.D. thesis "*Der aphasische Symptomengenkomplex*" he postulated that if higher cognitive functions arise through associative connections, disorders of higher function must derive from their breakdown. On the basis of this corollary he explained a disconnection syndrome that was to become the prototype for all others—conduction aphasia (*Leitungsaphasie*, Wernicke, 1874), that he later described as a language disorder characterized by normal comprehension and intact verbal fluency but impaired repetition due to a lesion of the fibers connecting Broca's and Wernicke's areas (Wernicke, 1908). In Breslau Wernicke established one of the most important associationist schools (Catani & ffytche, 2005). When the disconnection paradigm was applied not only to aphasia but also to other neurological (e.g., associative agnosia; Lissauer, 1890) and psychiatric (e.g., schizophrenia; Wernicke, 1906) disorders. However, it soon became evident that the disconnectionist paradigm per se was not sufficient to explain the association between certain manifestations and localization of lesion in one hemisphere (i.e., lateralization of symptoms). Surprisingly, Wernicke explained the lateralization of language disorders by postulating the existence of specialized language centers in the left hemisphere. Similarly, Jules Dejerine when describing a disconnection syndrome characterized by inability to read but preserved writing, namely pure alexia, localized the center specialized for reading in the left angular gyrus. It was one of Wernicke's students, Hugo Liepmann (see figure 7.4), who put forward an alternative explanation for the hemispheric dominance: the anatomical lateralization of connections.

Hugo Liepmann joined Wernicke's clinic as an assistant in 1895 and carried the Breslau associationist doctrine to Berlin when he left four years later (Goldenberg, 2003). Here he developed an interest in the motor system, which led him to propose a disconnectionist account of goal-directed movement disorders—the apraxias. Liepmann's theory of apraxia, first published in 1900, was based on his case study of a 48-year-old imperial counselor (*Regierungsrat*) who was admitted to the Berlin psychiatric service with a diagnosis of mixed aphasia and dementia (Liepmann, 1900). Although his spontaneous movements were normal (e.g., using a spoon while eating), a striking feature of the patient was that when asked to perform or copy gestures with his hand (e.g., point to your nose) or manipulate imaginary objects (e.g., show how you use a harmonica), he did so in an absurd fashion. Since the patient was able to understand the command, had no visual impairment, and had no evidence of paralysis, Liepmann formulated a network model for praxis (see figure 7.4) and



**Figure 7.4**

Hugo Liepmann and his diagrammatic explanation of the network underlying praxis and apraxia syndrome (from Liepmann, 1925). The model implies a general left-hemisphere (L. H.) dominance for movement control based on the asymmetrical distribution of association and commissural sensory-motor connections. The left motor region receives connections mainly from the temporal (Ct), parietal (Cp), and occipital (Co) cortex of the left hemisphere whereas the corresponding connections from the right hemisphere (R. H.) have only "subordinate significance" (dashed lines). Bars indicate possible lesion sites causing apraxia along the network. C.i., capsula interna.

hypothesized a disconnection of visual, auditory, and somatosensory areas from motor areas to explain the symptoms displayed by the counselor:

I do not think there is a praxis center, or even that it is located [...] in the supramarginal gyrus. I never postulated that the apraxia of the counselor is only due to a lesion in the supramarginal gyrus or that this is true for all cases of apraxia. In my case report I have postulated an interruption of the sensory-motor region of the right extremities from the most important cortical regions of both hemispheres, and thought that in this case the evidence is the disruption of the white matter of the supramarginal gyrus and the callosal connections from the other side. And I was right as the autopsy confirmed. (Liepmann, 1908, p. 77)

Liepmann generalized his conclusions to all cases of apraxia for which he postulated a disconnection mechanism at different segments and nodes of the network and speculated on the leftward asymmetry of the praxis networks to explain the higher frequency of left hemisphere lesions in these patients:

Eupraxic movement results from the collaboration of many brain regions with the hand area. Lesions to the cortical regions and especially their connections with the hand centre at different points can impair praxis. [...] Especially the left hemisphere hand centre including its connections to the rest of the brain in particular in the same hemisphere is irreplaceable, therefore, lesions to the left hemisphere are disastrous for praxis of all extremities. (Liepmann, 1908, p. 77)

Unlike his predecessors, Liepmann took an original position to explain the neurobiological underpinnings of left-hemisphere dominance for praxis. His model does not imply the existence of a left-dominant cortical area for complex movement control. Instead, left dominance for praxis is considered the result of an asymmetrical distribution of the sensory-motor pathways: "The contralateral connections are of subordinate importance as compared to the link of the left hand area with the rest of the brain."

Liepmann added that *his diagram is not only relevant to apraxia*, as if it could also explain other lateralized syndromes. Liepmann's explanation was highly speculative in the absence of experimental evidence to support his claims (for a review, see Goldenberg, 2003, 2009). If the associationist school and the disconnectionist paradigm were to replace cortical localizationism in the neurology clinics, anatomical support was urgently needed. In the next sections we review the methodological advancements that took place in the twentieth century and the main findings derived from applying them to the study of the asymmetry of white matter pathways.

### **From Postmortem to Neuroimaging Studies of White Matter Lateralization**

The techniques developed by early neuroanatomists for gross dissections of white matter tracts led to important anatomical insights but were inadequate for quantitative studies of tract lateralization. A methodological revolution in this field occurred at the turn of the nineteenth century with the development of new techniques of microscopy, specimen preparation, and staining. The introduction, for example, of staining for fiber degeneration, such as the method of Weigert-Pal or Marchi (Bolton, 1898), and the study of serial sections of the specimens allowed the visualization of tracts in the brain of patients with corticosubcortical lesions (mainly vascular) or in experimentally lesioned animal brains (Ranson et al., 1941). However, these methods as applied to the study of lateralization presented several limitations, including the rarity of lesions occurring in symmetrical regions of the human brain and the difficulty of reconstructing volumes of intercortical pathways from a series of slices along the course of the tracts.

Others tried to ameliorate previous techniques for gross blunt dissections using ingenious methods for preparing the specimens. Examples of this approach are Rosett's (1933) method based on the "microexplosions" of the brain in a gas-compressed tank, or Klingler's (1935) preparation based on the freezing of the brains for several weeks. Following these preparations, the bundles of the large tracts are

mechanically separated and can be manually isolated with great ease. However, blunt dissections require neuroanatomical knowledge, experience, and patience to obtain reliable results, and other methods for studying the cortical cytoarchitecture advanced at a fast pace (Brodmann, 1909). Thus, contrary to what one would have expected from the enthusiasm generated by the associationist ideas, in the first half of the twentieth century the scientific interest for anatomy shifted from connections to cortical cartography. As we will see in the next section, the only exception to this general trend was the study of the corticospinal tract (CST).

In the 1960s an enormous increase in knowledge about connectivity arose from the use of cellular transport mechanisms to detect connections between nerve cells (Lanciego & Wouterlood, 2000). Most of the axonal tracing methods are based on active transport mechanisms in the living cell. The tracer is injected into a special brain region and is transported via the axons into connected brain areas (Barbas & Mesulam, 1981; Petrides & Pandya, 1988). Although this method is not applicable to the study of human brain connections, the interest generated by monkey tracing studies revitalized the hodological theme. With the development of brain imaging many clinicians began to expand once again the clinicopathological correlation beyond cortical areas and alternative hypothesis emerged for classical cortical syndromes. Naser et al., for example, reported severe nonfluent aphasia in patients with lesions to the subcallosal tract of the left hemisphere, while Leibovitch et al. (1998) described unilateral neglect with lesions of the deep white matter tracts of the temporo-parietal junction (i.e., inferior and superior longitudinal fasciculus). At the same time, the convergence of neuropsychological studies in split-brain patients and the return to the clinicopathological correlation reawakened interest in the neuroanatomical correlates of functional lateralization (Geschwind & Levitsky, 1968). Nevertheless, despite networks and connections being a cardinal feature of most of the neurological models proposed at that time, the lack of adequate methodology did not allow for study of lateralization of white matter tracts beyond the CST. It is only in the last decade that MRI has been used in large cohorts to study asymmetry of white matter—in particular, to characterize changes during brain development. Below, the studies on the lateralization of white matter tracts derived from postmortem and structural neuroimaging are reviewed in detail. The advantages and limitations of these studies will be discussed before moving to the final section on diffusion tensor imaging (DTI).

### Corticospinal Tract and Other Projection Pathways

The CST is the main descending projection system between the motor cortex and the spinal cord and thereby subserves motor control functions for the muscles of the arms, legs, and trunk. It originates mainly from the precentral frontal region, passing through the internal capsule and brainstem to terminate in the spinal cord. Just before entering into the spinal cord, the CST crosses from one side to the other. The crossing of the CST

was first described by Domenico Mistichelli (1709) and François Pourfour du Petit (1710); but, it is only when Paul Emile Flechsig applied his myelogenetic method to sections of newborn brains that experimental evidence for CST asymmetry emerged. Flechsig found that in the majority of specimens (75%) most of the CST fibers cross from one side to the other, but the crossing pattern differs between the two sides in 40% of the brains (Flechsig, 1876). Among these asymmetrical cases, the uncrossed component was more often larger on the right side of the spinal cord than on the left. Yakovlev and Rakic (1966) used Flechsig's method in a larger sample, and they not only reiterated his findings but found that the decussating bundle of the left CST was larger and crossed the midline at a most dorsal level in 87% of cases. Considering that the fibers crossing at the most rostral level are likely to originate from the hand region of the precentral gyrus, these observations were thought to be of relevance to handedness. Kertesz and Geschwind (1971) studied the variation on the crossing pattern with respect to manual preference in adults. They confirmed the finding of Yakovlev and Rakic (73% of cases with left-to-right rostral crossing), but they found no correlation with handedness. Similarly Nathan and colleagues (Nathan et al., 1990) described a greater number of pyramidal fibers in the right side of the spinal cord in 75% of cases. Because of the higher incidence of right-handedness in the population, reaching approximately 90%, Nathan et al. (1990) rejected the hypothesis that CST asymmetry may be a structural correlate for the lateralization of handedness. A recent work studied hemispheric differences in the volume of the CST, which was found to be greater on the left as compared to the right in 70% of subjects (Rademacher et al., 2001).

Voxel-based morphometry (VBM) studies of MRI structural images (e.g., T1 weighted) show larger white matter volumes in the left internal capsule without a clear association with handedness (Good et al., 2001; Hervé et al., 2006). Application of MRI to large cohorts of children and adolescents shows a greater age-related increase in white matter density of the left internal capsule compared to the right throughout childhood and adolescence (Paus et al., 1999). A well-known problem with the VBM approach is the difficulty in attributing hemispheric differences to specific white matter tracts. For example, the differences in the internal capsule mentioned above are not necessarily located in the cortical spinal tract but could involve other fibers of the projection system.

The projection system also includes ascending pathways of which the *thalamic radiations* represent the largest portion. Most of the post-mortem and neuroimaging studies reported no difference between left and right thalamus with respect to volume and neuronal density. Eidelberg and Galaburda (1982) showed a slight rightward asymmetry of the medial geniculate nucleus and a leftward asymmetry of the lateralis posterior nucleus, which projects to the inferior parietal lobule. The latter findings have been suggested to have some association with development of left dominance for language. However, to date there are no studies that have addressed the lateraliza-

tion of the thalamic projections. Bürgel and colleagues (2006) recently showed asymmetries in the position and size of the human *optic radiation* using post-mortem dissections. In their sample of 10 subjects, nine showed a leftward asymmetry in the volume of the lateral geniculate and optic radiations.

### Association Tracts

The *uncinate fasciculus* is the main association tract between the anterior temporal lobe and the inferior orbitofrontal cortex and is considered part of the extended limbic system. Pathology involving the uncinate fibers and its cortical projections has been associated with several symptoms including memory impairment, language deficits, and neuropsychiatric syndromes (Mega et al., 1997). The asymmetry of the volume and density of fibers of the uncinate fasciculus has been revealed in only one study using microscopy on human brains. The uncinate fasciculus was asymmetrical in 80% of subjects, containing on average 30% more fibers on the right than the left hemisphere (Highley et al., 2002). VBM studies of the white matter region containing uncinate fibers (i.e., anterior floor of the external capsule) are contrasting with both leftward (Hervé et al., 2006) and rightward (Good et al., 2001) asymmetry reported.

The *arcuate fasciculus* is a large association tract connecting perisylvian areas of the frontal, parietal, and temporal lobes. The arcuate fasciculus is involved in higher cognitive functions showing various degrees of functional lateralization such as language, visuospatial processing, and social behavior. MRI has been used for VBM studies of the arcuate fasciculus. In general, the white matter regions containing fibers of the arcuate fasciculus are larger on the left compared to right (Good et al., 2001; Hervé et al., 2006). However, there is also some evidence for regional differences in the asymmetry within different segments of the arcuate fasciculus, with most ventral regions being larger on the left and dorsal regions being larger on the right (Good et al., 2001). Furthermore, an increase in white matter density in the left arcuate fasciculus during childhood and adolescence has been reported (Paus et al., 1999). In a recent study, Blanton et al. (2004) documented significant gender differences in the white matter of the left inferior frontal gyrus, a region containing anterior projections of the arcuate fasciculus: boys but not girls showed a linear age-related increase in the white matter volume in this region. It remains to be determined whether such differences are to be attributed to only the arcuate fasciculus or other tracts connecting perisylvian regions. This is an issue that has been partially resolved with diffusion-tensor imaging (DTI) tractography.

### DTI Contribution to Pathways Lateralization

In 1985, a modification of conventional MRI sequences permitted quantification of the diffusion characteristics of water molecules in vivo (Le Bihan & Breton, 1985).

Given that within cerebral white matter, water molecules diffuse more freely along myelinated tracts than across them -a property termed anisotropy of diffusion- (Moseley et al., 1990), it is possible to obtain *in vivo* estimates of white matter fiber orientation by measuring the principal direction of diffusivity of water (Basser et al., 1994). This has led to the development of diffusion tensor tractography (Basser et al., 2000; Conturo et al., 1999; Jones et al., 1999; Mori et al., 1999; Poupon et al., 2000), in which white matter tracts are reconstructed in three dimensions by sequentially piecing together discrete and shortly spaced estimates of fiber orientation to form continuous trajectories. Although these tracts are “virtual,” the connections being defined mathematically and not necessarily implying a true axonal pathway, the technique has been used with some success in the living human brain to study the major projection, association, and commissural tracts (Basser et al., 2000; Catani et al., 2002; Lawes et al., 2008; Mori et al., 1999). Diffusion tensor tractography offers the advantage of being completely noninvasive, as previously established methods for tracing fiber pathways, such as those used in axonal tracer studies, are restricted for use in nonhuman primates only. Furthermore, the MRI method used to provide data for the tractography process can be readily obtained on standard MRI systems with acquisition times typically ranging from 5 to 20 minutes (depending on image data quality required). Furthermore tractography offers the possibility of extracting quantitative diffusion indices along the dissected tract, thus obtaining tract-specific measurements indicative of the microstructural organization, composition, and integrity of the fibers of interest. The most used indices are fractional anisotropy (FA; an indirect measure of fiber organization and composition) and mean diffusivity (an indirect measure of tissue density; Jones, 2008). The number of streamlines is also commonly used as a surrogate measure of tract volume (Catani et al., 2007). These indices have been used in recent years to study the lateralization pattern of the macro- and micro-architecture of the projection and association pathways. Below, we review the DTI studies that have reported data on lateralization.

### **Projection Tracts**

DTI has been applied to study the *in vivo* asymmetry of the CST at different levels (e.g., corona radiata, internal capsule) using VBM, region-of-interest (ROI), and tract-specific approaches (see table 7.2; Catani, 2006).

Büchel et al. (2004) used VBM on DTI data sets to show, in a right-handed group of healthy adults, higher FA values in a region of the left hemisphere corresponding to the white matter of the precentral gyrus. The reverse pattern was found in a group of left-handers. Using a similar approach, Park et al. (2004) found higher FA in the right internal capsule (anterior limb) compared to the left, while Ardekani and colleagues (Ardekani et al., 2007) found reduced FA in the right internal capsule (posterior limb) compared to the left.

**Table 7.2**

Methods for the analysis of diffusion tensor imaging data (from Catani, 2006)

Data-led analysis	Hypothesis-led analysis
<p><i>Whole-brain voxel-based morphometry (VBM) analysis:</i></p> <p>This is an operator-independent approach that allows the analysis of the entire brain volumes without an a priori hypothesis regarding the anatomical location of between-groups differences. This can be very useful as exploratory analysis, especially where white matter changes are diffuse. Adapting the voxel-based morphometry approach, developed for functional and structural imaging data [14], to DT-MRI data, however, is not necessarily straightforward. Coregistration of low-resolution, high-contrast fractional anisotropy maps may generate significant misregistration and partial volume artifacts in regions of high and low anisotropy (e.g., around the ventricles). Also the accurate localization of differences is difficult as data are often heavily smoothed as part of the preprocessing. This results in low-resolution parametric maps from which to infer group differences. Anatomical identification of regions exhibiting significant group differences can be difficult, as clusters of voxels will not typically lie neatly within a single tract.</p>	<p><i>Region-of-interest (ROI) approach:</i></p> <p>The ROI approach allows the identification of between-groups differences in a specific brain region. Specification of the anatomical location of the putative differences is therefore a prerequisite. Hence, the ROI approach is often used to test findings derived from previous studies (e.g., voxel-based morphometry). The major problem with the ROI approach is the inability to attribute changes to a specific tract within regions containing two or more white matter bundles. Also, the manual definition of a ROI for the entire length of a tract is rarely achieved. Further, the conventional ROI approach may lack sufficient statistical power because of the high degree of intra- and intersubject variation of the fractional anisotropy values, even within a highly homogeneous tract.</p> <p><i>Tract-specific measurements:</i></p> <p>This approach allows the testing of between-groups differences within a specific tract of interest. It overcomes some of the limitations of the voxel-based morphometry and ROI analysis (e.g., better anatomical localization of the single tracts, analysis throughout almost the entire length of the bundle). However, it suffers from a number of problems including a priori knowledge of the anatomy (operator-dependent placement of regions from which tracking starts) and difficulties in resolving the crossing or meeting of different fibers. Hence reconstructions of the virtual tracts may be artifactual due to the presence of false negatives (partial reconstruction of the bundles) and false positives (visualization of nonexistent tracts).</p>

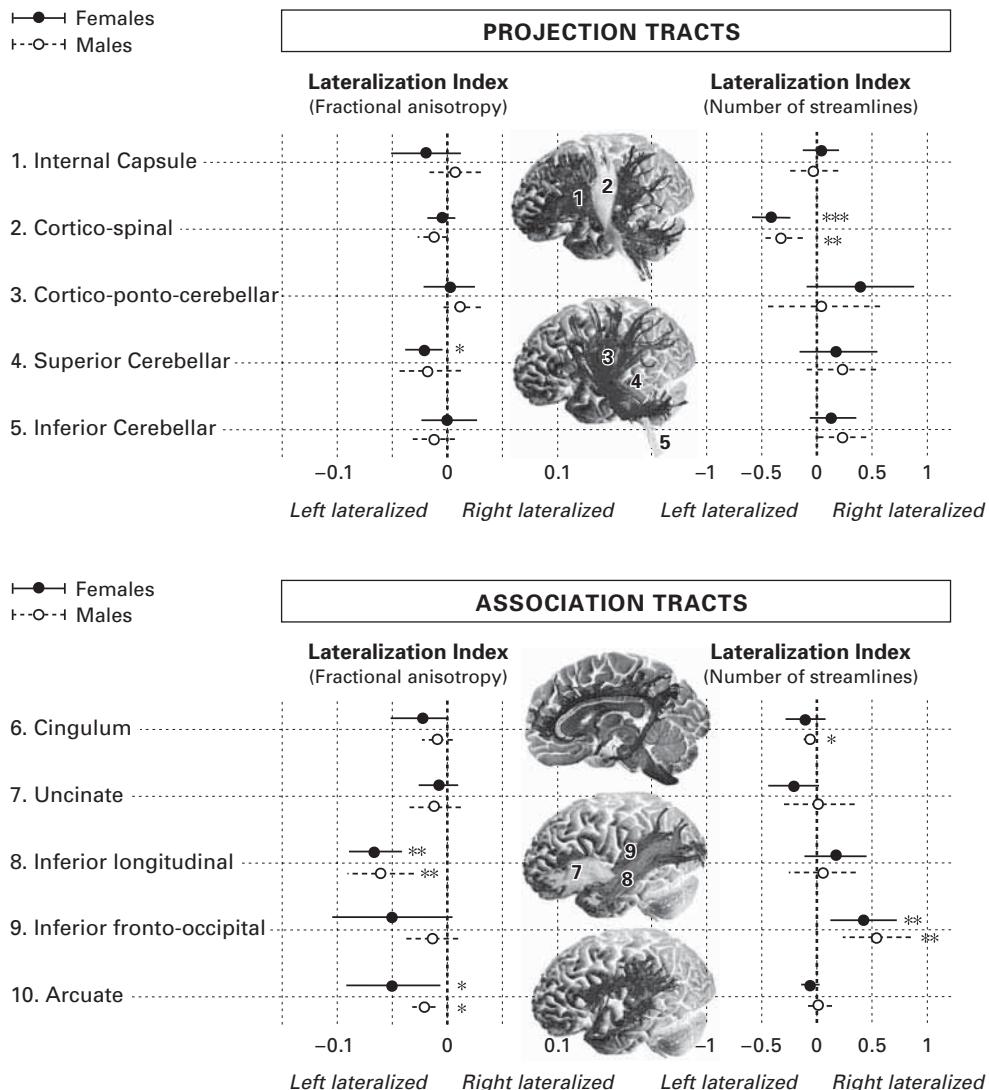
The same authors used a ROI approach to show higher FA in the anterior limb of the right internal capsule compared to the left but lower FA in the posterior limb of the right internal capsule compared to the left. Toosy et al. (2003) found higher FA on the right posterior internal capsule compared to the left with a similar ROI approach, while Westerhausen and colleagues (Westerhausen et al., 2007) obtained the opposite results, with higher FA on the left posterior internal capsule compared to the right. The latter authors were unable to show an interaction between asymmetry and handedness. Thus, overall VBM and ROI studies of FA maps show contrasting results for the asymmetry of the CST.

To partially overcome some of the limitations of the VBM and ROI approaches, some groups have used tract-specific measurements (i.e., sampling the diffusion parameters along the virtually dissected tract of interest). Reich et al. (2006) found no differences in volume and FA between the left and right CST in adults. Eluvathingal and colleagues (Eluvathingal et al., 2007) showed higher FA on the left CST compared to the right in 70% of a group of healthy children and adolescents. Differences between studies may be related to sample size, age range, DTI acquisition parameters, and selection of the ROI for tractography. Our investigation on a group of 40 right-handed adults (20 males and 20 females) with homogeneous age range (18–22 years; see figure 7.5/plate 3) shows that overall the CST volume has a moderate, but statistically significant, leftward asymmetry,  $T(39) = 5.3$  ( $p < .001$ ). This pattern of asymmetry is present in 70% (28/40) of the subjects, while 12.5% (5/40) have an opposite pattern. The remaining 17.5% (7/40) of the subjects show a bilateral and almost symmetrical distribution. There were no differences in FA and no differences between males and females for both volumes and FA. These results are very similar to the findings derived from previous postmortem dissections (Nathan et al., 1990; Rademacher et al., 2001). By extending the analysis to other fibers of the projection system, we were able to show that although some degree of lateralization is present in other tracts, the CST shows the most significant asymmetry (see figure 7.5/plate 3).

### Association Tracts

DTI has been applied to study the *in vivo* asymmetry of the larger association tracts. Büchel et al. (2004) used VBM and found higher left FA in a region corresponding to the arcuate fasciculus. Opposite results were reported by Park et al. (2004) with higher FA in the right arcuate fasciculus compared to the left. They also found lower FA on the left hemisphere for the uncinate and inferior and superior longitudinal fasciculus but reduced FA in the right cingulum compared to the right.

A ROI approach has been adopted for a number of regions containing the major association tracts. Higher FA was found in the left superior longitudinal fasciculus compared to the right (Makris et al., 2005), uncinate (Kubicki et al., 2002; Rodrigo et al., 2007), and cingulum (Gong et al., 2005; Huster et al., 2007).

**Figure 7.5 (plate 3)**

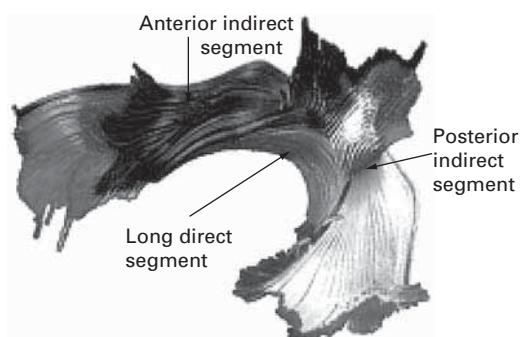
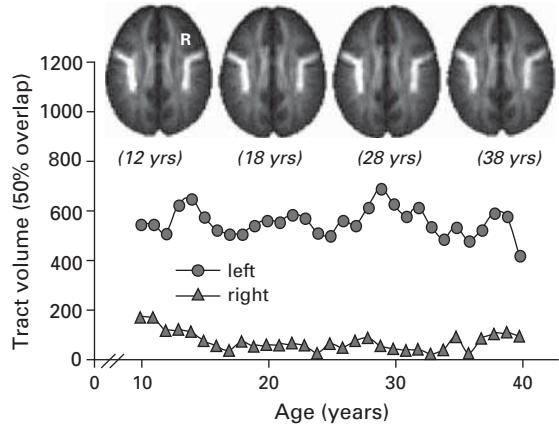
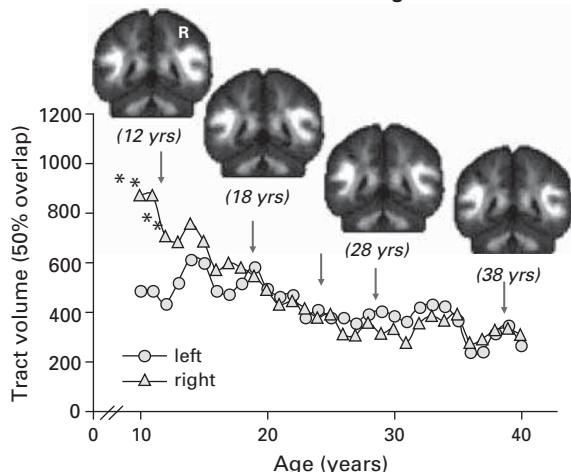
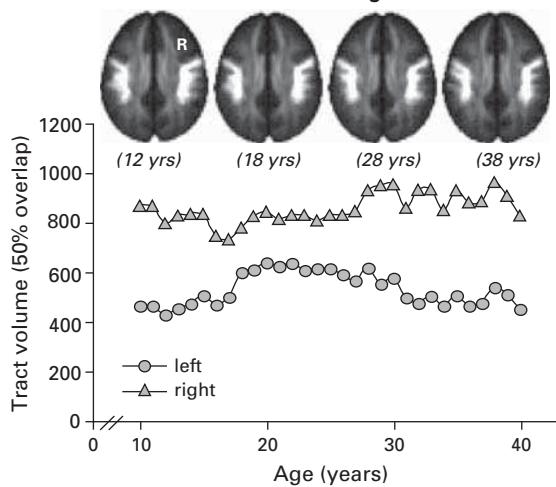
Asymmetry of the projection and association tracts. The images are based on tractography indices derived from the analysis of 40 healthy subjects. \* $p < .05$ ; \*\* $p < .01$ ; \*\*\* $p < .001$ . Intervals are 95% confidence intervals.

Eluvathingal et al. (2007) used tract-specific measurements and found higher FA in the left uncinate compared to the right in a group of children and adolescents. Wakana et al. (2007) dissected the major association tracts in 10 healthy subjects and found greater volume for the left superior longitudinal fasciculus, inferior longitudinal fasciculus, and cingulum. Ashtari et al. (2007) found higher FA in the left inferior longitudinal fasciculus. Our own data confirm a leftward FA asymmetry for the inferior longitudinal fasciculus,  $T(39) = 6.2$  ( $p < .001$ ), and the arcuate fasciculus,  $T(39) = 3$  ( $p < .01$ ). We also found a rightward asymmetry only for the number of streamlines of inferior fronto-occipital fasciculus (see figure 7.5/plate 3).

### **Asymmetry of Perisylvian Pathways and Behavioral Correlates**

The first tractography studies applied to the perisylvian pathways showed that the anatomy of the arcuate fasciculus is more complex than previously thought (see figure 7.6/plate 4 and figure 2, Catani, Jones, & ffytche, 2005; Parker et al., 2005). In addition to the long direct segment connecting Wernicke's area with Broca's territory (i.e., the arcuate fasciculus *sensu strictu*), there is an indirect pathway consisting of two segments, an anterior segment linking Broca's territory with the inferior parietal lobule (Geschwind's territory), and a posterior segment linking the inferior parietal lobule with Wernicke's territory (Catani et al., 2005). This arrangement not only supports the more flexible architecture of parallel processing (Mesulam, 1990) but also is in keeping with some of the classical neurological models of aphasia, contemporary models of verbal working memory (Baddeley, 2003), and recent functional neuroimaging findings (Jung-Beeman, 2005; Sakai, 2005; Stephan et al., 2003). Additional support for the existence of the three perisylvian segments of the "arcuate fasciculus" comes from other DTI studies (Eluvathingal et al., 2007; Lawes et al., 2008), human intraoperative electrocorticography (Matsumoto et al., 2004), functional connectivity (Schmithorst & Holland, 2007), post-mortem dissections (Lawes et al., 2008), and experiments in homologous parts of the monkey brain (Deacon, 1992).

Tractography is also revealing unexpected findings about the projection of the arcuate fasciculus, whose cortical terminations extend beyond the classical limits of Wernicke's and Broca's areas to include part of the posterior middle temporal gyrus and regions of the posterior middle frontal gyrus and inferior precentral gyrus, respectively (Catani et al., 2005). More anterior and ventral portions of Broca's territory seem to be connected to posterior temporal and occipital regions through the uncinate and the inferior fronto-occipital fasciculus of the ventral pathway system (Anwander et al., 2007; Barrick et al., 2007). Finally tractography applied to language pathways highlights the importance of the inferior parietal cortex as a separate primary language area with dense connections to classical language areas through the indirect pathway. Geschwind's territory corresponds to Brodmann's areas 39 and 40, and although its importance as a linguistic region has been recognized for some time, the exact role of

**A Virtual in vivo dissection of the arcuate****B Long direct segment****C Posterior indirect segment****D Anterior indirect segment****Figure 7.6 (plate 4)**

(A) Tractography reconstruction of the direct (long segment) and indirect pathway (anterior and posterior segment) of the arcuate fasciculus. (B–D) The lateralization of the three segments of the perisylvian network from childhood to adulthood. The lateralization remains stable for the long and anterior segment, while the posterior segment becomes progressively symmetrical.

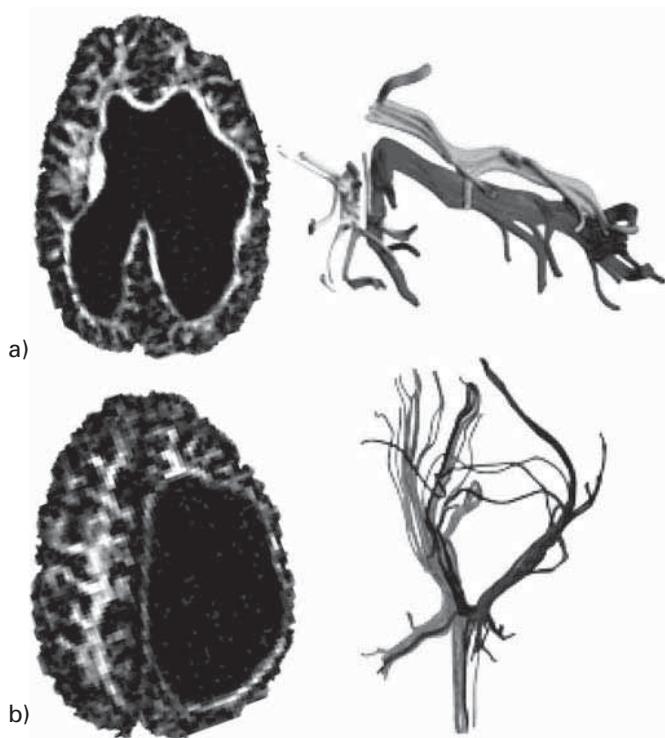
\*Indicates statistical significant difference.

(Panel A reprinted from Catani et al., 2005.)

this area is still largely unknown (Catani et al., 2005). Recent functional imaging studies have shown that Geschwind's territory is part of an extended network activated during comprehension of global coherence of narratives (Martin-Löches et al., 2008), processing concrete concepts (Sabsevitz et al., 2005), episodic memory retrieval of words (Vilberg & Rugg, 2008), and verbal working memory (Jacquemot & Scott, 2006). Also thanks to its anatomical position, Geschwind's territory is a convergence and integration zone for sensory and motor information and their temporal dynamics, and is therefore well suited to play a key role in self-awareness of speech and actions in general (Jardri et al., 2007). Furthermore cortical thickness of Geschwind's territory has been demonstrated to correlate in bilinguals with proficiency and age at acquisition of the second language (Mechelli et al., 2004).

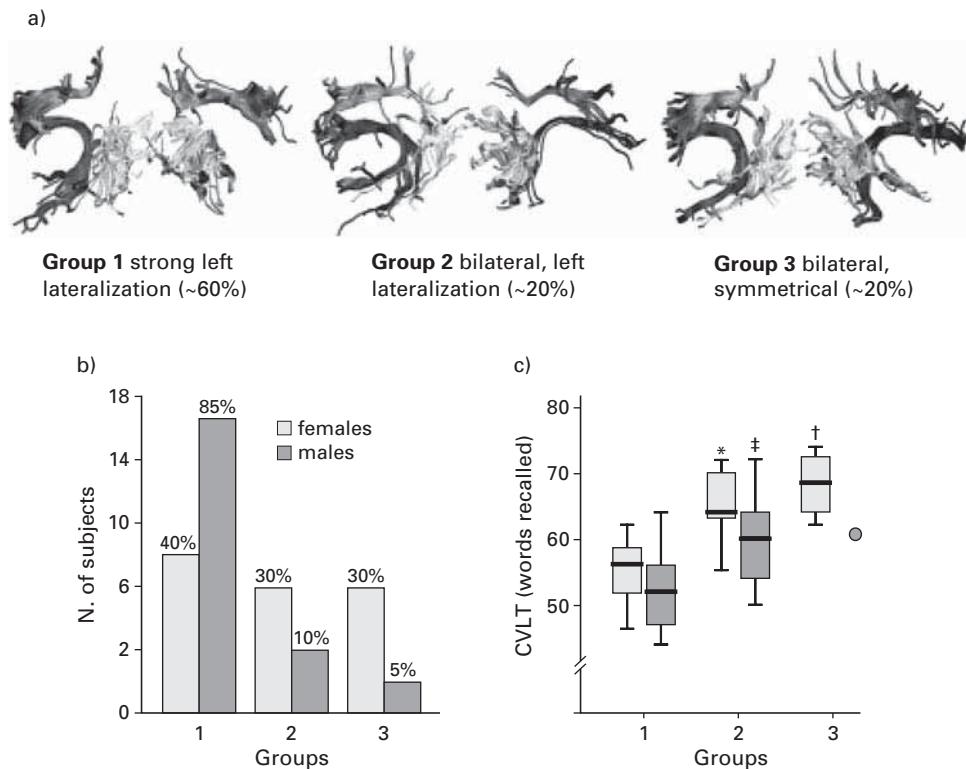
Tractography analysis reveals that the three segments of the arcuate differ in terms of lateralization. The long segment is larger in the left compared to the right, while the anterior segment is larger on the right compared to the left. Both segments remain lateralized throughout adolescence and early adulthood. The posterior segment shows a greater volume in the right compared to the left before adolescence, but throughout adolescence, its volume reduces more on the right than the left, thus causing a shift in the pattern of lateralization that becomes symmetrical (see figure 7.6/plate 4; Pugliese et al., 2008). These modifications in volume are likely to reflect biological changes in white matter accompanying cortical pruning occurring during adolescence. These preliminary data are of special relevance to the issue of plasticity after brain injury. Several functional studies have demonstrated the importance of the controlateral language networks for recovery in conditions including white matter vascular pathology, epilepsy, and brain injury. The application of DTI in these disorders could reveal important information on the mechanisms underlying these white matter reorganization after brain injury. Figure 7.7 (plate 5) shows the DTI images of an 18-year-old male born preterm at 26 weeks with very low weight (<1 kg). The images show severe ventricular dilation and almost complete absence of the corpus callosum. Tractography dissections reveal an extreme right lateralization of all three segments of the perisylvian pathways (complete absence of the left arcuate) and rightward asymmetry of the CST. The above patterns of lateralization are rarely observed in the male population and may have a compensatory significance considering the normal verbal IQ of the subject and his left-handedness.

After adolescence, the degree of lateralization of the long segment is quite heterogeneous. Figure 7.8 (plate 6) shows the pattern of lateralization of the long segment in the adult population. An extreme degree of leftward lateralization is observed in approximately 60% of the normal population (Catani et al., 2007). The remaining 40% of the population show either a mild leftward lateralization (~20%) or a bilateral, symmetrical pattern (~20%). Similar results are reported for left-handed subjects



**Figure 7.7 (plate 5)**

Diffusion-tensor imaging of an 18-year-old male born very preterm at 26 weeks of gestation. (a, b) The axial fractional anisotropy images show marked dilatation of the lateral ventricles, particularly in the left hemisphere. (c) Tractography reconstruction of the perisylvian language pathways was only possible for the right hemisphere. (d) The asymmetry of the corticospinal tract is also evident with a rightward lateralization, which is usually observed in less than 15% of the male population (red streamlines indicate the left CST). Considering the normal IQ of this subject and the left-handedness, a compensatory reorganization of the lateralization of language and motor tracts may have followed the white matter damage at birth.



**Figure 7.8 (plate 6)**

(a) Distribution of the lateralization pattern of the direct long segment (red) and (b) gender differences. (c) Performances on the California Verbal Learning Test (CVLT) according to the lateralization pattern and gender \* $p < .05$  vs. group 1; † $p < .01$  vs. group 1; ‡ $p < .05$  vs. group 1).

(Hagmann et al., 2006; Vernooij et al., 2007). Of particular interest is the report of a gender dimorphism with respect to the lateralization of the long segment, with females more likely to have a bilateral pattern compared to males (Catani et al., 2007; Hagmann et al., 2006).

An important question is the extent to which structural differences between the two hemispheres correlate with functional lateralization and whether the anatomical lateralization of language pathways reflect differences in language performance. Preliminary studies combining DTI tractography and fMRI show no correlation between the lateralization of the arcuate volume and the degree of functional lateralization as determined by fMRI during tasks of verbal fluency, verb generation, and reading comprehension (Powell et al., 2006; Vernooij et al., 2007). The lateralization of the frac-

tional anisotropy values of the arcuate fasciculus seems to correlate better with the functional lateralization as demonstrated in healthy individuals (Powell et al., 2006) and in patients with temporal lobe epilepsy (Rodrigo et al., 2008).

There are also preliminary findings showing that the extreme left lateralization of the direct long segment is associated with worse performance on a complex verbal memory task that relies on semantic clustering for retrieval (i.e., the California Verbal Learning Test; CVLT). The correlation remained significant after splitting the group according to gender, suggesting that the main determinant of CVLT performance is the anatomy (symmetry) of the language pathways, not the gender. Overall, these findings support the notion that lateralization of language to the left hemisphere is an important aspect of human brain organization, but paradoxically a bilateral representation might ultimately be advantageous for certain cognitive functions (Catani et al., 2007).

Other components of the perisylvian networks seem to have a more bilateral distribution or rightward lateralization. Interhemispheric differences have been found in the fractional anisotropy of the anterior indirect segment with higher values in the right side (Catani et al., 2007; Eluvathingal et al., 2007). Another tract connecting the superior temporal lobe to the superior parietal lobe shows a similar rightward lateralization (Barrick et al., 2007). This may be related to the specialization of the right parietal and frontal cortex for visuospatial processing (Doricchi et al., 2008; Thiebaut de Schotten et al., 2005; Thiebaut de Schotten et al., 2008).

## Conclusions

Although the hodological approach to cognition has a long history, the study of tract lateralization is surprisingly still at its infancy. If the lack of methods suitable for anatomical studies of connections in the living human brain can in part justify this gap in knowledge, the complete absence of data on the monkey brain, for which powerful axonal tracing techniques are indeed available, is unforgivable. For decades, anatomical drawings of tracts have been passed on to the anatomical textbook of the next generation, and often the presence of those tracts in both sides of the brain taken for granted. The recent flourishing of techniques based on diffusion imaging suggests that this leap of faith may not necessarily be true for tracts underlying unique human abilities. Clearly, we need a research program that sets off from the footsteps of the “great neuroanatomists” of the nineteenth century, leading us to address those questions that for too long have remained unanswered.

With unprecedented access to the connectivity of living human brain we can compare asymmetry of connections across species, formulate novel neuropsychological models based on anatomical findings on laterality, and take into account interindividual variability within the spared hemisphere to predict recovery in patients with

brain disorders. At the same time, we are well aware that, at present, the hodological approach is more aspirational than proven and stands or falls on the methodological developments and empirical contributions to come.

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## **8 Electroencephalographic and Magnetoencephalographic Indices of Hemispheric Asymmetry**

**Alfredo Brancucci**

### **Basic Properties of EEG and MEG**

Electroencephalography (EEG) and magnetoencephalography (MEG) are two sibling brain mapping techniques commonly considered as neuroimaging methodologies. EEG is sensible to variations of electrical potentials, while MEG detects variations of magnetic fields. Measurements are mass recordings made from the scalp mainly associated with the electromagnetic activity produced by the neurons in the brain. The EEG instrumentation consists of a set of scalp electrodes coupled to high-impedance amplifiers and a digital data acquisition system. MEG instrumentation, much more expensive, requires the use of superconducting quantum interference devices (SQUIDs)-based magnetometers housed in a magnetically shielded room. The number of sites from which neural activity is recorded can vary from 2 to 512 EEG electrodes or from few to 512 MEG sensors. EEG and MEG record neural activity directly, with a high temporal resolution. This means that these techniques are able to record even very fast events, lasting 1 ms or less. This property allows the investigation of transient neural activity, usually studied with event-related potentials (ERPs) or magnetic fields (ERFs), which are brain responses related to the presentation of a stimulus detectable with the averaging technique (Celesia & Brigell, 1992), but also the investigation of spontaneous or induced neural oscillations which are analyzed in the frequency domain (Pfurtscheller & Lopes da Silva, 1999) and require a methodology with fine temporal resolution because oscillations in the brain are very fast events, reaching 500 Hz or more.

The first human EEG recordings were accomplished by the German psychiatrist Hans Berger in the 1920s (Berger, 1929). He observed robust changes when the eyes of his subject were closed and when he performed mental arithmetic. The scientific community was at first quite skeptical that these scalp signals originated in brain tissue, but by 1934 their brain origins had been established (Binnie & Prior, 1994). MEG is a much younger technique, the first magnetic field produced from the brain having been recorded in 1968 by the physicist David Cohen, using a simple copper

induction coil as a detector. To reduce the magnetic background noise, the measurements were made in a magnetically shielded room. Later, a substantial improvement of MEG recording was made possible by the development of the SQUID detectors (Zimmerman et al., 1970; Cohen, 1972).

It is widely believed that the electromagnetic primary source of the signals recorded with EEG and MEG is the current flow in the apical dendrites of pyramidal cells in the cerebral cortex (Hämäläinen, 1992). However, to assess the precise site in the brain where a recorded activation has been produced is a difficult challenge for EEG and MEG researchers. Coherent activation of a large number of pyramidal cells in an area of the cortex can be modeled as an equivalent current dipole (ECD) which embodies the basic element used to represent recorded neural activation. The localization of the ECD constitutes the main limitation of EEG and MEG, reflecting their relatively low spatial resolution. This means that these techniques definitely cannot tell us in which precise location(s) the recorded signal has been generated. Observing brain activity by using EEG or MEG can be compared to watching TV through an opaque glass. Large light spots can be easily observed, but fine spatial details are lost. In order to try to overcome this limitation and to estimate the location of the activity within the brain, advanced signal processing techniques have been implemented which start from the electromagnetic data measured outside the head to estimate the location of the source which produced the recorded data. This procedure is referred to as the inverse problem. Conversely, the forward problem is a situation where we know where the source is and we are estimating the field at a given distance from the source. The primary technical difficulty in EEG and MEG is that the inverse problem does not have a unique solution, that is, there are infinite mathematically "correct" solutions whereas there is only one biologically correct solution—and the problem of finding the best solution is itself the subject of intensive research. In particular, EEG signals are highly sensitive to the conductivity of the brain, skull, and extracranial tissue, and solving the inverse problem to localize regions of neural activation requires accurate knowledge of these tissues, as these can significantly affect the propagation of the electrical signal.

Despite the similarity of EEG and MEG, which can be considered two sides of the same coin and are generated both by neurophysiological and electromagnetic processes, there are important differences between them (Rose & Ducla-Soares, 1990). A first difference concerning the costs of the machine as well as its maintenance is largely in favor of the EEG. An EEG setup can be bought with 30,000–40,000 U.S. dollars, and maintenance has practically no costs, whereas a MEG setup costs more than twenty times more, and maintenance is expensive. However, in contrast to scalp EEG, MEG is reference free and does not bear the artifacts that can be introduced in the data by an actually nonsilent reference. In contrast to electrical potentials, magnetic fields are less distorted by the resistive properties of the skull and scalp, which results in a better spatial resolution of MEG. The decay of magnetic fields as a function of

distance is more pronounced than for electrical fields. MEG is therefore more sensitive to superficial brain activity, which should be useful for the study of cortical activity. Moreover, as electrical and magnetic fields are oriented perpendicular to each other, the directions of highest sensitivity, usually the direction between the field maxima, are orthogonal to each other. Whereas scalp EEG is sensitive to both tangential and radial components of a current source in a spherical volume conductor, MEG detects only its tangential components. Consequently, MEG selectively measures the activity in the sulci, where the dendrites of pyramidal cortical neurons are oriented tangentially to the scalp surface, whereas EEG measures activity both in the sulci and gyri but appears to be dominated by the activity in the gyri, where the dendrites of pyramidal cortical neurons are oriented orthogonally to the scalp surface. These differences make MEG data easier to interpret. Regarding the cellular sources of EEG and MEG signals, EEG is sensitive to extracellular volume currents produced by postsynaptic potentials, whereas MEG primarily detects intracellular currents associated with the synaptic potentials because the field components generated by volume currents tend to cancel out in a spherical volume conductor (Lopes da Silva, 2004). Finally, it should be mentioned that EEG electrodes are positioned directly on the subject's scalp, whereas MEG sensors are independent from the subject's head. Thus, if the subject makes head movements during the recordings, this will not affect the spatial relation between electrodes and neural sources in EEG, but MEG users have to transform the recorded data on the basis of reference points in order to compensate for head movements. However, MEG and EEG should be considered as complementary rather than competing modalities, and more and more often MEG protocols routinely include simultaneous acquisition of multichannel EEG data.

MEG and EEG differ greatly from functional magnetic resonance imaging (fMRI) and positron emission tomography (PET), the other major functional brain imaging techniques, both in the physiological processes that they measure and in the properties of the inverse problem that must be solved in order to produce functional images. Neuronal activation can be detected with fMRI and PET only indirectly, through imaging of localized contrast changes that result from the hemodynamic effects of the activation. A first issue is that the neuronal activation and hemodynamic changes may not always share the same location in the brain. Moreover, methods based on hemodynamics are limited in temporal resolution since blood flow has time constraints which do not allow detecting events associated with neural activity lasting less than 1–2 seconds. In contrast, MEG and EEG signals are the direct (extracranial) manifestations of neuronal activation and allow the recording of changes on the millisecond scale. Consequently, it may be possible with MEG or EEG not only to detect networks of neuronal assemblies but also to determine fine temporality within these networks. The other major difference between MEG or EEG and fMRI or PET is in the form of the inverse problems. Both fMRI and PET involve reconstruction

of images from a large number of independent samples, so that stable images can always be computed at the expense of some mild loss in resolution. In contrast, the MEG or EEG inverse problem involves estimation of brain activation from tens of spatial samples, so that highly restrictive assumptions are required to compute a stable inverse. This presents significant challenges both in the selection of the model, which should reflect these assumptions, and in the interpretation of the resulting inverse solutions.

Numerous attempts have been made in order to solve the inverse problem in EEG and MEG, which has lead to different data analysis techniques. These can be roughly divided in two classes: dipolar and distributed source models. Dipolar source models assume a priori that a small number of current sources in the brain can adequately model the surface measurements. However, electrophysiological studies in primates (Bullier, 2001; Schroeder et al., 1998) and intracranial ERP studies in humans (Blanke et al., 1999; Thut et al., 2000) indicate fast and parallel activation of different brain areas during neural processing (Michel et al., 2004). Also, in epilepsy, interictal activity can propagate very rapidly, leading to activation of multiple or widely distributed sources at the peak of the surface spike (Huppertz et al., 2001; Lantz et al., 2003). Thus, reducing the number of sources by rejecting dipoles that are not within expected areas or that are explaining only a small amount of additional variance might not always be justified. Conversely, distributed source models do not make a priori assumptions on the number and locations of the dipoles in the brain and are based on reconstruction of the neural electrical activity in each point of a three-dimensional grid of solution points, which is greater than the number of measurement points on the surface. The low-resolution electromagnetic tomography algorithm method (Pascual-Marqui et al., 1994) is one of the most used distributed source modeling methods which provides the smoothest possible three-dimensional current distribution in the brain that can generate the observed scalp field. Other distributed source methods are the minimum norm solution (Hämäläinen & Ilmoniemi, 1994), local autoregressive average (Grave de Peralta & Gonzalez, 1994), beamforming (Gross et al., 2001; Sekihara et al., 2001), and Bayesian approaches (Baillet & Garnero, 1997; Phillips et al., 1997; D. M. Schmidt et al., 1999; Trujillo-Barreto et al., 2008).

As mentioned above, the high temporal resolution of EEG and MEG allows the recording of brain rhythms. Rhythmic activity is generated by synchronized oscillations of membrane potentials in large neural populations and appears to be a fundamental property of biological neural networks. It is organized in complex patterns strongly associated with the consciousness state of the individual and the operations the brain is performing, including aspects of perception, cognition, and action. Synchronized neural activity can occur locally between neurons within an area or over longer distances between areas of a wider network (Tallon-Baudry, 2004; Womelsdorf & Fries, 2007). A basic characteristic of rhythmic brain activity are oscillation frequen-

cies, which range from about 0.05 to 600 Hz (Buzsáki & Draguhn, 2004). The functional meaning of these frequencies and their interaction is still a field of intense research, although activity in distinct frequency bands has been associated with some aspects of behavior. Slow-wave sleep or some cerebral diseases are associated with low-frequency bands (delta and theta rhythms, about 1–7 Hz), whereas perceptual binding and conscious integration are associated with the high-frequency range (gamma band, faster than 30 Hz).

### **EEG and MEG in the Investigation of Hemispheric Asymmetry**

The two hemispheres can express their differences in specialization in a variety of forms that can be detected with EEG/MEG techniques possibly associated with behavioral measurements. They can differ in an absolute form, that is, only one hemisphere shows one (or more) areas which are active during a specific task, and they can differ in the number of areas which are active during the task or in the locations of the active areas. All these asymmetries refer to spatial asymmetries. On the other hand, the hemispheres may differ in the timing of their activations. For example, the left hemisphere may respond with different temporal patterns (e.g., shorter latency) compared to the right hemisphere in a particular task. Finally, the asymmetries can be observed also in the performance level of the hemispheres. With particular presentation techniques such as divided visual field (Bourne, 2006) or dichotic listening (DL; Tervaniemi & Hugdahl, 2003), it is possible to lateralize the input in order to be able to ascribe the outcome of a particular task to processes taking place in one or in the other hemisphere. In these cases it is possible to observe hemispheric asymmetries in accuracy and/or in the speed with which the two sides of the brain perform a particular task. For example, right- versus left-sided visual field presentations of verbal material could lead to an asymmetry in the accuracy rather than in the speed of the response commanded by one hemisphere, which may simply be more skilled in performing a particular task compared with the other one.

A legitimate question concerns the possibility of using measures of neural activation to make inferences about the specialization of the hemispheres for one particular behavioral function. Activation measures can actually be used to assess specialization in certain restricted contexts. Testing should be performed on a sample assumed to be homogeneous with respect to individual differences in specialization. Actually, the main aspect of hemispheric asymmetry which can influence task performance other than hemispheric specialization is individual differences in asymmetrical hemispheric activation reflecting the degree to which each hemisphere is engaged (Hagemann, 2004). These individual differences tend to be quite stable over time. Phasic differences in activation which can be elicited by selective priming should be considered as superimposed upon these two more tonic features.

Concerning asymmetry in latencies, the possibility should be taken into account that the differences in response latency depend on interhemispheric transmission time or on the time that one stimulus needs to reach the region in the hemisphere in which it is analyzed. With respect to this point, what produces the reaction time difference would be the duration required to transfer the information from the hemisphere which received it first to the hemisphere prepared to process that type of information or the time needed to perform the response. In these cases, the rough reaction time does not reflect differences in the skill of each hemisphere in the performance of the task. More accurate observations can be performed in split-brain patients in whom interhemispheric transfer does not occur or is strongly impaired. A less direct alternative approach to this issue is to analyze the absolute magnitude of the reaction time differences to ascertain that the difference which occurs is longer than that which plausibly could be produced by interhemispheric transfer time (Hoptman & Davidson, 1994).

Asymmetries in evoked activity or in spontaneous oscillations refer to the degree to which a hemisphere or an area within one hemisphere is differentially activated in response to stimulation or in terms of baseline, spontaneous processes. In other words, asymmetries reveal the presence of a greater or lower activation in one region compared to the homologous region on the other side. In general, measurement methods assume that increases in activation are associated with increases in neural activity, that is, with an increase in the number of neurons in which postsynaptic potentials have been elicited (whether excitatory or inhibitory is a matter of debate; Nunez, 2000). In the case of EEG, it has been shown that desynchronized activity (i.e., decreased alpha power) is associated with an increase in the number of action potentials from neighboring populations of neurons (Pfurtscheller & Lopes da Silva, 1999). However, it has never been demonstrated that these differences in specialization must be paralleled by differences in activations. For example, even if the left hemisphere is specialized in the processing of a certain verbal task, it is possible that it sometimes shows no more activation than the right one. It is even possible that a subject has a bias that results in accentuated EEG/MEG activation of the right hemisphere in presence of a left-hemispheric asymmetry.

One of the most commonly used methods to describe the asymmetry of brain activation is the laterality index. Although not formally statistically proving it, such an index serves to illustrate the brain's hemispheric specialization for a given task. Regarding EEG/MEG studies, a laterality index can be computed on ERP/ERF amplitudes, on ERP/ERF latencies, and from data in the frequency domain (Cajochen et al., 2008). Actually, the laterality index is not widely used, as researchers tend to prefer direct statistical comparisons between data recorded from the left and right hemisphere.

An issue that should be considered is that individual differences in EEG/MEG activation can predict performance on tasks requiring a different engagement of the two

hemispheres, while individual differences in specialization are in general not related to task performance. In fact, whereas no differences in verbal performance have been reported between left- and right-handed subjects, there is strong evidence indicating that greater left-sided posterior activation at rest is correlated with increased performance in some verbal tasks (Davidson et al., 1979).

EEG/MEG measures of hemispheric activation asymmetries within one subject show considerable stability over time. It has been found that alpha power test-retest reliability of resting EEG measures over a 10-month period is around .70 (Gasser et al., 1985; Allen et al., 2004). Individual differences are often underestimated or even ignored in current research in neuroimaging. It is important to note that individual differences exist in both regional activation and hemispheric specialization. Individual differences in hemispheric asymmetries are related to the degree to which one hemisphere can perform a particular type of task or process information in a specific way, and such individual differences in activation can exist among persons having the same pattern of specialization (Hariri, 2009). Individual differences in specialization are often associated with handedness and/or other motor asymmetries which are quite stable over time.

Even if there may be some patterns of hemispheric specialization which might confer an advantage in particular tasks (often: bilateral representation of language in certain left-handed subjects), the nature of the relation between differences in specialization among subjects and patterns of task performance is complex and frequently associated with the consequences of the bilateral representation of certain functions which in some contexts might be advantageous while in others disadvantageous. As an example, it has been shown that certain groups of left-handers, assumed to have bilateral representation of language, have an impaired performance in visuospatial tasks. It can be speculated that the possible relation between individual differences in specialization and task performance is the result of a competition between language and visuospatial skills within the right hemisphere which would impair performance of these subjects in visuospatial tasks.

### **Asymmetries in the Auditory Domain**

Among the perceptual systems, the auditory system is the one which shows the most anatomical and functional asymmetries. Language and music perception, two strongly lateralized functions of human brain, rely mainly on auditory function. In addition, the cortical areas underlying auditory function show the most evident anatomical asymmetries between the left and right hemisphere such as the Heschl's gyrus and the planum temporale (Dorsaint-Pierre et al., 2006; Kolb & Whishaw, 2003).

Concerning connections with the periphery, left and right auditory cortices receive input from both ears and are activated by sounds in both hemispaces (Brodal, 1981).

The auditory system is thus not as contralateral as other systems such as the visual or the somatosensory system in terms of *lateral symmetry*. The ascending auditory pathways coming from the two ears cross the midline at various levels in the brainstem. This crossing is not complete, and many fibers also project ipsilaterally. This generates ipsilateral and contralateral representation of auditory information at the various processing stages, in particular at more central (cortical) sites where, in addition, auditory information can cross the midline via the corpus callosum.

However, neuroanatomical, neurophysiological, and neuropsychological evidence suggest that, although there is an auditory representation of both ears in both cortices, the contralateral representations exceed the ipsilateral ones (King & Carlisle, 1995; Popper & Fay, 1992). For instance, pathway tracing studies in mammals have estimated that the number of afferent fibers crossing the midline is greater than the number of afferent fibers projecting ipsilaterally. In addition, mammalian neurophysiological studies recording from cells in the auditory central areas have indicated stronger excitatory responses to contralateral than to ipsilateral stimuli. This pattern of activity is related to the existence of EE (excitatory-excitatory) cells, which are excited by stimuli presented at both ears but usually more strongly by the contralateral ear, and EI (excitatory-inhibitory) cells, which are excited by contralateral stimuli and inhibited by ipsilateral ones. Lesion studies also suggest a contralateral predominance in the mammalian auditory system (Biedermann et al., 2008).

Several researchers have recorded electromagnetic activity to assess asymmetries in the human auditory system. A few direct intracranial recordings have investigated contralaterality and have reported that the evoked potentials are 30% larger in the hemisphere contralateral to the ear receiving the stimulation (Celesia, 1976). Scalp electrical recordings have shown that the N100 wave (a peak of voltage recorded with the EEG about 100 ms after stimulus onset), and the earlier P30 component, are about 10% larger contralaterally (Näätänen & Picton, 1987). However, EEG responses are affected by electrical volume conduction, which can reduce the contralateral-ipsilateral differences of the recordings. Conversely, MEG data are less sensible to volume conduction and allow assessing more precisely the side and site of origin of neural responses, especially within the sulci such as the sylvian fissure, where auditory cortices lie (Hämäläinen et al., 1993). These studies report that the M100 component (the MEG analogue of the N100) to monaural sounds recorded from the auditory cortex is 15% to 30% larger contralaterally than ipsilaterally (Mäkelä et al., 1993). A further study in which both fMRI and MEG were used investigated the relationships between lateralized auditory stimulation and lateralized processing in the auditory cortex (Woldorff et al., 1999). Stimulations were either monaural, delivered to the left or right ear, or binaural with brief interaural onset delays. The onset delay gives the binaural sounds a lateralized auditory perception and is thought to be a basic clue for sound localization. For the monaural stimuli, fMRI revealed a clear contralaterality in

auditory cortex (index 67%). In contrast, the fMRI activations to the binaural stimuli indicated no contralaterality (51%). The MEG recordings from the same subjects confirmed both the contralaterality for monaural tones and the absence of lateralization for the binaural tones. However, the MEG monaural contralaterality (55%) was less than the fMRI one (67%) and decreased during the poststimulus time period. In sum, these and other reports show that the N/M100 response to monaural stimuli starts earlier and is more sustained contralaterally than ipsilaterally (Pantev et al., 1986; Papanicolaou et al., 1990; Reite et al., 1981).

### Dichotic Listening

The DL technique allows testing separately left and right auditory cortices in a non-invasive manner. It consists of presenting to the subject two different simultaneous auditory stimuli to either ear. DL has been broadly used in the study of hemispherical asymmetries, and the main result that it yielded is that, in general, subjects with left-hemispheric language lateralization are faster and more accurate in reporting verbal items presented at the right ear (Kimura, 1961; Studdert-Kennedy & Shankweiler, 1970). Conversely, they exhibit a left-ear advantage for tasks involving the recognition of musical or environmental sounds (Boucher & Bryden, 1997; Brancucci & San Martini, 1999, 2003; Brancucci et al., 2005b; Brancucci et al., 2008a).

Regarding the functional anatomy underlying this topic, as previously mentioned it is known that monaural input to each ear is represented in both cerebral hemispheres, with an advantage for contralateral over ipsilateral pathways (Fujiki et al., 2002; Hall & Goldstein, 1968). However, when different stimuli are presented simultaneously (i.e., dichotically) to the two ears, interactions between auditory pathways make the situation more complex. On the basis of neuropsychological results, the so-called “structural theory” (Kimura, 1967) suggests that during DL the contralateral pathway suppresses the ipsilateral one. Evidence for this comes from studies testing commissurotomized patients with DL tasks (Milner et al., 1968; Springer & Gazzaniga, 1975). These patients have no difficulty reporting words or consonant–vowel (CV) syllables presented monaurally to either ear. However, when the same stimuli are presented dichotically, they fail to report items presented to the left ear. The lesion of the posterior part of the corpus callosum (splenium) prevents the input to the left ear from reaching the left hemisphere via the indirect contralateral route that goes initially to the right hemisphere and then crosses the callosal pathways (Pollmann et al., 2002). This indirect contralateral route going through the splenium would permit normal subjects to hear dichotic items in both ears, with a residual small advantage favoring the ear contralateral to the dominant hemisphere. In line with the structural theory, a neuroimaging study using PET has demonstrated that verbal dichotic stimuli induce stronger cortical responses in the left temporal lobe, whereas nonverbal stimuli induce stronger activity in the right temporal lobe (Hugdahl et al., 1999).

As an alternative view, the “attentional theory” attributes ear advantages to the priming effect of attending to a particular type of auditory stimulus rather than to a structural advantage (Kinsbourne, 1970). However, growing evidence indicate that both structural and attentional factors play a role in DL (Asbjørnsen & Hugdahl, 1995; Hugdahl et al., 2000; Jäncke et al., 2003; Thomsen et al., 2004).

We conducted two MEG studies aimed at testing whether, from a neurophysiological point of view, the amplitude of neuromagnetic responses induced by nonverbal (Brancucci et al., 2004) and verbal (Della Penna et al., 2007) dichotic stimuli reveals an inhibition of the ipsilateral right auditory pathway. Evoked magnetic fields were recorded from the auditory cortex during passive listening to a series of nonverbal (complex tones) or verbal (CV syllables) stimuli.

In the study using nonverbal material, results showed that the M100 amplitude over the right auditory cortex increased progressively when tones of increasing intensity were provided at the ipsilateral (right) ear. This effect on M100 was abolished when a concurrent tone of constant intensity was added dichotically at the contralateral (left) ear. That contralateral tone was effective on the inhibition of the M100 amplitude increase only when it had a fundamental frequency similar to the ipsilateral tone. This result points to an inhibition driven by the contralateral auditory pathway over the ipsilateral one during DL.

In the study using verbal material, an asymmetrical interaction pattern between the two auditory pathways was observed. Concerning the left auditory cortex, DL of CV syllables having similar versus different spectral content within the dichotic pair caused an inhibition of both ipsilateral (i.e., stimulus presented at the left ear) and contralateral (i.e., stimulus presented at the right ear) pathways. Moreover, considering the left auditory cortex, the inhibition of the ipsilateral pathway (i.e., the ipsilateral neural signal ascending from the left ear) was significantly stronger than the contralateral one. Conversely, concerning the right auditory cortex, ipsi- and contralateral pathways were inhibited to the same extent during DL of CV syllables having similar compared to dissimilar spectral content.

The interactions between contralateral and ipsilateral pathways generating the observed inhibitions would take place at the level of auditory cortex, since the above effects occurred at latencies not earlier than 100 ms after stimulus onset. The M50 component is the earlier auditory response whose source has been localized at cortical level, in the planum temporale of Heschl’s gyrus, containing the primary auditory cortex. Thus, the fact that at the responses at M50 latency no interaction effects were found suggests that the inhibition of the ipsilateral pathway does not occur at subcortical nor at the earliest cortical levels. Indeed, an inhibition effect at the subcortical level would have reduced the amplitude increment of all cortical evoked fields’ components, including both M50 and M100. As an alternative explanation, it could be argued that the M50, which is generated in the earliest stages of cortical auditory

input processing, is more strongly influenced by specific thalamic inputs than the M100. This could explain why M100 is more affected by cortical inhibitory networks during DL. On the whole, it can be speculated that the dichotic inhibition is associated with the information processing of primary and secondary auditory cortex, which is mainly reflected by M100 (Huotilainen et al., 1998; Reite et al., 1994; Yoshiura et al., 1996).

These findings validate the structural theory proposed by Kimura (1967), which explained dichotic ear advantage by reference to the anatomy and physiology of the auditory system. This model emphasizes the notion that the contralateral auditory pathways are dominant, more numerous and more rapidly conducting than the ipsilateral ones. Kimura further suggested that such differences between contralateral and ipsilateral pathways were exaggerated by an occlusion mechanism during dichotic stimulus application, whereby input from the contralateral ear would block the ipsilateral pathways and prevent information from reaching the auditory cortex via the direct ipsilateral route. It should be remarked that these results cannot exclude the possibility that the contralateral pathway, in addition to the ipsilateral one, also undergoes an inhibition during DL. Indeed, a partial inhibition of the contralateral pathway has been demonstrated by recent MEG studies on binaural hearing of simple tones (Fujiki et al., 2002; Kaneko et al., 2003).

Regarding the role of the spectral overlap in the occlusion mechanism, these studies give a physiological basis to previous laterality reports using tonal (Sidtis, 1981) or verbal (Springer et al., 1978) material. Sidtis (1981) demonstrated that a nearly three-fold difference in the magnitude of the laterality measure could be obtained by delivering dichotically tones with similar versus different fundamental frequencies. The fifth interval yielded minimal laterality effects, whereas intervals of a second, a minor third, or an octave as a special case yielded maximal laterality effects. Springer and coworkers (1978) have shown that while report of CV syllables presented to the left ear during dichotic testing was at chance, report of left ear digits under the same conditions was greater than 80% in four out of five commisurotomized patients tested. As the acoustic overlap between CV syllables is greater than the overlap between digits, they concluded that the availability of information from the ipsilateral auditory pathway is a function of the spectral acoustic overlap between competing dichotic stimuli. Similar results have been obtained with subjects who have undergone temporal lobectomy and hemispherectomy (Berlin et al., 1973). Thus, the described results and these previous reports indicate the existence of a strong relationship between the degree of spectral competition and the magnitude of the laterality effect. As the spectral overlap increases (i.e., frequency separation decreases), stimulus competition increases and laterality effects are maximized by favoring the contralateral pathways in each hemisphere. This suggests that the effects of stimulus competition have to be adequately considered in the interpretation of laterality effects, since not only

different types of auditory materials (i.e., verbal vs. tonal) but also small changes in the degree of competition between ipsilateral and contralateral information of the same type might significantly affect the magnitude of perceptual asymmetry.

A former MEG study on auditory M100, aimed at testing Kimura's structural theory (Yvert et al., 1998), used dichotically presented pure tones and found no strong inhibition of the ipsilateral pathway during DL. This may be due to the fact that pure but not complex tones were used. Indeed, it has been shown that the magnitude of DL effects is related to the number of harmonics of stimuli and that dichotic ear advantage is weaker with pure tones (Sidtis, 1988). Furthermore, the frequency interval between the stimuli was very large, as the smaller one was equal to a musical fifth interval. This may have attenuated the dichotic effects, since behavioral evidence has shown that the dichotic effect is strong when the spectral overlap between right and left ear inputs is high (Sidtis, 1981).

In conclusion, the hypothesis of an inhibition driven by the contralateral auditory pathway over the ipsilateral one during DL has been supported by the described analyses of the M100 auditory cortical responses. The inhibition seems to occur at cortical level and to be dependent on the spectral overlap between ipsilateral and contralateral stimuli, existing only for stimuli having similar fundamental frequencies or similar energy distribution on the spectrum.

This outcome should be considered as a first step toward the understanding of pathway interactions during DL. Future research should test the generalization of the present findings with respect to the selection of sounds (i.e., environmental sounds, vocalizations, and noise), possible further asymmetries between left and right pathways and additional peculiar roles of the hemispheres. Moreover, forthcoming studies using stereo-EEG in epileptic patients (presurgical functional monitoring) or single-unit recordings in animals may disclose the respective role of neuronal populations in primary auditory cortex having ipsilateral, contralateral, and bilateral receptive fields. Relevant literature (reviewed in Bear et al., 2001) shows that, beyond the main tonotopic organizational principle of the auditory cortex, there is a second organizational principle based on ear preference. In cat primary auditory cortex, there are alternating patches of neurons, which respond preferentially to binaural stimulation (being inhibited by monaural stimulation) or monaural stimulation (being inhibited by binaural stimulation). These neuronal populations may be a suitable substrate for the DL effects reported in the present study.

### **Language Lateralization**

Language is the main cognitive function in humans that shows asymmetries between the two hemispheres, and the question of lateralization is one of the main topics in language research. Language has been popularly known to be lateralized to the left hemisphere of the brain of most people since the reports of Broca (1863) and Wernicke

(1874) in the nineteenth century. Then, little by little, hemispheric specialization for language has become one of the most robust findings of cognitive neuroscience. Language lateralization has been studied extensively using invasive methods, such as the intracarotid sodium amytal procedure (Wada test), and more recently using noninvasive techniques. EEG and MEG have been used progressively more to obtain additional information about lateralized processes related to language, mainly due to their high temporal resolution, which provides a different view compared to other imaging techniques on the mechanisms implicated in cortical language processing, especially as language is itself based on a rapid sequence of events which requires fast neural processing.

According to the current view of functional lateralization, left-hemispheric specialization for language should be read under a parameter- rather than domain-specific perspective (Zatorre et al., 2002). Language processing is located in the left hemisphere not because it is language that is processed but because “language” processing needs invariantly a general kind of analysis of sensory input, that is, rapid serial processing of streams of sensory input. This kind of analysis is performed better in the left hemisphere possibly because of a different microanatomical structure compared to that of the right hemisphere. Conversely, analyses in the frequency domain, such as those which are required to discriminate the timbres of two musical instruments or simply the pitch of two tones, are better performed in the right hemisphere. Hence, the classic domain-related dichotomy (left–speech vs. right–music) has changed to a physical dichotomy which assigns a better temporal resolution at the left auditory cortex and a better spectral resolution to the right auditory cortex (Hickok & Poeppel, 2007; Tallal & Gaab, 2006; Zatorre, 2003).

Concerning speech perception, the asymmetrical time sampling theory (Poeppel, 2003) proposes that auditory processing occurs preferentially at sample rates tuned to fundamental speech units. The left auditory cortex would integrate auditory signals preferentially into 20-to-50-ms segments that correspond roughly to the phoneme length, whereas the right auditory cortex would preferentially integrate signals over 100 to 300 ms and thus optimize sensitivity to slower acoustic modulations, such as voice and musical instrument periodicity, speech prosody, and musical rhythms (Belin et al., 2004; Peretz & Zatorre, 2005; Schneider et al., 2005). EEG and MEG are the most appropriate techniques to investigate neural events in those time windows. As with other theories on language processing, the asymmetrical time sampling theory links speech processing to neural oscillations. Neural oscillations can be recorded continuously and everywhere from the scalp and reflect spontaneous brain activity which is not related to any specific feature processing. These oscillations undergo profound modulations during speech perception and production, and it has been recently suggested that endogenous cortical rhythms provide temporal and spatial constraints on the neuronal mechanisms underlying speech processing (Giraud et al., 2007). It

appears plausible that oscillations at frequencies matching those of speech features could constitute an intrinsic property of language brain areas.

An important area of language research focuses on the functional role that the two hemispheres play in decoding simple speech signals. Recent neuroimaging experiments suggest a hierarchical organization of the phonetic processing stream with early auditory analysis of the speech signal occurring bilaterally in Heschl's gyri and the superior temporal lobes and later stages of phonetic processing occurring in the middle and anterior superior temporal gyrus and superior temporal sulcus of the left hemisphere, specialized for language processing (Liebenthal et al., 2005). The magnetic mismatch negativity (mMMN; a cortical response elicited by infrequent stimuli) to language stimuli has been shown to be lateralized to the left hemisphere in right-handed subjects for vowels (Näätänen et al., 1997), fricative sounds (Lipski & Mathiak, 2007), syllables (Shtyrov et al., 2000), and words (Pulvermüller, 2001) and may be used to analyze cortical activity during language processing. A further MEG study devoted to investigating neuromagnetic fields elicited by vowels and tones showed that the left auditory cortex had nearly twice as many satisfactory ECD fits as the right one in response to vowels but not to tones (Szymanski et al., 1999). Another study investigating functional specialization of the human auditory cortex in processing phonetic versus musical sounds presented subjects with sequences consisting of frequent and infrequent phonemes (/e/ and /o/) or chords (A major and A minor). Results indicated that within the right hemisphere, the mMMN elicited by an infrequent chord change was stronger than the mMMN elicited by a phoneme change, whereas in the left hemisphere, the mMMN strength for a chord versus phoneme change did not significantly differ. Furthermore, the mMMN sources for the phoneme and chord changes were posterior to the primary auditory areas and the mMMN source for a phoneme change was superior to that for the chord change in both hemispheres. This study indicates that there are spatially distinct cortical areas in both hemispheres specialized in representing phonetic and musical sounds (Tervaniemi et al., 1999).

At a superior level of analysis, the measurement of electromagnetic brain activity attempts to investigate the temporal course and interplay between different neuro-functional subsystems involved in language processing which operate in the milliseconds domain (Friederici et al., 1993; Neville et al., 1991). Recorded responses involve a sequence of deflections (i.e., components of the brain response) that reproduce stages of linguistic information processing in the brain. Language-related EEG/MEG components with different temporal and spatial characteristics of brain activity have been identified. Three different ERP components have been reported to correlate with different aspects of language processing during comprehension. Semantic processes are reflected in the so-called N400 component, a bilateral centroparietally distributed negativity that arises about 400 ms after the onset of a word which is not expected

given the prior semantic context (Kutas & Hillyard, 1980). Studies that utilized intracranial electrode recordings suggest the anterior part of the left inferior temporal lobe as a possible generator for the scalp recorded N400 (Nobre & McCarthy, 1995). Syntactic processes have been found to correlate with two scalp recorded ERP components: a left anterior negativity either between 150 and 200 ms for phrase structure violations (Friederici et al., 1993) or between 300 and 500 ms for morphosyntactic agreement violations between lexical elements (Coulson et al., 1998) and a late, bilateral, centro-parietally distributed positivity around 600 ms, the so-called P600 (Osterhout & Holcomb, 1992).

The evaluation of language lateralization constitutes also a very important part of neurosurgical planning in order to prevent postoperative language deficits. In this context, EEG and MEG were compared with the Wada test, a standard invasive method (Wada & Rasmussen, 1960), also in combination with fMRI (Kamada et al., 2007; Steinbeis & Koelsch, 2008), demonstrating that they are reliable tools for the determination of language dominance. The most common approaches implemented to determine language lateralization have used ERF, which averages MEG signals from multiple trials, and ECD fitting (Papanicolaou et al., 1999; Szymanski et al., 2001). These approaches have been successfully used to localize linguistic cortical activity as compared to the Wada test (Kamada et al., 2007; Merrifield et al., 2007). In addition, event-related synchronization (ERS) and event-related desynchronization (ERD) techniques, which do not take MEG polarity and phase resetting into consideration, can provide complementary information elucidating phase-unlocked oscillatory brain activity, which disappears with signal averaging. ERS-ERD techniques have been used to estimate the average dynamic changes in the amplitude of the MEG frequency spectrum as a function of time relative to an experimental event (Dietl et al., 1999; Wei et al., 1998). In previous literature involving the use of synthetic aperture magnetometry, ERD in the beta or gamma bands was consistently imaged in left-hemispheric language areas during silent reading in healthy subjects (Hirata et al., 2007; Pulvermüller et al., 2003; Yamamoto et al., 2006). Some EEG and MEG studies have further focused on the localization of specific language regions in patients with epilepsy. While healthy subjects show well-known left-hemispheric dominance (Herdman et al., 2007; Liassis et al., 2006; Ressel et al., 2006; Shtyrov et al., 2005), patients with epilepsy show a more atypical language organization (Breier et al., 2005; Pataraia et al., 2005), pointing toward a possible role of the EEG/MEG in presurgical examinations (Sobel et al., 2000). Ressel et al. (2006) developed a tool to investigate hemispheric dominance and time-dependent aspects of cortical language processing based on a verb generation task and a vowel identification task. MEG hemispheric differences were found for both tasks in cerebral language areas. Robust left-lateralization in frontal brain regions was observed with the verb generation task, whereas the vowel identification task yielded significant left lateralization in posterior language regions.

These observations confirm outcome from previous fMRI and more invasive studies, making EEG and MEG valuable supports for noninvasive language assessment in healthy and difficult populations.

### Frontal Asymmetries

In the last 30 years, several studies have investigated the relation between asymmetrical electrical frontal activity and emotion, affective style, and dispositional affect (Coan & Allen, 2004; Davidson, 1998). On the whole, the findings from these studies suggest that greater relative right frontal electromagnetic alpha activity at rest predicts a behaviorally inhibited temperament style, associated with experience of negative emotions, whereas greater relative left frontal electromagnetic alpha activity at rest predicts a socially extroverted temperament style associated with more positive emotions (Davidson, 1988; Kline & Allen, 2008). In general, frontal electromagnetic asymmetry appears to be a quite stable individual trait showing high test-retest reliability and good internal consistency (Allen et al., 2004; Jetha et al., 2009; Towers & Allen, 2009; L. A. Schmidt, 2008; Vuga et al., 2008). Frontal brain asymmetry constitutes the most clear example of lateralized brain activity related to psychological traits and has been conceptualized as a biological substrate of the fundamental dimensions of emotion, approach, and withdrawal (Coan & Allen, 2004).

This evidence is based on the fundamental assumption that alpha band power is an inverse measure of cortical activation in the region underlying the recording electrode(s). This assumption is founded on the well-known effects of alpha blocking by sensory stimulation. Recently, studies combining EEG and hemodynamic imaging methods have shown that cortical alpha activity in one cerebral region is negatively correlated with cerebral perfusion (Cook et al., 1998) and cerebral glucose metabolism in that region (Oakes et al., 2004). These findings generally support the utility of EEG/MEG alpha power as an inverse indicator of regional cortical activation, although the relationships described above are not entirely consistent across cortical regions and recording conditions, and more studies are needed to further clarify the functional significance of alpha oscillations.

Several EEG and some MEG studies have investigated frontal electromagnetic asymmetries both as an acute affective response and as a dispositional traitlike variable related to individual differences in emotional responding. Davidson and Fox (1982) found that infants watching two videotaped segments of happy or sad facial expressions showed greater relative left frontal activity in response to the happy segments. Fox and Davidson (1986) found that babies exhibited greater left frontal EEG activity in response to sucrose (a pleasant taste) compared to water (a neutral taste) and citric acid (an unpleasant taste). Kline and coworkers (2000) reported that elderly women showed greater relative left frontal activity in response to vanilla (a pleasant odor)

compared to water (a neutral odor) and to valerian root (an unpleasant odor). Reeves and colleagues (1989) observed that negative television material produced greater cortical arousal in the right frontal region, while positive television material produced arousal in the frontal areas of the opposite hemisphere. Enhanced left frontal asymmetry has also been associated with self-reported increased positive affect and decreased negative affect in both women (Tomarken et al., 1992) and men (Jacobs & Snyder, 1996). Additionally, research has shown that prominent right frontal activity is associated with more intense negative affect in response to negative film clips in adults whereas stronger left frontal activity is associated with augmentation of positive affect in response to positive film clips (Wheeler et al., 1993).

However, according to some authors, motivational direction (i.e., approach or withdrawal) reflects frontal asymmetries better than affective valence. Harmon-Jones and Allen (1998) reported that a negative though approach-related emotion, such as dispositional anger, was related to greater left anterior activity and less right anterior activity. Harmon-Jones and Allen (1997) also showed that higher levels of behavioral activation sensitivity are associated with greater relative left frontal activity. Accordingly, Sutton and Davidson (1997) reported that higher levels of behavioral activation sensitivity were associated with greater left frontal activity, while higher levels of behavioral inhibition sensitivity exhibited greater right midfrontal activity. Research also indicates that behaviorally inhibited children exhibit greater right frontal activity than noninhibited children (Schmidt, 2008).

It has also been reported that during the menstrual cycle frontal asymmetries can undergo considerable modulations (Hwang et al., 2009). Gonadotropic hormones play an important role in the regulation of emotion, and it has been demonstrated that estrogen can modulate appetitive (approach-positive) and aversive (avoidance-negative) affective behaviors. MEG observations on healthy women during the peri-ovulatory and menstrual phases showed significant interaction of resting MEG alpha activity between hemispheric side and menstrual phases. Difference in spontaneous frontal alpha asymmetry pattern across the menstrual cycle was also noted. Relatively higher right frontal activity was found during the peri-ovulatory phase, whereas relatively higher left frontal activity was noted during the menstrual phase. Another study from the same group observing evoked magnetic fields revealed that the menstrual cycle was coupled with a shift of asymmetrical lateralization of frontal activation across different menstrual phases (Hwang et al., 2008). Evoked magnetic field activity demonstrated significant interactions between hemispheric side and menstrual phase. The right-hemispheric dominance in the peri-ovulatory phase changed to left-hemispheric dominance in the menstrual phase. Significant association between the anxiety score and the left prefrontal cortex activation was mainly observed in the menstrual phase. This study revealed a strong flexibility of functional organization of human brain and a dynamic automaticity of interhemispheric coordination for

possible adaptive regulation under the aversive confrontation in accordance with hormonal fluctuation during the menstrual cycle.

Developmental studies have shown that individual differences in infants' behavior in approach and withdrawal strategies reflect frontal asymmetries which emerge early in life (Kagan & Snidman, 1999; McManis et al., 2002). Kim & Bell (2006) hypothesized that regulatory skills and behaviors developing rapidly during childhood would play a critical role in linking frontal EEG asymmetries to emotional reactivity in children. They followed 25 children from early to middle childhood and tested them at two different points in time with a 4-year interview interval. Results showed that individual variations in a number of regulatory behaviors among children are significantly associated with frontal EEG asymmetries, providing support for the possibility of frontal EEG asymmetry informing the study of the development of regulation in children. Although exhibiting specific patterns of frontal EEG asymmetry in early childhood does not necessarily portend either difficulties or ease in developing important regulatory abilities, right frontal asymmetry was associated with relatively low-level regulatory behaviors and left frontal asymmetry with more favorable regulatory skills. Other studies demonstrated that children of depressed mothers exhibit reduced left frontal activation at the age of 1 month (Harmon-Jones & Allen, 1997) and at 13–15 months (Dawson et al., 1997), and frontal asymmetries had greater sensitivity than behavioral measures in discriminating between infants of depressed and nondepressed mothers (Dawson et al., 1997). These findings suggest that frontal asymmetries can be a biological marker of familial and, possibly, genetic risk for mood disorders, which can potentially have important implications for psychiatric genetic research.

Frontal asymmetries can also serve as a marker of depression or even as an indicator of risk for depression. Individuals with a history of depression, independent of current clinical status, demonstrate a pattern of asymmetrical resting EEG activity over the frontal cortex that distinguishes them from never-depressed persons (Allen et al., 2004; Davidson, 1998; Debener et al., 2000; Hagemann, 2004; Reid et al., 1998). The EEG asymmetry is characterized by relatively greater left versus right frontal alpha-band power as an indicator of decreased left frontal activity (Allen et al., 2004). This pattern of relatively less left frontal EEG activity has been found among persons potentially at risk for depression, such as infants with depressed mothers (Dawson et al., 1997) and adolescents of depressed mothers (Tomarken et al., 2004). Allen and collaborators (2009) investigated risk for depression in subjects with or without a history of depression, using frontal EEG asymmetry as a putative endophenotype for depressive risk. They manipulated serotonergic activity via tryptophan depletion. Response to tryptophan depletion is known to index an underlying vulnerability to depression and may hold prognostic value in the prediction of future affective disorders. Results showed that the magnitude of tryptophan-depletion-induced change in frontal EEG asymmetry significantly predicted the development of depression in the

subsequent months, with greater sensitivity than symptomatic response alone. These preliminary results suggest that tryptophan-depletion-induced changes in frontal EEG asymmetry may provide a more sensitive indicator of risk for imminent depression than symptomatic response to tryptophan depletion.

### Electromagnetic Functional Connectivity

The study of connectivity has its roots in Hebb's classic work *The Organization of Behavior* (1949) and constitutes today one of the major challenges in the investigation of neural mechanisms underlying cognitive function, including perception, attention, consciousness, memory, language, and motor behavior. All these functions are implemented in the brain via large-scale networks comprising different brain regions and, to understand their basic mechanisms, coordination between distant brain areas has to be studied systematically (Varela et al., 2001). Connectivity can be studied on many spatial and temporal scales. In space, it ranges from the axonal wiring in local circuits to the connections between distant brain regions based on large fiber bundles. In time, it extends from the instantaneous functional connectivity established through active synapses to the genetically outlined macroscopic structure of white matter connections. The approach examining the spatial and temporal relationships among the nodes of the brain's neural network (i.e., structural and functional connectivity) is today the most promising way of describing biological bases of cognitive function (Rykhlevskaia et al., 2008).

In comparison to lesion studies, mainly focused on the role of only one area or two in cases of disconnection syndromes, brain imaging methods are better suited for the investigation of complex interactions between different brain structures because they allow researchers to measure simultaneously the anatomical and functional properties from several sites. Functional connectivity refers to the concurrent activity of different cortical regions and typically analyzes the patterns of synchronization of brain activity measured at different locations with different techniques, including EEG (Pfurtscheller & Andrew, 1999) and MEG (Schnitzler & Gross, 2005), as well as PET (Friston et al., 1993) and fMRI (Bhattacharya et al., 2006), in the time and frequency domain. One key distinction concerning connectivity is that of functional versus effective connectivity (Friston, 1994). Measures of functional connectivity do not explicitly address directed interactions between neuronal assemblies; they only quantify statistical dependencies between neuronal signals. Conversely, measures of effective connectivity quantify directed influence that one neuronal system exerts over another.

Since neural activity occurs largely at high-frequency rates, EEG and MEG are the most suitable methods available for recording from the whole brain, as they offer high temporal resolution, which is basically important for this purpose. However, interarea

coordination cannot be read directly from the raw signals registered, as the activity of well-defined parts of cortex does not yield well-defined patterns at their respective sensors. The most common approach to quantifying synchronization is based on computing covariances–correlations among the brain activation time series recorded from the locations of interest. The temporal and spatial information provided by different techniques may influence the way in which functional connectivity can be interpreted. PET and fMRI data typically do not provide fine-grained temporal information, thus limiting the modeling of structure–function relationships of these approaches to the network's components. In contrast, EEG and MEG can reveal the functional order in which these components are activated as well as connectivity indices strictly based on fine temporal features such as synchronization of brain rhythms. In EEG recordings, synchronization is often quantified with coherence, the frequency domain analogue of the cross-correlation coefficient (Rykhlevskaia et al., 2008), and is usually computed using nonparametric spectral estimation techniques, such as Fourier or wavelet transforms. Regarding effective connectivity, estimates of directed interactions between brain areas in the frequency domain can be obtained from parametric spectral estimators, using multivariate autoregressive models. The most used methods are directed transfer function (Kamiński & Liang, 2005), partial directed coherence (Kamiński & Blinowska, 1991; Baccalá & Sameshima, 2001), and dynamic causal modeling (David & Friston, 2003).

One popularly used way to observe cooperation between brain areas with EEG/MEG consists of determining whether the recorded signals at two or more recording sites or neural sources have the same phase (i.e., whether they are phase locked) at a given frequency such as, for instance, the individual alpha frequency. If the two signals have the same phase (i.e., if they are synchronized), it is assumed that the corresponding brain–cortical areas are working in cooperation for the execution of a particular task (Kelso, 1995; Winfree, 2002). Local oscillations would be induced to fuse at a single frequency irrespective of their own natural oscillation rate, and their phases would be coerced to maintain the same relationships. This interpretation has led to many scientific debates concerning both physiological plausibility and technical issues (Llinás et al., 1998). More recently, it has been shown that coupling can also occur between phase and power, showing that cross-frequency coupling can be detected. Osipova and coworkers (2008) computed coherence during rest with closed eyes between the time course of the power in each frequency band and the signal itself within every MEG channel. They found that, even if per se not detectable, high-frequency gamma power (30–70 Hz) was phase locked to alpha spontaneous oscillations (8–13 Hz). The topography of the coupling was similar to the topography of the alpha power and was strongest over occipital areas (Sauseng et al., 2008).

Concerning limitations in the measurement of functional coupling, it should be remarked that EEG, but not MEG, suffers from problems of volume conduction and

active reference electrode, which can add similar components to EEG signals recorded at different electrodes, yielding thereby false coherence values associated, in particular, with the presence of strong sources (Guevara et al., 2005). A typical EEG can show frequent episodes of phase synchronicity, but these should not always be taken as evidence of coordination in the brain because volume conduction can create spurious correlation between electrodes (Nunez et al., 1997). Theories of EEG point out that the spread of neuronal activity depends not only on the strength but also on the orientation of active sources (Niedermeyer, 2004). Structurally, the brain consists of a convoluted outer surface composed by an arrangement of six horizontal layers constituting the neocortex. Dendritic fields of pyramidal cells, which are largely present in layers 3 and 5, are accepted as the main generator of the EEG signal (Mitzdorf, 1987). Their open ionic fields propagate in all directions but are maximal in a direction normal to the cortical layer (Niedermeyer, 2004). In the EEG, spurious phase synchronization can be generated by cortical surfaces running parallel to the scalp which are found in the gyri and at the bottom of the sulci. These radial sources generate a single blurred maximum on the scalp which can be accurately centered but extends spatially much further than circumscribed by the source. Another source of spurious phase synchronization is constituted by patches of cortical tissue orthogonal to the skull which are found in the walls of the sulci. These tangential sources create a pair of smeared maxima called a dipolar pattern. Each end of the dipole forms a basin of isopolar electrical activity within which phase locking is also seen. Thus, phase synchronization in EEG can result from several configurations: only one or several neural sources, with or without coupling. Because a single source cannot create spatially discontinuous phase patterns at the scalp, real synchronization among two or more areas is endorsed if coherence spatial discontinuity is detected. Conversely, when spatial discontinuity is not observed, real phase synchronization cannot be asserted univocally at the level of raw EEG.

In addition to phase locking, empirical observations contain frequent episodes of antiphase locking (Tognoli & Kelso, 2009). However, studies of neural cell assemblies have shown little interest in investigating antiphase synchronization, possibly because antiphase patterns are not better evidence of functional coupling than their phase counterparts. Volume conduction occurs here again, but as tangential patterns are intrinsically discontinuous in space, unlike phase synchronization, spatial discontinuity of the scalp pattern is of no help in deciding the presence of one or two sources.

On the contrary, MEG does not suffer from these problems mainly due to two physical differences between electrical potentials and magnetic fields: (1) Magnetic fields propagate through biological tissue without distortion, whereas electrical potentials are strongly distorted in the route between neural source and recording sites, and (2) the amplitude of magnetic fields decreases faster than electrical potentials with

distance, which reduces the possibility that the activity in regions underlying one recording site is reflected in signals recorded from other sites.

To estimate functional connectivity between bilateral auditory cortices during DL, we performed an EEG study focusing on functional coupling between these areas and on possible influence of right over left auditory cortex during DL of complex nonverbal tones having near compared with distant fundamental frequencies (Brancucci et al., 2005a). We hypothesized that the dichotic stimulation would induce a decline of functional coupling between the two auditory cortices, which could be revealed by a decrease of EEG coherence. EEG was recorded from T3 and T4 scalp sites overlying, respectively, left and right auditory cortices, and from Cz scalp site (vertex) for control purposes. Event-related coherence (i.e., the difference between prestimulus and post-stimulus coherence) between T3 and T4 scalp sites was significantly lower for all EEG bands of interest (delta, theta, alpha, beta, and gamma) during DL of tones having similar fundamental frequencies ("true" DL) compared to tones having distant fundamental frequencies ("sham" DL). This was a specific effect, since event-related coherence did not differ in a monotic control condition in which the same tone pairs were presented in one channel. Furthermore, event-related coherence between T3 and Cz and between T4 and Cz scalp sites showed no significant effects. Conversely, the directed transfer function, a further measure of connectivity estimating the direction of information flow mentioned above, showed negligible influence at group level of right over left auditory cortex. These results suggest a decrease of functional connectivity between bilateral auditory cortices during the processing of dichotic stimuli as one possible neural substrate for the lateralization of auditory stimuli during DL.

A further study from our group used MEG to test the hypothesis of a phase synchronization (functional coupling) of cortical alpha rhythms within a "speech" cortical neural network, comprising bilateral primary auditory cortex and Wernicke's areas, during DL of CV syllables (Brancucci et al., 2008b). Dichotic stimulation was done with the CV-syllable pairs /da/-/ba/ (true DL, yielded by stimuli having high spectral overlap) and /da/-/ka/ (sham DL, obtained with stimuli having poor spectral overlap). Whole-head MEG activity was recorded from healthy right-handed nonmusicians, which showed a right ear advantage in a speech DL task. Functional coupling of alpha rhythms was defined as the spectral coherence at the following bands: alpha 1 (about 6–8 Hz), alpha 2 (about 8–10 Hz), and alpha 3 (about 10–12 Hz) with respect to the peak of individual alpha frequency (Doppelmayr et al., 1998). Results showed a complex pattern of functional coupling: During DL of speech sounds, event-related spectral coherence of the high-band alpha rhythms increased between neural sources in the primary left auditory cortex and Wernicke's areas with respect to sham DL, whereas it decreased between neural sources in the primary left and right auditory areas. The increase of functional coupling within the left hemisphere would underlie the processing of the syllable presented to the right ear, which arrives to the left audi-

tory cortex without the interference of the other syllable presented to the left ear, whose signal is inhibited (Della Penna et al., 2007). Conversely, the decrease of interhemispherical coupling might be due to the fact that the two auditory cortices do not receive the same information from the ears during DL. These results agree with those of the previous study and suggest that functional coupling of alpha rhythms can constitute a neural substrate for the lateralization of verbal auditory stimuli during DL.

### Combination with Other Techniques

The potential of EEG and MEG in the investigation of hemispheric asymmetries can be enhanced by means of the integration with other techniques. Actually, each neuroimaging method is limited either in terms of temporal or spatial resolution, and combining it with complementary techniques can aid in overcoming these limitations.

The most simple method used to combine encephalographic data with data from other methodologies is to seek converging evidence. Although this is not an explicit attempt to combine observations from different techniques, results from, for example, an fMRI study or a lesion or cortical stimulation study made with transcranial stimulation (transcranial magnetic stimulation, TMS, Thut & Miniussi, 2009; transcranial direct current stimulation, TdCS; Schlaug & Renga, 2008; or transcranial alternate current stimulation, TaCS; Kanai et al., 2008) which are consistent with the outcome of an EEG or MEG study in terms of lateral asymmetry or of more local activations can be a valuable support in the interpretation of the data. Converging evidence can be searched at different levels: a review of studies measuring different physical responses but investigating the same issue, multiple-time repetition of the same experimental protocol by recording brain activity with different techniques, and simultaneous recording with different techniques during the execution of one experimental protocol. In the two last cases, two data sets are directly combined using mathematical-statistical algorithms (George et al., 1995). The main assumption is that the activations recorded with the different techniques correspond to the same set of underlying neural generators. The method most often used to combine electromagnetic and hemodynamic data, called “dipole seeding,” uses the local maxima obtained with fMRI or PET as constraints for the localization of EEG/MEG dipole sources, which are assumed to be limited in number (Ahlfors et al., 1999). This method should be used without forgetting that each cognitive function is based in reality on the activation of many neural assemblies. Actually, the physiological relationship between fMRI or PET and EEG/MEG recorded activity is not completely clear. For example, a question to be resolved to achieve an appropriate interpretation of fMRI results is to assess to what extent the recorded signals reflect excitatory and/or inhibitory neuronal activity. Early

studies using 2-deoxyglucose in animal models showed that strong inhibition could be associated with increased glucose uptake (Ackermann et al., 1984). However, indirect evidence has been recently accumulated suggesting that inhibition may not be associated with increased local cerebral blood flow (Waldvogel et al., 2000; Wenzel et al., 2000). To understand the relationships between EEG/MEG and hemodynamic data is one of the most effective means toward achieving a better knowledge of the neural mechanisms underlying human cognitive functions. The use of fMRI and/or optical imaging methods in animals along with electrophysiological recordings may allow researchers to obtain a more precise picture of how the coupling between electromagnetic activity and blood flow occurs (Heeger et al., 2000; Rees et al., 2000).

MEG and fMRI are frequently used in combination in clinical practice related to hemispheric asymmetries, in particular for presurgical mapping to assess language lateralization but also to evaluate abnormal functional lateralization processes. Kircher et al. (2004) used MEG and fMRI to investigate neural mechanisms in the left and right hemispheres underlying mMMN in schizophrenic patients, which is reduced compared to healthy controls. mMMN is an event-related brain response sensitive to deviations within a sequence of repetitive auditory stimuli, which reflects short-term sensory memory. Patients with schizophrenia and matched comparison subjects were studied. Measurements of mMMN to deviant auditory stimuli were generated using the switching noises from the fMRI scanner in order to avoid any interfering background sound. Stimuli included deviants of amplitude, consisting of lower intensity noise, and of duration, consisting of shorter noise bursts. Neuromagnetic and hemodynamic responses to the identical stimuli were compared between the patients and comparison subjects, and it was observed that MEG mismatch fields were smaller in the patient group and a right-hemispheric lateralization for duration deviance was found in the control group. For the relative amplitude of the fMRI signal, differences emerged in the secondary but not primary auditory cortex. Duration deviants achieved a right-hemispheric advantage only in the comparison group, and a stronger lateralization to the left was found for the deviant amplitude stimuli in the patients. This study is in line with previous evidence pointing to the presence of altered hemispheric interactions in the formation of the short-term memory traces necessary for the integration of auditory stimuli. This process is predominantly mediated by the secondary auditory areas such as the planum temporale. Distorted interactions within bilateral secondary auditory areas could be a neural counterpart of psychopathological symptoms in schizophrenia such as hallucinations and formal thought disorder.

A frequent case of imaging techniques combination is when MEG sources have to be precisely mapped onto anatomical brain structure, usually obtained with conventional high-field magnetic resonance imaging (MRI). It was demonstrated recently that MEG and ultra-low-field (ULF) MRI signals can be measured simultaneously and

separated by filtering during data processing (Volegov et al., 2004). This finding is producing a new technique combination to investigate brain function, which is currently being tested. This technique is based on MEG sensor arrays used to perform MRI at ULF intensity. In this imaging method (Mossle et al., 2005), the nuclear spin population in a sample is prepolarized by a relatively strong (up to 0.1 T) magnetic field, and the spin precession is encoded and detected at a measurement field in the microtesla range after the prepolarizing field is removed (McDermott et al., 2004). The combination of these two methods will allow simultaneous functional MEG and structural ULF MRI imaging of the brain, which could replace MEG–MRI coregistration, performed until today with nonsimultaneous recordings, making the process faster and more reliable and reducing imaging costs.

Another promising technique combination is the one with noninvasive brain stimulation. This can be achieved by recording EEG or MEG during (or after, in the case of MEG) the stimulation with TMS, TdCS, or TaCS. To record EEG in concomitance with TMS has been possible since relatively recently, after the development of amplifiers which rapidly stop and restart EEG recording immediately before and after the TMS pulse and, more recently, after the implementation of direct current amplifiers able to deal with saturated currents, which allow for continuous EEG recording even during TMS stimulus application.

The theoretical temporal resolutions of TMS and EEG are very similar, with TMS having only the limitation in the duration of the pulse and EEG having only the limitation in the sample rate. A TMS pulse lasts approximately 1 ms, and EEG sampling rate is usually performed at 1000 Hz, yielding a temporal resolution of 1 ms for each technique. However, the temporal resolution of the TMS–EEG combination is determined not only by the nature of the two techniques taken separately but also by their interaction. Since EEG amplifiers take several milliseconds to reset after TMS is applied and since it needs time for the neural tissue to react to TMS by producing a kind of activity that is detectable at the scalp, which can imply also the generation of neural oscillations, the temporal resolution of the EEG–TMS combination is somewhat slower, around 1/20 of a second (Litvak et al. 2007). Conversely, the spatial resolution of the EEG–TMS combination is relatively low, in the order of 1 cm, similar to the one of the two techniques taken separately. Other than the resolution of the problems related to the interaction between magnetic stimulus and EEG amplifiers referred to above, the combination of the two techniques requires the consideration of other issues, including the distance of the TMS coil from the scalp surface, which is increased by the presence of the EEG electrodes, and the fact that TMS induces tactile and auditory artifacts which should be taken in account. This last point requires that the effects of the stimulation of the active area be compared with ones yielded by the stimulation of a control site. This is especially important in combined TMS–EEG studies in order to disentangle the changes in EEG signals that reflect neural activity caused by the

magnetic stimulation from those evoked by the unwanted sensory stimulation. Moreover, at the same time that it is affecting neural activity, each TMS pulse also transiently activates the muscles in the underlying region of scalp, creating a twitching sensation and additional EEG artifacts.

One issue involving lateral asymmetry in which the use of EEG and TMS together can be crucial involves the role of the medial frontal cortex (MFC) in the voluntary control of action. The MFC has been reported to be active in those tasks in which the need for action selection is increased (Dosenbach et al., 2006). Taylor and coworkers (2007) applied repetitive TMS to the left MFC during a task which required discriminating whether the central arrow in an array is pointing to the left or to the right, responding with the left or right hand. Responses were slower and less accurate if peripheral flanking arrows pointed in an incongruent direction compared to the central arrow. This experimental manipulation of action selection has a robust EEG correlate which consists in the modulation of the lateralized readiness potential (LRP; Coles, 1989). The LRP to congruent and incongruent trials were different, in accordance with behavioral outcome, with the incongruent waveform peaking later, as it takes longer for the primary motor cortex to be activated by the higher level motor systems. TMS–EEG was used to test for a functional link where the MFC acted down on primary motor cortex to select the appropriate action. Left MFC TMS increased the congruence effect on the LRP. This was due to a specific effect on incongruent trials, with the LRP being shifted further away from the congruent waveform, in the direction consistent with continued uninhibited activation of the incorrect response plan. The effects of TMS on behavior and on the LRP showed a correlation where subjects whose incongruent waveform was deflected the most by TMS also showed the greatest worsening of performance after TMS on incongruent trials and were specific for right-hand responses. These effects did not occur when TMS was applied to a posterior control site. This provides evidence that during action selection the MFC interacts with downstream motor cortex, separating the correct motor action plan from the conflicting options.

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#### **IV Hormones, Sex Differences, and Sleep Asymmetry**



## **9 Sex Hormonal Effects on Hemispheric Asymmetry and Interhemispheric Interaction**

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People differ in their pattern of hemispheric asymmetry and in the way in which the two hemispheres interact. This phenomenon had been neglected for a long time. The current research investigates potential sources of individual variation in hemispheric asymmetries with various behavioral and neuroimaging techniques. Using the visual half-field (VHF) technique, Kim, Levine, and Kertesz (1990) concluded that about half of the variation (45.2%) in patterns of hemispheric asymmetry and in the ways the cerebral hemispheres interact is attributable to individual differences in characteristic perceptual asymmetries. Hellige (1993) has claimed that a large amount of this individual variation was treated as random error and usually ignored in the past. Today, we know that many of these individual differences are reliable and sometimes underlie variations in, for example, cognitive abilities. A deeper understanding of these individual differences allows insights in lateralized processes and extends our knowledge about the mechanisms and the origin of hemispheric asymmetries and functional cerebral organization in general. This chapter focuses on sex hormonal factors as one major source of inter- and intraindividual variation in hemispheric asymmetries and interhemispheric interaction.

### **Sex Differences in Hemispheric Asymmetries**

Besides handedness, sex is probably one of the most frequently investigated factors of interindividual variation in hemispheric asymmetry and interhemispheric crosstalk. Indeed, hemispheric asymmetries in language-related tasks (e.g., Bryden, 1979; Franzon & Hugdahl, 1986; Shaywitz et al., 1995), spatial orientation (e.g., Chiarello, McMahon, & Schaefer, 1989; Corballis & Sidey, 1993; Witelson, 1976), and face recognition (Borod & Koff, 1983; Rizzolatti & Buchtel, 1977) have been found to be sex specific. Although several contradictions exist (e.g., Ashton & McFarland, 1991; Sommer, Aleman, Bouma, & Kahn, 2004), the vast majority of studies which found sex differences revealed reduced hemispheric asymmetries in females when compared with males (e.g., Corballis & Sidey, 1993; Hausmann, Ergun, Yazgan, & Güntürkün,

2002; Hausmann & Güntürkün, 1999; Hausmann, Waldie, & Corballis, 2003; Inglis & Lawson, 1981; Juárez & Corsi-Cabrera, 1995; McGlone, 1980; Meinschaefer, Hausmann, & Güntürkün, 1999; Rasmjou, Hausmann, & Güntürkün, 1999; Shaywitz et al., 1995; Voyer, 1996). Moreover, there is some evidence that larger interindividual variability in the magnitude of hemispheric asymmetries exists within the female group, whereas in males prototypical asymmetries are rather robust (Hausmann, Behrendt-Körbitz, Kautz, Lamm, Radelt, & Güntürkün, 1998).

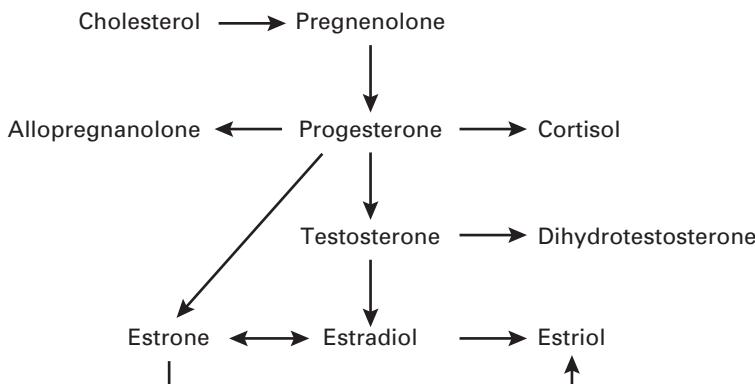
Early clinical data also support these findings. After localized brain lesions, men tend to display verbal deficits after left-hemisphere injuries and nonverbal deficits following right-hemisphere damage, whereas the deficits are less hemisphere specific for women (McGlone, 1977, 1978; McGlone & Kertesz, 1973; Wechsler, 1955). However, as mentioned above, not all studies were able to show sex differences (see also chapter 10 in this book). Reviewing an important part of the literature, Voyer (1996) concludes that even in the majority of studies focusing on hemispheric asymmetries, no interaction with sex occurs. If some studies reveal sex differences while others do not, this is most likely indicative of other interindividual factors which have been overlooked and thus have not been controlled.

Several biological and social factors have been considered to explain the *small difference* in hemispheric asymmetries. With respect to biological explanations, there is ample evidence that sex differences in cognitive brain functions arise at least partly because of distinct hormonal environments in men and women. Moreover, sex-hormone levels are not stable but fluctuate within relatively short-term intervals—for example, during the menstrual cycle in women, which might contribute to the larger variability in hemispheric asymmetries in women depending on the hormonal status at the time of testing.

On the following pages it is argued that sex hormones have powerful neuromodulatory properties that dynamically change the functional brain organization (i.e., hemispheric asymmetries and interhemispheric interaction) and cognitive behavior not only during prenatal development but throughout life. Besides a better understanding of sex hormonal effects on cognitive brain functions, this research may significantly contribute to addressing the question of whether sex differences in cognitive brain functioning truly exist and where they originate.

### **Sex Hormones in Action**

Hormones are biologically active substances that are released by endocrine glands and transported through the bloodstream to another tissue where they regulate functions of the target tissue. The present review focuses on sex hormones (i.e., gonadal steroid hormones), which are mainly synthesized by gonads (i.e., ovaries and testes) and adrenal glands. Additionally, some steroid hormones are directly produced within the brain (neurosteroids; Rupprecht, 2003).

**Figure 9.1**

Biosynthetic pathway of steroids (selection). Arrows represent at least one metabolic step in biosynthesis. See Schumacher et al. (2007) for details.

Sex hormones are synthesized via conversion from cholesterol into pregnenolone, the main precursor of sex hormones. Pregnenolone is then converted by specific enzymes into gestagens, such as progesterone (P) and allopregnanolone, and androgens, such as testosterone (T) and dihydrotestosterone (DHT). T (but not DHT) can be aromatized into estradiol (E) by the enzyme aromatase in only one metabolic step (see figure 9.1).

All steroids are fat soluble and pass easily through cell membranes. Sex hormonal effects can be mediated by slow genomic mechanisms through nuclear receptors as well as by fast nongenomic mechanisms through membrane-associated receptors and signaling cascades (e.g., McEwen & Alves, 1999). Thus, genomic and nongenomic steroid hormone effects within the central nervous system provide the molecular basis for a broad spectrum of steroid actions on neuronal functioning and plasticity.

As a result, sex hormones have several basic effects on (neuro)physiology which are not only restricted to sexual and reproductive behavior but can also be extended to nonsexual behavior, such as cognitive functioning. Thus, it comes as no surprise that sex hormones have been shown to be one potential source of individual differences in cognitive behavior, particularly for those cognitive abilities that are assumed to be sex sensitive. Up to now, however, it remains relatively unclear what exactly the underlying hormonal mechanisms are that lead to powerful changes in functional brain organization (Wisniewski, 1998) which then can affect the performance in various cognitive domains.

### Organizing Effects of Hormones on Hemispheric Asymmetries

Gonadal steroid hormones have organizing and activating effects. The distinction between these sex hormonal effects has been extremely heuristically valuable to con-

ceptualize hormone-behavior interactions. Organizing effects of sex hormones affect the neuronal development underlying cognitive behavior. Activating effects of steroid hormones modulate functional interactions with existing neuronal structures (Phoenix, Goy, Gerall, & Young, 1959). However, this is a simple classification, and the large variety of effects of sex hormones on cognitive abilities and hemispheric asymmetries cannot simply be placed in two discrete categories (Arnold & Breedlove, 1985).

Although some contradictions exist, the majority of studies suggest that gonadal steroid hormones affect functional development during early ontogenesis (Murphy et al., 1994). Moreover, these studies suggest that genetic factors can change the normal hormonal environment which eventually affects hemispheric asymmetries as epigenetic factors during ontogenesis. The following paragraphs give some examples of clinical groups that provide an ideal opportunity to investigate the organizing effects of atypical hormone concentration during pre- and perinatal development on hemispheric asymmetries.

### **Unusual Prenatal Hormonal Environment**

Congenital adrenal hyperplasia (CAH) in boys and girls results from an enzymatic deficiency which affects the feedback loop involving the production of cortisol. The consequence is the overproduction of androgens, which is usually stopped by cortisol therapy after birth. Tirosh, Rod, Cohen and Hochberg (1993) showed that lateralization in a verbal task was significantly enhanced in CAH children compared with healthy right-handed controls, particularly in female CAH patients. Although in other studies researchers did not observe any specific effects of gonadal steroid hormones on hemispheric asymmetries (Cappa et al., 1988; Helleday, Siwers, Ritzen, & Hugdahl, 1994; Mathews, Fane, Pasterski, Conway, Brook, & Hines, 2004), this finding suggests an androgenic role in language lateralization.

Besides the assumption of a masculinizing role of T and its metabolite DHT, it has been suggested that E (aromatized from T) plays a defeminizing role for male development. For example, Hines and Shipley (1984) observed that right-handed women who were prenatally exposed to diethylstilbestrol (DES) for at least five months revealed a more masculine pattern of lateralization than did their unexposed sisters on a verbal dichotic listening task. Similarly, Scheirs and Vingerhoets (1995) suggested that intrauterine exposure to DES in people results in atypical patterns of hemispheric asymmetries. However, another study (Smith & Hines, 2000) did not replicate any differences between DES-exposed women and unexposed sisters on a verbal dichotic listening task. The authors concluded from this finding that there might be a critical period for hormonal influences. Hormonal effects related to DES exposure seem to occur only relatively early (i.e., prior to week nine of gestation). Although this explanation might indeed account for different effects among studies, the neuronal mechanisms underlying the DES-related changes in lateralization are still unknown.

### Chromosomal Aberrations

Studies on clinical groups with anomalies in sex chromosomes and related atypical concentrations in sex-hormone levels support the idea of a modulation in functional cerebral organization. Dichotic listening studies by Netley (1977; Netley & Rovet, 1982) and Gordon and Galatzer (1980) revealed that patients with X Turner syndrome (X0 condition), which is characterized by a gonadal dysgenesis, suffering from low pre- and postnatal levels of E and P, showed more symmetrical performance between hemispheres. This rather suggests a feminizing role of early E exposure during sensitive periods in women.

Moreover, Netley and Rovet (1984) reported that boys with XXY Klinefelter syndrome and concomitant low T levels showed reduced asymmetries in verbal left-hemispheric and larger asymmetries in nonverbal right-hemispheric tasks. A recent functional magnetic resonance imaging (fMRI) study (Van Rijn, Aleman, Swaab, Vink, Sommer, & Kahn, 2008) in 15 Klinefelter men revealed a reduced hemispheric specialization for language as a result of a decreased asymmetry in the superior temporal gyrus and the supramarginal gyrus (part of Wernicke's area). However, it remains unclear whether these effects are due to the androgen deficit during prenatal development or to androgen supplementation later in life. The authors even consider the possibility of direct, nonhormonal effects of sex chromosomes on brain maturation.

### Activating Effects of Hormones on Hemispheric Asymmetries

Besides organizing effects during early ontogenesis, gonadal steroid hormones also influence hemispheric asymmetries later in life, throughout adulthood (Forget & Cohen, 1994). Studies on lateralization in transsexuals who underwent a hormonal cross-gender treatment for at least several months provide an interesting opportunity to investigate whether patterns of lateralization are influenced by biological–genetic sex or by the actual hormonal environment (Forget & Cohen, 1994). The observation that men and genetically male transsexuals reveal differences in lateralization strongly suggests that the influence of sex hormones on cerebral structures and functions is not fixed prenatally. Specifically, it has been shown that women and male-to-female transsexuals reveal similar functional asymmetries (Cohen & Forget, 1995). However, atypical lateralization has not been reported in all studies (Herman, Grabowska, & Dulko, 1993; Sommer et al., 2008).

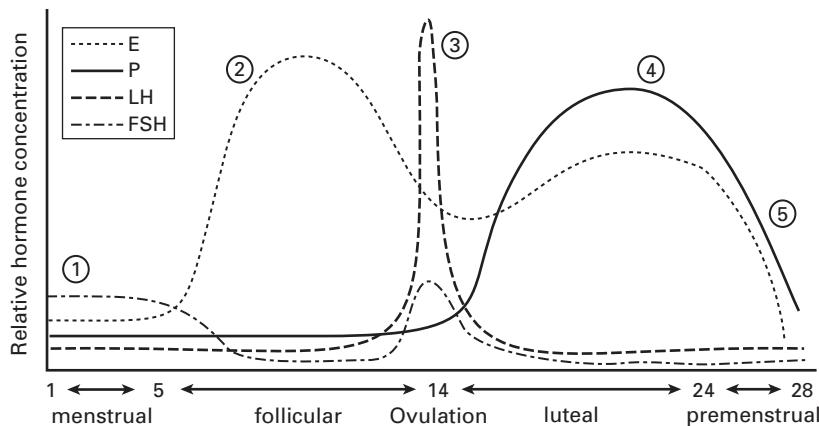
For example, a recent fMRI study (Sommer et al., 2008) showed that, although cerebral activation was related to sex hormonal changes, lateralization in a verbal and spatial task was not affected by cross-sex hormonal treatment but rather remained stable. Another study (Cohen-Kettenis, van Goozen, Doorn, & Gooren, 1998) investigated male-to-female and female-to-male transsexuals, who were not yet hormonally treated, and found the degree of lateralization in both transsexual groups to be between those of healthy male and female controls. This suggests that cross-gender

identity can affect lateralization and cognitive behavior even before hormonal treatment, perhaps as a result of organizational hormonal influences.

### Hemispheric Asymmetries during the Menstrual Cycle

The most dramatic hormonal changes in women within physiologically normal ranges and within short time periods occur during the menstrual cycle (see figure 9.2). For this reason, the menstrual cycle has been the focus of studies investigating cognitive behavior and its underlying functional brain organization.

Several studies suggest that sex-sensitive cognitive behavior can fluctuate across the menstrual cycle (e.g., Gordon et al., 1986; Hampson, 1990a, 1990b; Gordon & Lee, 1993; Epting & Overman, 1998; Hausmann, Slabbekoorn, Van Goozen, Cohen-Kettenis, & Güntürkün, 2000; Mumenthaler et al., 2001; Rosenberg & Park, 2002). For



**Figure 9.2**

The menstrual cycle. Schematic illustration of fluctuations in sex-hormone (estradiol, E; progesterone, P) and gonadotropin levels (luteinizing hormone, LH; follicle-stimulating hormone, FSH) during an average 28-day menstrual cycle. LH and FSH secretion by the pituitary gland determines the menstrual cycle. Cycle day 1 is defined by the discharge of blood from the nonpregnant uterus. During the menstrual phase (1), cycle days 1 to 5, the concentrations of E and P are lowest. Beginning with cycle day 6, E level continuously increases, approaching its maximum about one day before ovulation (follicular phase; 2). P level remains low during the follicular phase. About 14 days after menstruation begins, LH secretion initiates ovulation (3). E level drops slightly. After ovulation, the small cells that surround the egg undergo chemical changes (luteinization). During this luteal phase, E and P are secreted by the luteinized cells. About 7 to 8 days postovulatory, E level approaches its second maximum together with P. P level reaches its peak at around cycle day 22 (midluteal phase, 4). Levels of E and P fall rapidly between cycle day 24 and 28 (premenstrual phase, 5) and a new cycle begins (Asso, 1983).

example, it has been shown that accuracy in specific spatial tasks, such as mental rotation, changes during different cycle phases, indicating higher accuracies during the menstrual phase (cycle day 2; low E and P levels) than during the midluteal phase (cycle day 22; high E and P levels). In this study (Hausmann et al., 2000), accuracy in mental rotation was positively and negatively related to T and E levels, respectively. However, menstrual-cycle-related fluctuations in cognitive abilities were not always found (e.g., Gordon & Lee, 1993; Epting & Overman, 1998; Rosenberg & Park, 2002), and the specific relationship between sex-hormone levels and cognitive performance in normally cycling women is also inconsistent.

Beside hormonal influences on cognitive behavior, it has been shown that hemispheric asymmetries also fluctuate across the menstrual cycle, presumably as a result of cycle-related hormonal variations (e.g., Bibawi, Cherry, & Hellige, 1995; Hampson, 1990a, 1990b; Hausmann, 2005; Hausmann & Güntürkün, 2000; Hausmann, Becker, Gather, & Güntürkün, 2002; Heister, Landis, Regard, & Schroeder-Heister, 1989; Holländer et al., 2005; Mead & Hampson, 1996; McCourt, Mark, Radonovich, Willison, & Freeman, 1997; Rode, Wagner, & Güntürkün, 1995; Sanders & Wenmoth, 1998). However, the results are somewhat controversial (see table 9.1), and the underlying mechanisms for these dynamic cycle-related changes in hemispheric asymmetries are almost completely unknown.

Regarding the potential mechanisms underlying cycle-related changes in hemispheric asymmetries, some studies suggest that hormonal influences are restricted to a single hemisphere (e.g., Hampson, 1990a), but there is dispute as to which one. Using the VHF paradigm, Bibawi et al. (1995) found a left-hemisphere superiority in a nonlateralized chair-identification task during the midluteal phase and concluded that high levels of sex hormones selectively activate the left hemisphere. The idea of unilateral activation was supported by Sanders and Wenmoth (1998) in a dichotic listening study. In contrast to Bibawi et al. (1995), however, these authors found that it was mainly the right-hemisphere performance that was suppressed during the midluteal phase, resulting in a stronger left-hemispheric advantage for a verbal task during this phase and a stronger right-hemispheric advantage for a music task during menses. An alternative mechanism has been proposed by McCourt et al. (1997). The authors concluded from their visuomotor task that both the left and right hemisphere might have been nonspecifically activated midluteally, rather than there being a suppression of the right hemisphere.

The vast majority of these studies did not measure hormone levels, which is a fundamental prerequisite for validation of cycle phases and to directly relate sex-hormone levels to performance measures and hemispheric asymmetries. In fact, it has been shown that only about 60% of younger women ovulate during each menstrual cycle (Metcalf & Mackenzie, 1980), and the timing of hormone fluctuations varies between and within women. Studies including hormone assays (e.g., Gordon, Corbin,

**Table 9.1**  
Studies on menstrual-cycle-related changes in functional cerebral asymmetries

Study	Participants	Cycle phases (cycle days)	Hormone assay	Main results
<i>Dichotic listening studies</i>				
Altelmus et al. (1989)	39 normally cycling women (mean age = 30 years)	Follicular phase (6–12) Premenstrual phase (21–28)	No	Fused rhymed words tests (three versions) and emotional words test (two versions): Reduced REA during follicular phase (degree of asymmetry, accuracy).
Hampson (1990a)	45 normally cycling women (mean age = 23.7 years)	Menses (3–5) Midluteal phase (18–23)	No	Dichotic words test: No significant effects of cycle phase on REA.
Hampson (1990b)	50 normally cycling women (mean age = 26.4 years)	Menses (3–5) Follicular phase (12–13)	E, P, LH (blood)	Dichotic words test: Reduced REA during menses (accuracy). E positively related to the degree of asymmetry (accuracy).
Mead & Hampson (1996)	36 normally cycling women (mean age = 23.7 years)	Menses (3–5) Midluteal phase (18–23)	E (saliva)	Emotional words test—verbal component: Reduced REA during midluteal phase (accuracy, only for women tested first during the midluteal phase). Emotional words test—nonverbal component: Reduced LEA during menses (accuracy).
Weekes & Zaidel (1996)	45 normally cycling women	Menses Luteal phase	No	Verbal task: Reduced REA in women during menses (accuracy, between-participants analysis).
Sanders & Wenmoth (1998)	32 normally cycling women (mean age = 24 years)	Menses (3–5) Midluteal phase (20–22)	No	Consonant–vowel identification task: Reduced REA during menses (accuracy).
Alexander et al. (2002)	30 normally cycling women (mean age = 32 years)	Menses (1–7) Follicular phase (8–14) Midcycle phase (15–21)	No	Musical chord recognition task: Reduced LEA during midluteal phase (accuracy). Fused rhymed words tests (three versions) and emotional words test (two versions): Reduced REA during premenstrual phase compared with follicular phase (degree of asymmetry, accuracy).
Wadnerkar et al. (2008)	25 normally cycling women (mean age = 22.6 years) 20 men (mean age = 22.2 years)	Premenstrual phase (22–28) Menses (2–5) Midluteal phase (18–25)	No	Men revealed stable but generally smaller REAs. Consonant–vowel test: Reduced REA during menses (accuracy). Men (tested once) revealed a strong REA different to that in women during menses.

**Table 9.1**  
(continued)

Study	Participants	Cycle phases (cycle days)	Hormone assay	Main results
<i>Visual half-field studies</i>				
Heister et al. (1989)	12 normally cycling women (age range = 22–39 years)	Menses (1–3) Follicular phase (8–14) Luteal phase (15–22) Premenstrual phase (23–28)	No	Lexical decision: No significant effects of cycle phase on RVFA. Face discrimination task: Reduced LVFA during premenstrual phase compared with menses (response times).
Chiarelli et al. (1989)	24 normally cycling women (mean age = 23.5 years) 24 men (mean age = 23.0 years)	Menses (2–3) Follicular phase (10–12) Midluteal phase (23–25)	No	Lexical decision task: Stricter response bias ( $\log \beta$ ) in LVF than RVF during follicular and luteal phase; reversed pattern during menses. No cycle effects in discrimination index $d'$ (signal detection theory). Men revealed the stricter response bias in LVF during corresponding time intervals (different to that in women during menses).
Bibawi et al. (1995)	13 normally cycling women 16 men	Menses (3–5) Midluteal phase (17–19)	No	Line orientation task: No significant effects of cycle phase on LVFA. Chair identification (nonlateralized): Significant RVFA during the luteal phase but not during menses (accuracy). Men revealed no VHF effect during corresponding testing session.
Rode et al. (1995)	17 normally cycling women (mean age = 26.3 years)	Menses (2) Luteal phase (22–25)	E, P (blood)	Face processing: No significant effects of cycle phase on LVFA. Word matching task: No significant effects of cycle phase on RVFA. Figural comparison task: Reduced LVFA during luteal phase (response times). E and/or P were not significantly related to performance measures.

**Table 9.1**  
(continued)

Study	Participants	Cycle phases (cycle days)	Hormone assay	Main results
Mead & Hampson (1996)	36 normally cycling women (mean age = 23.7 years)	Menses (3–5) Midluteal phase (18–23)	E (saliva)	Rhyming words task (eliciting RVFA): Significant decrease in LVF performance during midluteal phase (accuracy, within-participants analysis, simple comparisons).
Weekes & Zaidel (1996)	45 normally cycling women	Menses Luteal phase	No	Face recognition task: Reduced LVFA during menses (response times, between-participants analysis). Significant decrease in LVF performance during midluteal phase (accuracy, within-participants analysis, simple comparisons).
Compton & Levine (1997)	24 normally cycling women (mean age = 24 years)	Menses (2–5) Follicular phase (8–11) Midluteal phase (19–22)	No	Lexical decision task: No significant differences in RVFA between groups (between-participants analyses).
Hausmann & Güntürkün (2000)	26 normally cycling women (mean age = 30.4 years) 9 men (mean age = 29.3 years) 21 postmenopausal women (mean age = 56.1 years)	Menses (2) Midluteal phase (21–23)	P (saliva)	Lexical decision task: No significant effects of cycle phase on RVFA.
Hausmann, Becker et al. (2002)	12 normally cycling women	15 testing sessions over 6 weeks in consecutive intervals of 3 days	E, P, T, LH, FSH (blood)	Face decision task (two versions): No significant effects of cycle phase on LVFA. Word matching task: Reduced RVFA during midluteal phase (accuracy): Figural comparison task: Reduced LVFA during midluteal phase (accuracy). P negatively related to degree of asymmetry (accuracy). Face discrimination task: Reduced LVFA during midluteal phase (accuracy). Controls revealed stable VHF effects in all tasks during corresponding time intervals. Word matching task: E positively related to degree of asymmetry (accuracy, longitudinal design). Figural comparison task: P negatively related to degree of asymmetry (accuracy and response times) and positively and negatively related to RVF accuracy and RVF response times, respectively (longitudinal design). E negatively related to degree in asymmetry (response times, longitudinal design).

(continued)

Study	Participants	Cycle phases (cycle days)	Hormone assay	Main results
<i>Functional magnetic resonance imaging studies</i>				
Dietrich et al. (2001)	6 normally cycling women (age range = 21–31 years) 6 men (age range = 22–29 years)	Menses Follicular phase (11–12)	E, T (blood)	Word stem completion task, Mental rotation task, Motor task: No significant effects of cycle phase on performance of any task. Cognitive tasks and brain activity: Reduced cortical activation during menses. Increased general activation in women during follicular phase than men.
Fernández et al. (2003)	12 normally cycling women	Menses (2–4) Midluteal phase (21)	E, P, T, LH, FSH, SHBG, DHEA (blood)	Synonym judgment task: No significant effects of cycle phase on performance. Brain activity: Reduced left-lateralized activation during midluteal phase. P negatively related to degree of asymmetry in activation.
Weis et al. (2008)	14 normally cycling women (mean age = 26.8 years) 14 men (mean age = 27.4 years)	Menses (1–3) Follicular phase (9–11)	E, P (blood)	Word matching task: Reduced RVFA (response times), which was related to reduced inhibitory influence on the right inferior frontal gyrus during follicular phase. E negatively related to degree of interhemispheric inhibition. Men revealed stable RVFA. No changes in interhemispheric inhibition on the right IFG during corresponding time intervals.

Note. REA, right-ear advantage; LEA, left ear advantage; LVF, left visual field; RVF, right visual field; RVFA, right visual half-field advantage; E, estradiol; P, progesterone; T, testosterone; LH, luteinizing hormone; FSH, follicle-stimulating hormone; SHBG, sex-hormone binding globulin; DHEA, dehydroepiandrosterone; IFG, inferior frontal gyrus.

& Lee, 1986) had to eliminate nearly half of their female participants from further analyses because post hoc hormone assays revealed that women were not tested in the expected cycle phase. Different properties of the task (modality, task difficulty, sex sensitivity of the task) and carry-over effects due to repeated measures (Hausmann & Güntürkün, 1999) are also likely to contribute to inconsistencies in the literature.

Taking these methodological issues into account, Hausmann and Güntürkün (2000) tested normally cycling women (not taking hormonal contraceptives) during menses (low E and P levels) and during the midluteal phase (high E and P levels) on a prototypical left-hemispheric VHF task (word matching) and two prototypical right-hemispheric VHF tasks (figural comparison, face discrimination). Cycle phases were validated post hoc by measuring hormone levels from saliva samples. Additionally, age-matched men and postmenopausal women (without hormone therapy; HT) were tested in corresponding time intervals. The authors found a decrease in hemispheric asymmetries during the midluteal phase in all three VHF tasks, albeit differing in the size of the effect, as a result of an increase in performance of the subdominant hemisphere. Lateralization patterns in men and postmenopausal women were similar to those in women during menses and remained stable over time. Moreover, P levels in normally cycling women were negatively related to the degree of hemispheric asymmetry in the figural comparison task. This finding has been replicated in a follow-up study, in which normally cycling women were tested 15 times at three-day intervals (Hausmann, Becker, et al., 2002). This approach additionally allowed for longitudinal analyses of asymmetry–hormone relationships over more than an entire menstrual cycle. In both the cross-sectional and the longitudinal analyses, the authors again found that high P levels were related to reduced hemispheric asymmetries as a result of an increase in left-hemispheric performance in the figural comparison task. In this study, E levels were related to the performance of both VHFs, and hence, hemispheric asymmetries were not affected.

### **Hypothesis of Progesterone-Modulated Interhemispheric Decoupling**

Based on the findings of task-independent changes in hemispheric asymmetries, Hausmann and Güntürkün (2000; Hausmann, Becker, et al., 2002) concluded that sex hormones do not selectively modulate either the left or right hemisphere but, instead, influence the interaction between them, and for P in particular. This idea is based on the assumption that interhemispheric inhibition via the corpus callosum is a fundamental prerequisite for the manifestation of hemispheric asymmetries (Cook, 1984; Chiarello & Maxfield, 1996). Specifically, it has been assumed that the superior hemisphere for a particular task inhibits the inferior hemisphere (perhaps to avoid identical cognitive processes).

Although corticocortical transmission is mainly excitatory, the longer lasting effect of callosal activation seems to be inhibitory (Innocenti, 1980), because most callosal

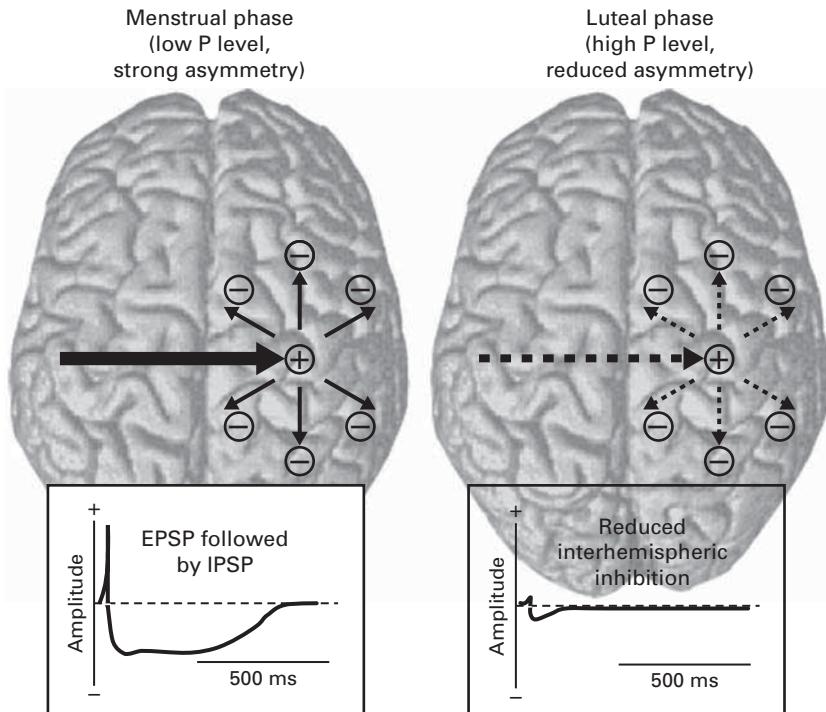
fibers terminate on pyramidal neurons, which then probably activate GABAergic interneurons (Toyama & Matsunami, 1976; Toyama, Tokashiki, & Matsunami, 1969). Thus, it seems that the corpus callosum induces a short excitatory postsynaptic potential followed by a sustained inhibition (Kawaguchi, 1992).

In their hypothetical model, Hausmann and Güntürkün (2000, Hausmann, Becker et al., 2002) proposed that high levels of P during the midluteal phase attenuate interhemispheric inhibition, resulting in a functional decoupling of the two hemispheres. This then might lead to reduced hemispheric asymmetries with the performance of the subdominant hemisphere being increased (see figure 9.3).

At a physiological level, it was proposed that P and its metabolites, such as allo-pregnanolone, reduce interhemispheric inhibition by suppressing the excitatory responses of neurons to glutamate as well as by enhancing their inhibitory responses to GABA (Hausmann & Güntürkün, 2000; Hausmann, Becker, et al., 2002). In fact, pharmacological studies have demonstrated that P suppresses the excitatory neural responses to glutamate, an effect which was due to an attenuation of non-NMDA glutamate receptors (Smith, 1991; Smith, Waterhouse, & Woodward, 1987, 1988). The magnitude of decrease was directly proportional to the dose of P. At the same time, P has been shown to increase GABA-induced inhibitory responses of neurons by modulating GABA<sub>A</sub> receptors. In contrast, E increases neuronal responses to glutamate. The combined action of P and E, however, is similar to that of P alone. Thus, it was assumed that during the midluteal phase increased E and P levels might temporarily lead to a functional decoupling of the two hemispheres, resulting in reduced hemispheric asymmetries (Hausmann & Güntürkün, 2000; Hausmann, Becker, et al., 2002).

### Effects of Estradiol on Hemispheric Asymmetries

E alone (without P) seems to affect both hemispheres similarly and thus does not alter hemispheric asymmetries (Hausmann, Becker, et al., 2002). Parallel E-related changes in left- and right-hemispheric neuronal activity have been previously demonstrated by Dietrich et al. (2001). This fMRI study investigated neuronal activity during motor and cognitive tasks in normally cycling women during menses and the follicular phase (high E levels). The results showed an E-related increase in overall cortical activation of both hemispheres. However, using a verbal task (synonym judgments), another imaging study (Fernández et al., 2003) found an increase in bilateral neuronal activity in normally cycling women during the midluteal phase. Moreover, in line with previous behavioral studies (Hausmann, Becker, et al., 2002; Hausmann & Güntürkün, 2000), Fernández et al. (2003) showed that P rather than E was related to this effect. The two imaging studies presented here, however, do not provide a possible neuronal mechanism underlying menstrual-cycle-related and sex-hormone-related changes in hemispheric asymmetries.



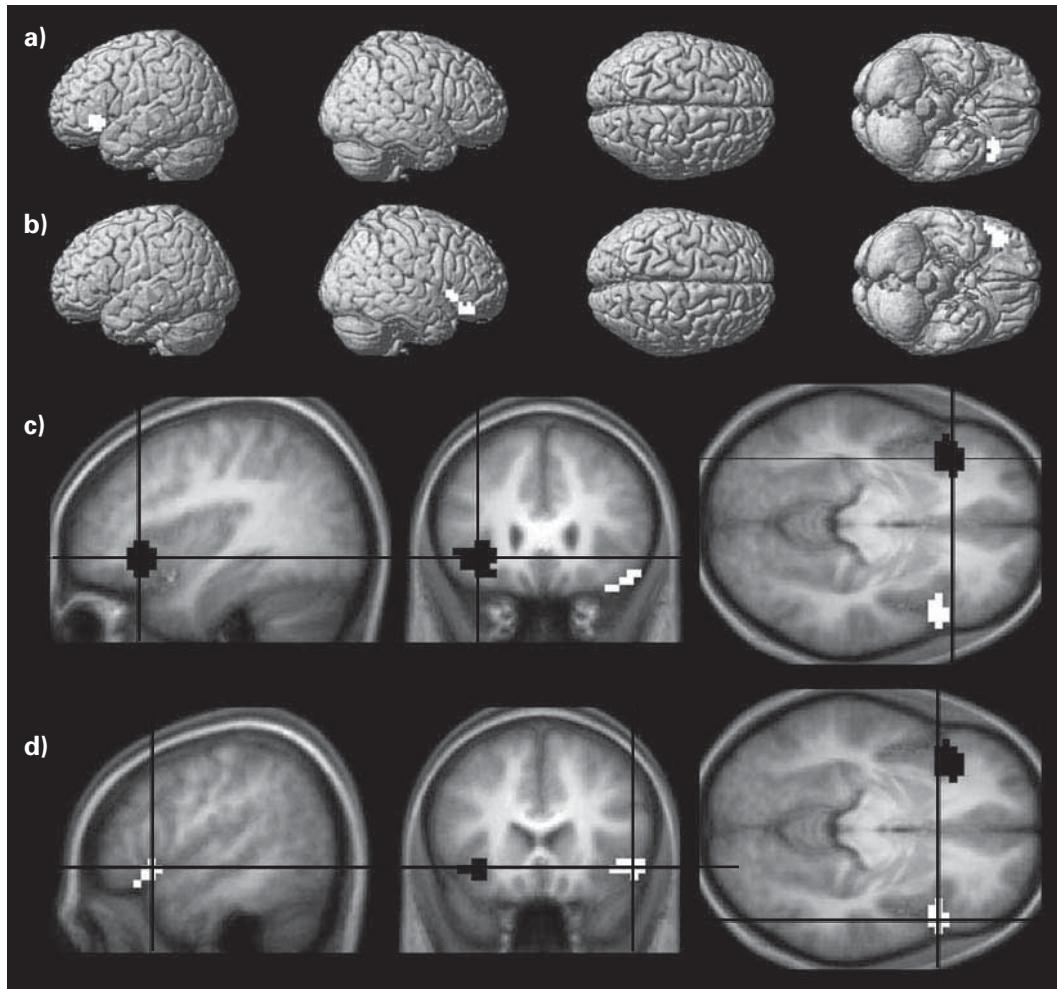
**Figure 9.3**

Schematic illustration of the hypothesis of progesterone-modulated interhemispheric inhibition. The left panel illustrates the process of interhemispheric inhibition. Although the corticocortical transmission is mainly excitatory, the main and longer lasting effect in the contralateral hemisphere appears to be inhibitory, probably because most excitatory callosal fibers terminate on pyramidal neurons, which then activate inhibitory interneurons. These activated inhibitory cells could then induce a widespread inhibition in homotopic regions of the contralateral hemisphere. According to Hausmann and Güntürkün (2000; Hausmann, Becker, et al., 2002), progesterone reduces corticocortical transmission during the midluteal phase by suppressing the excitatory responses of neurons to glutamate and by enhancing their inhibitory responses to GABA. The combined effect would result in the functional hemispheric decoupling and, thus, to a temporal reduction in functional asymmetry (right figure). P, progesterone; EPSP, excitatory postsynaptic potential; IPSP, inhibitory postsynaptic potential.

In this respect, a recent fMRI study (Weis, Hausmann, Stoffers, Vohn, Kellermann, & Sturm, 2008; see figure 9.4) significantly contributes to the understanding of sex hormonal effects on hemispheric asymmetries. This study used a connectivity analysis to directly determine the inhibitory influence of the dominant hemisphere on homotopic areas of the subdominant contralateral hemisphere. Normally cycling women were tested during the low-steroid menstrual phase and during the high-E follicular phase on a verbal VHF task (word matching), identical to that used in previous studies (e.g., Hausmann & Güntürkün, 1999, 2000). Dynamic changes in hemispheric asymmetry were found not only behaviorally in this study. The connectivity analyses additionally revealed that the inhibitory influence of the dominant on the nondominant hemisphere fluctuates in relation to changes in E levels, whereas interhemispheric inhibition in control males remained stable across corresponding time intervals. It is important to note that no significant differences between the menstrual and follicular phase were found when the analyses were restricted to the comparison of activation in the left inferior frontal gyrus, which is known to be the central functional area involved in the processing of semantic aspects of verbal information, word reading, and internal speech (Dapretto & Bookheimer, 1999; Fiez & Petersen, 1998; Hinke et al., 1993).

In line with Hausmann and Güntürkün's predictions, Weis et al. (2008) found that the process of interhemispheric inhibition is a key mechanism in generating hemispheric asymmetries. More importantly, however, this fMRI study strongly suggests that high sex-hormone levels are positively related to an attenuation of interhemispheric inhibition, resulting in reduced hemispheric asymmetries, which is in line with the proposed mechanism underlying hormone-related changes in lateralization (Hausmann & Güntürkün, 2000). In the study of Weis et al., however, it was E, not P, which was related to the effects. The results suggest that both E and P have similar effects on interhemispheric inhibition during the follicular and the luteal phase, respectively. Since E and P have been shown to possess partly opposite neuromodulatory properties on glutamate and GABA receptors, it seems likely that E and P affect the cascade of neuromodulatory processes similarly but at different sites, or both E and P serve as precursors of the active steroid hormone (Weis et al., 2008). This notion has been supported previously (Hausmann, Tegenthoff, Sänger, Janssen, Güntürkün, & Schwenkreis, 2006).

In this transcranial magnetic stimulation (TMS) study, E and P had similar effects on transcallosal inhibition during the follicular and the midluteal phases, respectively. In this study, TMS was applied to the primary motor cortex, evoking a short suppression of tonic voluntary muscle activity in the corresponding contralateral and ipsilateral hand muscle. The ipsilateral silent period (ISP) is mediated by transcallosal fibers, and thus ISP is assumed to reflect transcallosal inhibition. Normally cycling women were tested during menses, follicular, and midluteal phases. It has been found that E



**Figure 9.4**

Functional imaging and connectivity analysis (adapted from Weis et al., 2008). The most significant activation during word matching as compared to rest across cycle phases in 14 normally cycling women was located in left inferior frontal gyrus (IFG) (a). A seed region was defined in each female participant as a sphere around the individual local maximum located closest to the maximum of group activation. Then a psychophysiological interaction (PPI) analysis was used to identify those brain regions on which the seed region exerts a significantly stronger inhibitory influence for word matching during the menstrual as compared to the follicular phase. The only such region was located in right IFG (b). The activation maps conjunction analysis at  $p < .01$ , corrected for multiple comparisons in part a, PPI analysis at  $p < .01$ , corrected for multiple comparisons in part b) are shown overlaid onto a canonical brain rendered in three dimensions. The anatomical location of the most significant activation in left IFG (shown in black) and the area in right IFG which is inhibited more significantly during the follicular phase (shown in white) is shown overlaid onto the mean high-resolution T1 scan of the female group at the maximum of the left IFG activation (c) and the maximum of the inhibited area (d).

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and P levels during the follicular and luteal phase, respectively, were negatively related to iSP. The results suggest that dynamic cycle-related changes also apply to transcallosal inhibition in the motor system.

### **Activating Effect of Sex Hormones on Interhemispheric Interaction**

Whether the hypothesis of sex-hormone-modulated interhemispheric decoupling also applies to interhemispheric interactions, other than interhemispheric inhibition, has been investigated in several recent studies (Bayer & Hausmann, 2009a; Bayer, Kessler, Gündürkün, & Hausmann, 2008; Compton, Castello, & Diepold, 2004; Hausmann, Waldie, Hamm, & Kirk, 2009, *in preparation*). These studies have focused on interhemispheric transfer time (IHTT) and interhemispheric integration.

#### **Interhemispheric Transfer Time during the Menstrual Cycle**

One of the first studies investigated normally cycling women during the menstrual and midluteal cycle phase on the well-established Poffenberger paradigm (Poffenberger, 1912). In this simple reaction time task, participants must respond to visual stimuli presented either in the left visual field (LVF) or the right visual field (RVF) with the right and the left hand. The crossed–uncrossed difference (CUD), in which median response time under the two uncrossed conditions (stimuli presented in the VHF ipsilateral to the responding hand) is subtracted from median response time under the crossed conditions (stimuli presented in the VHF contralateral to the responding hand), can be used as an estimate of IHTT (Poffenberger, 1912). However, it has been shown that CUDs as estimated by response times did not fluctuate across cycle phases (Bayer et al., 2008; Hausmann et al., 2009, *in preparation*). The negative findings might be because CUD, as an indirect estimate of IHTT, is not sensitive enough to detect cycle- and hormone-related changes in IHTT. In fact, Hausmann et al. (2009, *in preparation*) have estimated IHTTs by visual evoked potentials, using electroencephalography (EEG), and found that the ipsi- and contralateral N170 evoked by visual stimulation was prolonged during the midluteal phase when E and P levels were increased.

#### **Interhemispheric Integration during the Menstrual Cycle**

A second line of studies has focused on the Banich–Belger paradigm (Banich & Belger, 1990), which provides a measure of interhemispheric integration. Specifically, this paradigm measures the efficiency of integration of information across hemispheres by comparing bilateral and unilateral processing. It has been shown that across-VHF integration allowing for a division of labor between the hemispheres enhances performance when task complexity increases (across-field advantage; AFA) but impedes performance on less demanding tasks (Banich & Belger, 1990).

Investigating the AFA in 20 normally cycling women during menses and the mid-luteal phase, one study (Bayer et al., 2008) found cycle-dependent fluctuations in interhemispheric integration. Specifically, normally cycling women during the luteal phase showed a strong AFA for the more demanding name-identity task, which was virtually identical to that of age-matched men and postmenopausal women, who showed a robust AFA in corresponding time intervals. In contrast, no AFA has been found during menses. The results suggest that the menstrual cycle and concomitant changes in sex-hormone levels also affect interhemispheric crosstalk, other than interhemispheric inhibition. However, interhemispheric integration seems to be differently organized in postmenopausal women and men. Here, a stable hormonal environment with low sex-hormone levels seems to promote a stable interhemispheric integration.

### **Hormone Therapy in Postmenopausal Women**

The vast majority of studies focusing on activating effects of sex hormones on hemispheric asymmetry and interhemispheric crosstalk have focused on normally cycling women. Only a little is known about the effects of direct exogenous hormonal manipulations on functional brain organization in healthy participants. An ethically acceptable approach is to investigate postmenopausal women on HT, which has so far been done in only a small number of studies (Bayer & Erdmann, 2008; Bayer & Hausmann, 2009a, 2009b).

### **Hormone Therapy and Hemispheric Asymmetries**

One recent study (Bayer & Hausmann, 2009b) investigated the effects of HT on lateralization in postmenopausal women receiving either estrogen therapy (ET), combined HT (cHT; estrogen and synthetic gestagens), or no HT. Hemispheric asymmetries were measured by a left-hemisphere-dominated verbal task (word matching) and a right-hemisphere-dominated visuospatial task (figural comparison). In line with a previous study (Hausmann & Güntürkün, 2000), postmenopausal women without HT revealed typical hemispheric differences with a left-hemispheric advantage in the verbal task and a right-hemispheric advantage in the visuospatial task. The results suggest that the decline in sex hormones after menopause stabilizes hemispheric asymmetries. Moreover, the results showed an E-related decrease in right-hemispheric performance in the visuospatial task, leading to reduced asymmetries. This effect was evident in both the ET and cHT group.

Another study also reported a decrease in asymmetries in postmenopausal women using ET (Bayer & Erdmann, 2008). Here, however, verbal functioning of the sub-dominant right hemisphere was enhanced, leading to reduced verbal asymmetries. Together with Bayer and Hausmann (2009b), the results suggest that ET in postmeno-

pausal women exerts a task-specific effect on the right hemisphere. Moreover, reciprocal changes in right-hemisphere performance in verbal and visuospatial tasks suggest that modulations in hemispheric asymmetries across different cognitive domains might not occur independently from each other. The findings of both studies are relevant for the understanding of HT-related effects on general cognitive performance in postmenopausal women. Particularly, they suggest a right-hemispheric mechanism that might account for differential HT effects on cognitive abilities which mainly rely on left- and right-hemispheric functioning (Maki, Zonderman, & Resnick, 2001; Resnick et al., 2006; Wolf & Kirschbaum, 2002).

The idea of an E-related modulation of *intrahemispheric* processing, and right-hemisphere processing in particular (Bayer & Hausmann, 2009b), challenges the notion that changes in hemispheric asymmetries occur as a result of hormonal modulations of *interhemispheric* interaction as has been suggested for normally cycling women (e.g., Hausmann & Güntürkün, 2000; Hausmann, Becker et al., 2002; Weis et al., 2008). However, contradictions between findings in normally cycling women and postmenopausal women might be explained by age-related neuromorphological changes and different endogenous (menstrual cycle) and exogenous (HT) hormonal changes. These aspects will be addressed in detail below.

### Hormone Therapy and Interhemispheric Interaction

Using the same approach as Bayer et al. (2008), another study focused on whether IHTT and interhemispheric integration (Banich & Belger, 1990) are also susceptible to direct hormonal manipulations induced by HT. Again, postmenopausal women received either ET, cHT, or no HT. Overall, the findings in the interhemispheric integration tasks replicate the results from a previous study (Bayer et al., 2008), showing that across-hemisphere processing becomes advantageous in postmenopausal women as task demands increase. More importantly, Bayer and Hausmann (2009a) revealed a significant impact of HT on interhemispheric integration. Specifically, ET and cHT groups differed from postmenopausal women without HT in *intrahemispheric* processing, which was improved across both tasks.

However, in all three groups, the benefits of *interhemispheric* processing equally increased in the more demanding task, indicating an efficient interhemispheric integration in postmenopausal women with and without HT. Thus, although the *absolute* increase in the AFA from the easier to the more demanding task was similar in all groups, women using HT showed a reduced *relative* efficiency of interhemispheric integration (i.e., strongly reduced AFA) as a result of an enhanced within-hemisphere performance. This finding suggests that HT can positively affect *intrahemispheric* processing. Specifically, the missing AFA in the two hormone groups indicates that HT enhances intrahemispheric performance at a processing stage critical for the manifestation of AFA.

A recent fMRI study (Pollmann, Zaidel, & von Cramon, 2003) focusing on interhemispheric integration found that the AFA in a more demanding task was related to increased activation in the lateral occipital gyrus and fusiform gyrus of the contralateral hemisphere. These activations were associated with a spreading activation of homotopic brain areas in the ipsilateral hemisphere, indicating a bilateral resource sharing. Notably, these effects were restricted to the occipital cortex, which suggests the visual letter processing as the most likely processing stage at which the resources of a single hemisphere become taxed, leading to the need to recruit bilateral brain areas (Pollmann et al., 2003). With respect to the findings from Bayer and Hausmann (2009a), it seems likely that HT, and ET in particular, might modulate neuronal circuitries within the occipital cortex involved in unilateral visual processing.

In contrast, *interhemispheric* processing is essentially unaffected by HT, which is further supported by the finding that IHTTs, as another aspect of interhemispheric interaction, did not differ between HT and control groups (Bayer & Hausmann, 2009a). It should be noted, however, that cycle-phase-related changes in IHTTs in normally cycling women seem to be only detectable if measured with EEG (Hausmann et al., 2009, *in preparation*), not behaviorally (Bayer et al., 2008).

### **Estrogen Therapy versus Combined Hormone Therapy**

Notably, in both studies (Bayer & Hausmann, 2009a, 2009b) the combined estrogen plus synthetic gestagen therapy did not differentially affect the functional brain organization compared with the single ET, suggesting a pivotal role of estrogen in mediating the observed effects. This assumption finds direct support by the result of E-related changes in hemispheric asymmetries. An additional role of synthetic gestagens which may differ from the effects of ET cannot completely be ruled out. However, postmenopausal women of the cHT groups received different synthetic gestagens which might have different pharmacological properties (e.g., Schindler et al., 2003). For example, norethisterone acetate (NEA) and medroxyprogesterone acetate (MPA) are endowed with a similar affinity to androgen receptors (ARs), thereby exerting androgenic effects. Other gestagens (e.g., dionogest and medrogestone) show anti-androgenic effects with lower or even absent AR affinity (e.g., P). In addition, different gestagens can differentially affect sex-hormone-binding globulin levels, which in turn influence circulating hormone levels (e.g., Campagnoli, Clavel-Chapelon, Kaaks, Peris, & Berrino, 2005; Kuhl, 2006).

### **Contrasting Menstrual Cycle and Hormone Therapy Effects**

Overall, it seems that both endogenous hormonal fluctuations in normally cycling women and exogenous administered sex hormones in postmenopausal women using HT affect interhemispheric integration, but probably through different mechanisms.

While cycle-related changes in functional cerebral organization result from hormonal modulations of interhemispheric processing, HT in postmenopausal women seems to mainly affect within-hemisphere processing. These differences are at least partly confounded by (1) differential effects of endogenous, natural fluctuations in sex hormones during the menstrual cycle and exogenous sex hormonal manipulations following HT and (2) age-related neuromorphological differences between normally cycling and postmenopausal women.

### **Endogenous versus Exogenous Sex Hormonal Effects**

To date, HT cannot adequately simulate hormonal fluctuations as they occur during the menstrual cycle. For example, sex-hormone levels in normally cycling women naturally and dynamically change, whereas synthetic sex-hormone levels during HT are relatively stable. Furthermore, synthetic estrogens and gestagens affect E and P metabolism in a different manner from endogenous E and P (e.g., Kuhl, 2006). For example, during the menstrual cycle, E levels have two characteristic peaks, one during the late follicular and the other during the midluteal cycle phase. In contrast, conjugated estrogens (CEs), which are widely used in HT, are predominantly converted into estrone, resulting in a shift of an E/estrone ratio, favoring estrone (e.g., Gleason, Carlsson, Johnson, Atwood, & Asthana, 2005). The neuromodulatory properties of estrone are not yet fully clear. Given that estrone is biologically weaker than E, effects of HT including CE might not be equivalent to either endogenous or exogenous E. Specifically, variations in receptor binding affinity (e.g., Kuiper et al., 1997) and potency for cell-membrane-mediated pathways (e.g., Deecher, Swigard, Frail, & O'Connor, 2003) make it likely that CE and E modulate brain functions differentially.

However, the most significant difference between natural and exogenous manipulations in sex-hormone levels during the menstrual cycle and HT, respectively, is the use of synthetic gestagens in cHT, which fundamentally differ from endogenous P. This might be one reason why P-related effects were not revealed in those studies (Bayer & Hausmann, 2009a, 2009b). Endogenous P, for example, is converted to the GABA<sub>A</sub> receptor-active metabolite allopregnanolone, whose relevance has been outlined earlier in this chapter. Although synthetic gestagens are also extensively metabolized, their metabolites are not well characterized (e.g., Schumacher et al., 2007). Some of the P-derived gestagens may have the potential to be converted to neuroactive metabolites. Specifically, NEA has been shown to exert anxiolytic actions, an effect which is probably mediated by GABA<sub>A</sub>-receptor modulations (e.g., Schumacher et al., 2007). Whether some metabolites of NEA directly act on GABA<sub>A</sub> receptors needs to be clarified. MPA, on the other hand, which does not exhibit GABA<sub>A</sub>-receptor actions, has been demonstrated to enhance the inhibitory transmission mediated by this receptor type by inhibiting the metabolism of allopregnanolone (e.g., Belelli & Herd, 2003).

Hence, MPA might be assumed to exert P-like central effects. Such effects have not yet been demonstrated for other specific synthetic gestagens.

### **Age-Related Effects**

Postmenopausal women participating in the studies summarized above had a mean age of about 60 years during time of testing. However, the majority of normally cycling women tested in those studies are usually recruited from the student population with a mean age of about 25 years. Thus, differential hormonal effects in normally cycling and postmenopausal women also need to be explained within the context of age-related neuromorphological changes, such as white and gray matter atrophy, a reduction of synaptic spine density, and neurochemical alterations (e.g., Cabeza, Anderson, Locantore, & McIntosh, 2002).

More specifically, for example, age-related changes have been found in parieto-occipital brain regions (e.g., Sowell, Peterson, Thompson, Welcome, Henkenius, & Toga, 2003) which are known to be involved in visuoperceptual tasks (e.g., Puce, Allison, Asgari, Gore, & McCarthy, 1996; Pollmann et al., 2003). These changes have been suggested to be particularly pronounced within the right hemisphere, which might explain why cognitive functions that are associated with the right hemisphere underlie age-related decline more than those associated with the left hemisphere (e.g., Ellis & Oscar-Berman, 1989). Likewise, several studies using visual-perceptual tasks found that right-hemispheric performance was more affected by aging than left-hemispheric performance (e.g., Gerhardstein, Peterson, & Rapcsak, 1998; Rastatter & McGuire, 1990).

In contrast, age-related changes in the morphology of the corpus callosum and associated alterations in interhemispheric integrity seem to be relatively small, particularly in elderly women (e.g., Cowell, Allen, Zalatimo, & Denenberg, 1992; Cowell et al., 1994; Dubb, Gur, Avants, & Gee, 2003; Suganthy et al., 2003; Sullivan, Rosenbloom, Desmond, & Pfefferbaum, 2001). It has even been suggested that the recruitment of contralateral brain resources via the corpus callosum serves as a compensatory strategy to counteract age-related decrements in the efficiency of specialized unilateral brain regions (e.g., Cabeza, Anderson, Houle, Mangels, & Nyberg, 2000; Reuter-Lorenz et al., 2000). These findings rather suggest that right-hemisphere functions are especially affected by aging and age-related effects, which might explain why the right hemisphere is also more susceptible to HT (Bayer & Hausmann, 2009b).

### **The Hypothesis of Sex-Hormone-Modulated Cortical Interaction**

The original model requires revision with respect to the following observations, which have to be confirmed by future research using different methodological approaches. First, interhemispheric decoupling seems not to be restricted to the neuromodulatory

properties of P. The revised model also has to take the effects of other sex hormones into account. Several studies have revealed that particularly E (and the metabolites of P and E) can also affect hemispheric asymmetries, probably via modulations of interhemispheric inhibition (e.g., Hausmann, 2005; Hausmann et al., 2006; Holländer et al., 2005; Weis et al., 2008). Second, activating effects of sex hormones on functional cerebral organization are not restricted to interhemispheric inhibition, which has been assumed to be the key mechanism in generating hemispheric asymmetries. For example, it has been shown that IHTT (Hausmann et al., 2009, in preparation) and interhemispheric integration (Bayer et al., 2008; Bayer & Hausmann, 2009a) are also affected by the menstrual cycle and/or HT-related hormonal changes. These findings strongly suggest that sex hormones also modulate other aspects of interhemispheric crosstalk, rather than only those involved in the manifestation of hemispheric asymmetries. Third, activating hormonal effects are not restricted to the modulation of interhemispheric crosstalk but can also apply to cortical interactions within hemispheres. Hemispheric asymmetries and interhemispheric crosstalk might simply be a useful model to investigate these effects because of comparatively clear functional and structural isolation of the hemispheres. In principle, it is possible that similar hormonal fluctuations also affect the interaction between cortical (and subcortical) areas within cerebral hemispheres. In fact, studies in postmenopausal women using HT revealed that it is especially right-hemispheric performance that is modulated by (synthetic) estrogens (or its metabolites; Bayer & Erdmann, 2008; Bayer & Hausmann, 2009b).

One further assumption of the revised hypothesis is that changes in the overall cortical activation might influence the interaction between cortical areas and thus affect the cerebral organization of various cognitive abilities. Finally, it should be highlighted that hormonal modulations in hemispheric asymmetries and various aspects of interhemispheric interactions are not restricted to specific sensitive periods during early ontogenesis and reproductive age but can also occur as a result of exogenous hormonal manipulation, such as HT in postmenopausal women.

## Conclusion

In summary, sex hormones reveal powerful neuromodulatory actions on the dynamics of functional brain organization in the female brain. These hormone-related changes in hemispheric asymmetries and cortical interaction in general seem to occur particularly in neuronal networks (and corresponding cognitive abilities) that are known to be sex sensitive. The majority of studies focusing on neuromodulatory properties of sex hormones on hemispheric asymmetries and interhemispheric cross-talk have been investigated in normally cycling women during hormonally distinct cycle phases because this approach provides a unique opportunity to study the hor-

monally linked dynamics and plasticity in functional brain organization. The results indicate that hemispheric asymmetries are not fixed prenatally but underlie plastic hormone-related changes in relative short time periods throughout life. Although men have usually been included only as control participants in these studies, it is more than likely that similar hormone-related dynamic changes in functional brain organization can also be found in men—for example, as a result of circadian or seasonal hormonal changes (Moffat & Hampson, 1996, 2000).

Besides providing a better understanding of neuronal effects of sex hormones on hemispheric asymmetries and interhemispheric crosstalk, this research also contributes to establishing the potential origin and the true extent of sex differences in functional brain organization and cognitive abilities. Only very few previous (neuroimaging) studies on sex differences in lateralization controlled for cycle phase and sex-hormone levels. Thus, it is not surprising that a recent meta-analysis (Sommer et al., 2004) of neuroimaging studies of sex differences in hemispheric asymmetries quantifies sex differences as relatively small to nonexistent. To control for potential hormonal effects, some previous studies have only included male subjects (e.g., Ortigue, Michel, Murray, Mohr, Carbonnel, & Landis, 2004), a procedure which is relatively common in animal research. Thus, conclusions drawn by these studies are based on samples that represent roughly 50% of the population. Other studies (e.g., Galea, Gomez, Gonzalez-Bono, Espert, & Salvador, 2005; Gizewski, Krause, Wanke, Forsting, & Senf, 2006; Halari et al., 2006) include only women in identical cycle phases to reduce interindividual variability within the female group. Although the latter approach is far more sophisticated than the first one, it implicitly suggests what a representative hormonal condition in women is. Nevertheless, both types of studies suggest that authors are aware of sex hormones as potential confounding factors. If studies were to take cycle phase and/or sex-hormone levels more routinely into account, we would get a much clearer picture of sex differences in the brain.

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## **10 Sex Differences in Handedness, Brain Asymmetry, and Language Lateralization**

**Iris E. C. Sommer**

The issue of sex differences in language lateralization has been heavily debated over the last two decades, as there are ardent advocates as well as opponents. A milestone in this discussion was the work by Shaywitz et al. (1995), published in *Nature*. Shaywitz and colleagues used functional magnetic resonance imaging (fMRI) to study 19 male and 19 female subjects during orthographic (letter recognition), phonological (rhyme), and semantic (semantic category) language tasks. They observed a sex difference during the phonological task, with more bilateral activation in females, while lateralization of the other two tasks was similar in males and females. This finding supported a long-held view that language is strongly lateralized to the left in men and more bilateral in women. However, replication studies have been inconsistent, with several large studies failing to find a sex difference (Springer et al., 1999; Pujol et al., 1999; Knecht et al., 2000; Plante et al., 2006). Twenty-four years after Shaywitz's initial publication, there is still no consensus about the existence of sex differences in language lateralization, and it remains a heavily discussed topic (Clements et al., 2006; Sommer et al., 2008; Wallentin, 2009).

There are several reasons why this topic has remained in the center of attention for so many years. First, there are considerable differences between girls and boys in the development of language abilities. When speaking first begins, girls generally articulate better than boys and produce longer sentences (Luotonen, 1995). Perhaps as a consequence of this advantage, girls tend to have larger working vocabularies and better use of grammar than boys. Some years later, girls typically have superior reading abilities compared to boys. Part of this verbal advantage for girls may survive into adult age, especially in the domain of verbal fluency and use of grammar (Weiss et al., 2006; Thilers et al., 2007; but see Wallentin, 2009). Furthermore, language disabilities, both of severe and mild type, affect boys more frequently than girls, with reported sex ratios between 3:1 and 7:1 (reviewed by Liederman et al., 2005). A third sex difference is observed in the prevalence of psychiatric disorders, such as autism, attention-deficit/hyperactivity disorder and schizophrenia, which are rarer in females

as compared to males (reviewed by Afifi, 2007). Finally, women appear to recover better from aphasia than males after left cerebral stroke (Pedersen et al., 1995). If women indeed have more bilateral language lateralization than men, this could provide an explanation for all these observed sex differences. In other words, a more bilateral pattern of language lateralization in women as compared to men might provide the neurobiological basis for behavioral sex differences in language development, language performance, prevalence of associated disorders, and recovery from aphasia. However, evidence for such a neurobiological substrate is inconsistent.

This chapter aims to provide an overview of the current literature on sex differences in language lateralization as reflected in handedness, asymmetry of the planum temporale (PT), and functional language lateralization.

## Methods

Handedness is associated with language lateralization, though this correlation is complex (Pujol et al., 1999). Handedness therefore provides a reflection of language lateralization. While this reflection is not very accurate, as 70% of left-handers have standard leftward language lateralization, it can be observed easily and has been assessed in large samples of males and females. We have selected three other measurement methods that correlate with language lateralization and have frequently been applied in the study of healthy males and females, which are as follows:

1. Asymmetry of the PT, measured with magnetic resonance imaging (MRI) or directly in postmortem brains.
2. The right-ear advantage (REA) measured with dichotic presentation of verbal stimuli.
3. Asymmetry of language activation as assessed with functional imaging techniques—fMRI, positron emission tomography (PET) and functional TransCranial Doppler (fTCD)—using verbal stimuli (words, phonemes, sentences, or stories).

## Search Criteria

The literature on handedness and language lateralization comprises more than 40 years of research and is estimated to consist of over 10,000 studies. This meta-analysis cannot, therefore, provide a complete review of all studies reporting sex differences in handedness or lateralization. Explored databases were Embase, PsycLit, PubMed, and Science Direct, using combinations of the following search terms: "handedness," "sex," "left-handed," "gender," "planum temporale," "REA," "dichotic listening," "fMRI," "language lateralization," "fTCD," and "PET." Reference lists from retrieved articles were also assessed for cross-references. Only English publications from inter-

national journals were selected. In addition, the last five volumes of three journals (*Brain and Language*, *NeuroImage*, and *Human Brain Mapping*) were searched manually to check for other suitable studies. Papers were included if they met the following criteria:

1. The study used exactly the same method to assessed handedness, asymmetry of the PT, or functional language lateralization as measured either with dichotic listening or with functional imaging in males and females.
2. The study included individuals who were not selected on the basis of a special condition that may be related to language lateralization (such as individuals with dyslexia, schizophrenia, or epilepsy; professional mathematicians; homosexuals; or subjects with a history of birth trauma). The unselected control groups for specific population subsets were, however, included.
3. Twin studies were excluded, since there is reason to assume that handedness and lateralization in twins is different from that in singletons.
4. Sufficient exact data were available in the paper to calculate effect sizes for the sex difference or could be provided post hoc by the corresponding author.

More than 1,000 studies were selected and screened for suitability. Approximately half of these articles did not assess sex differences in their sample. From the studies that did mention a sex effect, the majority reported that there were no significant sex differences. These studies could have been included by presuming that the main effect of sex would have an *F* value of zero. This would have been a quite conservative approach and might have led to an underestimation of the sex effect. We therefore preferred to exclude these studies, at the disadvantage of overestimating the true sex effect. Only studies that provided percentages (for handedness) or means and standard deviations per sex (PT asymmetry, language lateralization) or exact *F*, *t*, or *p* values for the main effect for sex were included.

### Combination of Measurement Methods

**Handedness** Studies assessing handedness have used a variety of handedness scales. A large unpublished, but frequently cited, meta-analysis by McManus found that the incidence of left-handedness was not related to the method of measurement, or the length or number of response items included in handedness inventories. Whether handedness is assessed by a questionnaire, by a performance measurement, or by a simple question (such as "writing hand" or "handedness of the subject") appears not to affect the observed incidence of left-handedness. We therefore felt confident in combining percentages of right-handedness obtained with different methods. When several handedness criteria were provided, we selected data based on writing hand in order to increase uniformity among studies.

**Planum Temporale** Studies assessing asymmetry of the PT have also applied different methods of measurement. Some studies measured the surface of the PT, while others measured PT volume. Determination of the borders of the PT also showed minor differences between studies. However, in all studies, right and left PT were measured in a similar fashion. The effect size for asymmetry that was calculated from PT sizes may therefore be more comparable between studies than the absolute data of the size of right and left PT. In addition, effect sizes for asymmetry were compared between men and women from the same study before combining them with other studies to calculate a mean weighted effect size.

**Dichotic Listening** Studies measuring language lateralization with the dichotic listening paradigm have applied several different stimuli. Studies were included that used either a consonant–vowel (CV) or consonant–vowel–consonant (CVC) task, a fused word or a rhyme word task, or binaural presentation of different digits or words (triad task and other recall tasks) to elicit an REA. One study (Lamm & Epstein, 1997) provided data on two different paradigms. Data sets from these tasks were entered as separate studies. The type of paradigm applied to elicit an REA may affect the degree of language lateralization. It is therefore possible that the paradigm also affects the sex difference in perceptual asymmetry. In order to assess this possibility, paradigm was entered in the analysis as a potential moderator.

**Functional Neuroimaging** In parallel to dichotic listening studies, studies applying functional imaging to assess language lateralization have used several different language paradigms, such as verb generation, story listening, picture naming, and semantic decision making. One study (Plante et al., 2006) provided data on four different paradigms. Data sets from these paradigms were entered as separate studies. Again, the type of language paradigm was entered as a potential moderator.

**Children and Adults** Handedness is a rather stable individual characteristic from about 7 years of age (Michel & Harkins, 1986). We have therefore included handedness data from both children (above age 7) and adults. Subject's age may, however, be a factor that affects language lateralization (Holland et al., 2001) and possibly asymmetry of the PT. A significant interaction between age and sex has frequently been described in studies on language lateralization (Plante et al., 2006; Gaillard et al., 2006). We therefore marked whether data were obtained from children, from adults, or from a mixed group. An additional analysis was performed to assess possible differences in the sex difference in lateralization between children and adults.

**Percentage of Left-Handed Subjects** Many studies on PT asymmetry and on language lateralization have restricted inclusion to right-handed subjects. Selection of

only right-handed subjects may affect the sex differences in PT asymmetry or in language lateralization. The percentage of left-handed subjects per study was correlated to the effect size for the sex difference to assess the potential influence of this factor.

**Nationality** Since nationality of the study sample may influence the sex difference in handedness, this factor was entered as a potential moderator.

**Publication Bias** One of the main pitfalls of meta-analyses is the “file-drawer problem” (Rosenthal, 1971), that is, the possibility that published studies are a biased sample of the studies that are actually carried out, as it is presumed that only experiments with significant results are published. This problem is associated with the inclusion of only published studies in a meta-analysis. The exclusive use of published studies is likely to result in an overestimation of the effects under study. In the present meta-analysis, we emphasized the inclusion of studies that did not focus on sex differences but rather reported information on sex differences as a by-product in order to minimize the file-drawer problem. For example, studies that examined the effect of age or occupation were included as were data from control groups of studies examining the effects of schizophrenia or epilepsy on lateralization. It was noted whether or not sex differences were the main objective of a study, and this variable was entered as a potential moderator to obtain a reflection of the influence of publication bias. Furthermore, for the meta-analysis on dichotic listening studies, we could compare the included data to the unpublished data on sex differences from the Bergen Dichotic Listening Database (courtesy of Kenneth Hugdahl). Comparing the results of our meta-analysis on published dichotic listening studies to the large database of Professor Hugdahl provides a reflection of the impact of the file-drawer problem.

### Meta-Analytic Techniques

**Handedness** From the handedness studies, odds ratios were calculated from the percentage of right-handed women compared to the percentage right-handed men. Odds ratios of all studies were combined to calculate a mean weighted odds ratio and a corresponding *p* value using the program Comprehensive Meta-analysis (<http://www.meta-analysis.com/>). We used random effects, since handedness assessment and study population differed between studies. In addition, a homogeneity statistic ( $I^2$ ) was calculated to assess the heterogeneity of results across studies.  $I^2$  quantifies the effect of heterogeneity, providing a measure of the degree of inconsistency in the studies' results (Higgins et al., 2003). Negative values of  $I^2$  are put equal to zero so that  $I^2$  lies between 0% and 100%.  $I^2$  describes the percentage of total variation across studies that is due to heterogeneity rather than chance; a value of 0% indicates no observed heterogeneity, and larger values show increasing heterogeneity (Higgins et al., 2003).

**Planum Temporale** From studies on PT asymmetry, a mean weighted effect size for asymmetry was first calculated from the right and left PT size for males and females separately. In a third meta-analysis, effect sizes of females' asymmetry were compared to those of males. If means and standard deviations were not provided per sex in the study, exact  $F$ ,  $t$ , or  $p$  values were transformed into effect sizes using Rosenthal's (1991) formula. Effect sizes for sex differences in asymmetry from all studies were combined and weighted for sample size of the studies to obtain a mean weighted effect size, Hedge's  $g$  (Hedges & Olkin, 1985), and  $p$  values using the random effects module of Comprehensive Meta-analysis software. A homogeneity statistic ( $I^2$ ) was calculated, to assess the heterogeneity of results across studies (Higgins et al., 2003).

**Dichotic Listening** An effect size, Hedge's  $g$ , was calculated for each study. When means and standard deviations were not available, effect sizes were computed from exact  $p$ ,  $t$ , or  $F$  values (Rosenthal, 1991). After computing effect sizes for each study, the meta-analytic method was applied to obtain a combined effect size (mean Hedge's  $g$ ), which indicated the magnitude of the association across all studies. Effect sizes were weighted for sample size, in order to correct for upwardly biased estimation of the effect in small sample sizes using the random effects module of Comprehensive Meta-analysis software. A homogeneity statistic ( $I^2$ ) was calculated to assess the heterogeneity of results across studies (Higgins et al., 2003).

**Functional Neuroimaging** From studies on language lateralization measured with functional imaging, the mean and standard deviation of the lateralization index were compared between the sexes. The lateralization index is defined as language activity in the left hemisphere minus language activity in the right hemisphere, divided by the total activity in both hemispheres. Language activity was measured as the number of "active" voxels in brain regions involved in language processing. If means and standard deviations of the lateralization indices were not provided per sex, exact  $F$ ,  $t$ , or  $p$  values for the main effect of sex on asymmetry were transformed into effect sizes using Rosenthal's (1991) formula. Effect sizes of all studies were combined and weighted for sample size to obtain a mean weighted effect size (Hedge's  $g$ ) using the random effects module of Comprehensive Meta-analysis software. A homogeneity statistic ( $I^2$ ) was calculated to assess the heterogeneity of results across studies (Higgins et al., 2003).

## Results

### Sex Differences in Handedness

We included 43 studies on handedness providing information on 241,573 subjects. Figure 10.1 shows the included studies assessing handedness for males and females from several countries. The mean weighted odds ratio was 1.25 ( $p < 0.0001$ ), indi-

cating a 25% higher prevalence of non-right-handedness in males. The  $I^2$  value for heterogeneity was 78%, indicating large variability among studies that cannot be explained by chance alone. Since culture or race may be involved in this sex difference in handedness, studies that assessed handedness in Western countries (European countries, Australia, Canada, and the United States) were compared to those assessing handedness in non-Western countries (countries in Asia, Africa, and the Near East). The mean weighted odds ratio of 31 studies assessing Western populations was 1.19 ( $p < 0.0001$ ), while the mean odds ratio of 12 studies assessing non-Western populations was 1.5 ( $p < 0.0001$ ). The difference in odds ratios for sex differences between Western and non-Western countries was significant ( $Q = 5.0$ ,  $p = 0.03$ ).

### Sex Differences in Asymmetry of the Temporal Plane

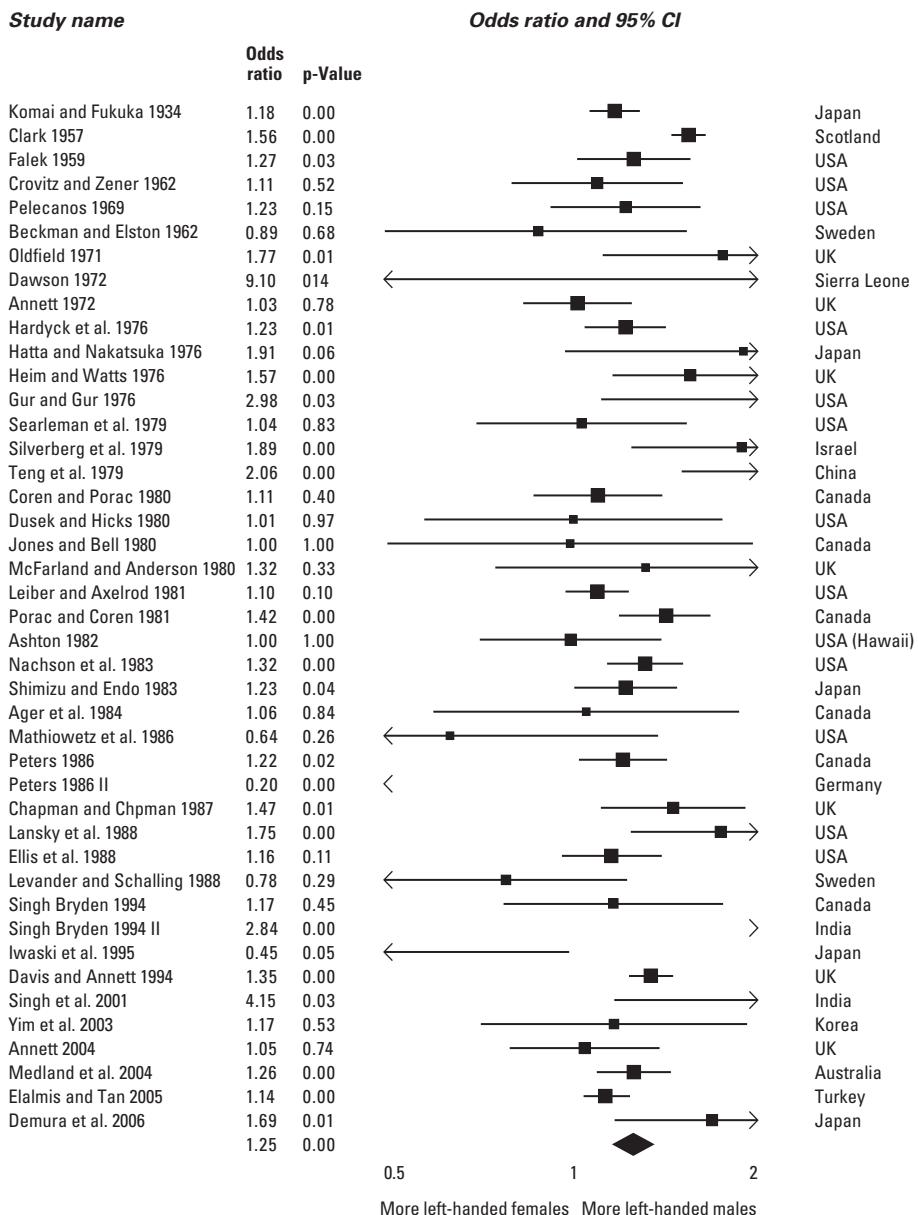
Thirteen studies could be included that provided data of right and left PT size per sex. Twelve studies applied MRI measurements, and one study measured postmortem brains. All studies included only adult right-handed subjects. Meta-analyses of the PT asymmetry per sex showed that there was significant leftward asymmetry of the PT, both in males (Hedge's  $g = 0.98$ ,  $p < 0.001$ ) and in females (Hedge's  $g = 0.98$ ,  $p < 0.001$ ; see figure 10.2). The meta-analysis comparing asymmetry between males and females included 807 subjects and yielded no significant sex difference: Hedge's  $g = -0.11$ ,  $p = 0.68$ . The  $I^2$  value for heterogeneity was high: 92%. The same analysis was repeated after exclusion of the postmortem study in an attempt to reduce heterogeneity, but the results were rather similar: Hedge's  $g = -0.16$ ,  $p = 0.6$ ,  $I^2 = 92\%$ . Separate analyses were conducted for studies measuring the surface of the PT ( $n = 5$ ) and those measuring the volume of the PT ( $n = 3$ ). Hedge's  $g$  for the surface measurements was  $-0.19$ ,  $p = 0.25$ , and  $0.19$ ,  $p = 0.14$ , for the volume measurements. However, heterogeneity in the separate analyses remained high: 94% for the surface measurements and 81% for the volume measurements.

In order to assess the possible influence of publication bias, studies that focused on sex differences were compared to studies that reported sex differences as a by-product. Five studies reported sex differences as their main topic, including a total of 184 subjects. Hedge's  $g$  of these studies was  $0.35$ ,  $p = 0.64$ . The  $I^2$  value for heterogeneity increased to 93%, indicating that the studies of this subanalysis are even more heterogeneous. Eight studies provided the sex differences in PT asymmetry as a by-product. These studies included a total of 623 subjects, and Hedge's  $g$  was  $-0.32$ ,  $p = 0.28$ . Again, studies remained highly heterogeneous ( $I^2 = 91\%$ ).

### Sex Differences in Language Lateralization Measured with Dichotic Listening Tests

For the meta-analysis on language lateralization measured with dichotic listening techniques, 12 studies could be included that provided means and standard deviations

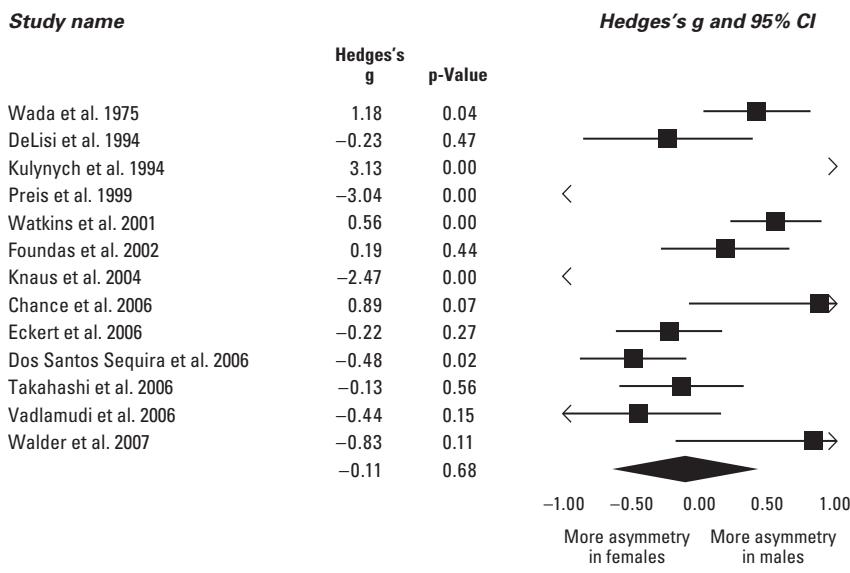
### Sex differences in handedness



**Figure 10.1**

Meta-analysis of sex differences in handedness. CI, confidence interval.

### Sex differences in Planum Temporale asymmetry

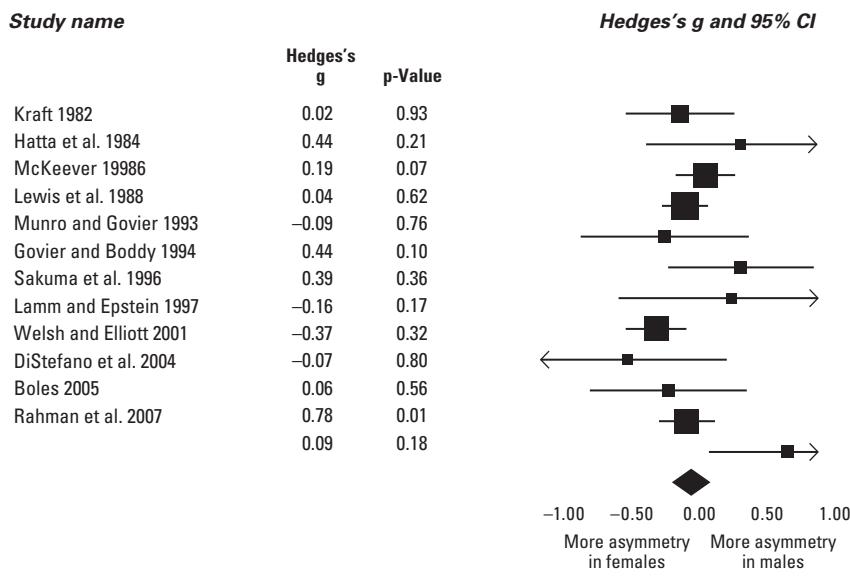


**Figure 10.2**

Meta-analysis of sex differences in asymmetry of the planum temporale. CI, confidence interval.

of the REA for both sexes separately. All studies included adult subjects. Several studies included both right- and non-right-handed subjects. Data were available from a total of 3,822 subjects. The mean weighted effect size for a sex difference in lateralization was 0.09 ( $p = 0.18$ ), indicating no significant difference (see figure 10.3). The heterogeneity value  $I^2$  was 35%. Several potential moderators were assessed. First, a correlation was calculated between the percentage of non-right-handed subjects per study and the effect size for sex, which was not significant (Pearson's rho = −0.07,  $N = 12$ ,  $p = 0.82$ ). This indicates that the inclusion of non-right-handed subjects has no major influence on the sex difference in language lateralization measured with dichotic listening techniques. We also assessed type of paradigm as a possible moderator. Studies were divided into three categories: those using CV or CVC tasks, studies applying rhyme words or fused words, and studies using sets of digits or words (including triad tasks). Seven studies applied a digit or word task, including a total of 1,762 subjects. The sex difference was not significant (Hedge's  $g = -0.02$ ,  $p = 0.72$ ), and studies were homogeneous ( $I^2$  value = 6%). Four studies applied the CV(-C) task including 506 subjects. A significant sex difference was observed favoring larger asymmetry in males (Hedge's  $g = 0.30$ ,  $p = 0.05$ ), but studies were more heterogeneous than in the total

### Sex differences in the Right Ear Advantage



**Figure 10.3**

Meta-analysis of sex differences in the right-ear advantage. CI, confidence interval.

analysis ( $I^2 = 45\%$ ). Only one study applied the fused word task ( $n = 48$ ), which yielded no significant sex difference (Hedge's  $g = -0.07$ ,  $p = 0.8$ ). This implicates paradigm as a moderator of the sex difference in language lateralization assessed with the dichotic listening paradigm. However, the subdivision into studies applying different paradigms largely overlaps with the division into studies that either focused on sex differences or reported sex differences as a by-product. None of the studies that reported a sex difference as a by-product applied the CV(-C) task, while the majority of studies that focused on sex differences did apply the CV(-C) task. To assess the potential influence of publication bias, studies were divided on the basis of their main topic (sex difference or otherwise). Seven studies focused on sex differences, including a total of 1,076 subjects. Meta-analysis of these studies yielded a significant mean weighted effect size (Hedge's  $g = 0.25$ ,  $p = 0.01$ ), and heterogeneity increased ( $I^2 = 39\%$ ). Four studies did not focus on sex differences, including 1,240 subjects. Meta-analysis of these studies yielded no significant sex difference (Hedge's  $g = -0.04$ ,  $p = 0.56$ ), while these studies were homogeneous ( $I^2 = 15\%$ ). It appears that the main topic of a study (focus on sex differences or not) is a confounder for paradigm, which also is a sig-

nificant moderator. To assess the potential influence of publication bias, we compared the subanalysis of the published studies applying the CV(-C) task to a large database (Bergen Dichotic Listening Database; courtesy of Kenneth Hugdahl, see also Hugdahl, 2003; Hugdahl et al., 2001) consisting of 1,507 subjects who also performed the CV syllables task. The effect size of the sex difference in this database was 0.07 ( $p = 0.17$ ), indicating no significant sex difference in asymmetry.

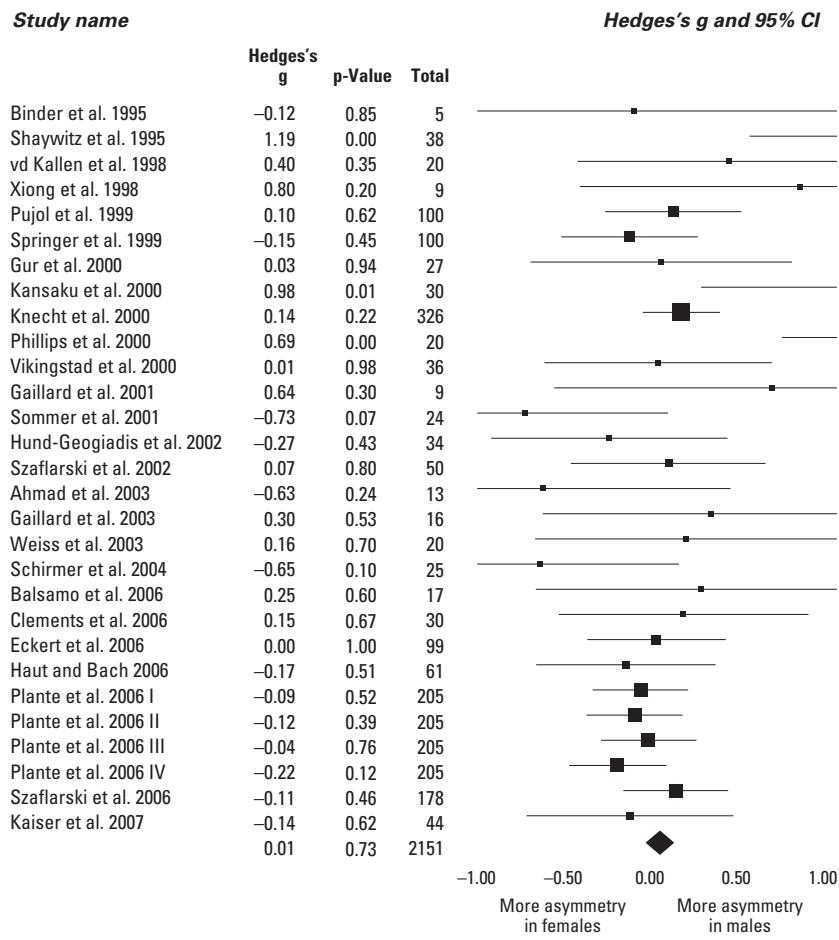
### **Sex Differences in Language Lateralization Measured with Functional Imaging**

Twenty-six functional imaging studies could be included that provided data on language lateralization from males and females separately. A total of 2,151 subjects could be included in the meta-analysis. All studies included only right-handed subjects, both children and adults. The difference in language lateralization between males and females was not significant (Hedge's  $g = 0.09$ ,  $p = 0.24$ ), and there was heterogeneity among studies ( $I^2 = 44\%$ ). We assessed several potential moderators. First, we compared sex differences in lateralization between children and adults. Twenty studies assessed language lateralization in 1,098 adult subjects. Meta-analysis of these studies yielded no sex difference (Hedge's  $g = 0.12$ ,  $p = 0.24$ ), and heterogeneity remained ( $I^2 = 40\%$ ). Five studies assessed language lateralization in children. Again, no significant sex difference emerged (Hedge's  $g = 0.01$ ,  $p = 0.96$ ), but these studies were homogeneous ( $I^2 = 0\%$ ).

To assess the possible influence of the applied language paradigm on sex differences in lateralization, separate analyses were performed for word generation tasks, such as verbal fluency and verb generation, for semantic decision tasks, and for listening tasks (either to speech, stories, or single words). Twelve studies applied a word generation task and included a total of 1,075 subjects. No sex difference was found in this analysis (Hedge's  $g = -0.12$ ,  $p = 0.15$ ), and studies were homogeneous ( $I^2 = 0$ ). Eight studies on 510 subjects applied a semantic decision task. Again, no sex difference emerged (Hedge's  $g = 0.01$ ,  $p = 0.95$ ), and studies were homogeneous ( $I^2 = 0$ ). Five studies applied a listening task and included 293 subjects in total. Analysis of these studies retrieved no sex difference (Hedge's  $g = 0.24$ ,  $p = 0.36$ ), but these studies were heterogeneous ( $I^2 = 82\%$ ).

Finally, we compared studies that focused on sex differences to studies that reported sex differences as a by-product. Sixteen studies including a total of 1,036 subjects had a different main topic and reported sex differences as a by-product. Meta-analysis of these studies yielded no sex difference (Hedge's  $g = 0.06$ ,  $p = 0.37$ ; see figure 10.4), and these studies were homogeneous ( $I^2 = 0\%$ ). Ten studies did focus on sex differences and included 1,115 subjects. Analysis of these studies found no sex difference (Hedge's  $g = -0.02$ ,  $p = 0.69$ ), but these studies remained heterogeneous ( $I^2 = 76\%$ ).

### Sex difference in language lateralization measured with functional imaging



**Figure 10.4**

Sex differences in asymmetry of language activation. CI, confidence interval.

## Discussion

This study aimed to provide an overview of possible sex differences in relation to language lateralization. Meta-analyses were performed of studies on handedness, asymmetry of the PT, dichotic listening tests, and functional imaging paradigms.

A significant sex difference was observed for handedness, with more right-handedness in females. We observed no sex difference in PT asymmetry, in language lateralization as measured with dichotic listening, nor in language lateralization as assessed with functional imaging. Subanalyses of dichotic listening studies applying a CV(-C) task did reveal a significant sex difference with lower degrees of language lateralization in females. This sex difference could not be replicated in a large unpublished database applying the same task and is probably the result of publication bias. The different meta-analyses will be discussed in detail below.

### Handedness

Males were found to have a 25% higher prevalence of non-right-handedness than females. Though the higher prevalence of non-right-handedness in males was a rather consistent finding, there was considerable variation in the extent of the sex difference, producing heterogeneous results. Heterogeneity may in part be caused by the variety in culture, or possibly in race, of the included subjects. The sex difference in non-Western samples was higher than in Western studies, indicating that cultural (or possibly racial) differences are a moderator of the sex difference in handedness. Our finding of higher left-handedness in men as compared to women was recently replicated in a meta-analysis by Papadatou-Pastou et al. (2008), who reported a very similar odds ratio of 1.23 (we calculated 1.25).

### Planum Temporale Asymmetry

Males, having a higher prevalence of non-right-handedness, may be expected to have a lower degree of asymmetry of the PT as well, since non-right-handedness is associated with decreased PT asymmetry (Hervé et al., 2006). This expectation was not met, since no sex difference emerged from the meta-analysis. It remains, however, possible that a sex difference is present in other asymmetrical brain structures. Since results were heterogeneous, subanalyses of studies were performed for studies measuring surface or volume of the PT, but heterogeneity remained high in both subanalyses. Subanalyses were also performed on studies that focused on sex differences and studies that had another main topic. These subanalyses differed in the direction of their mean sex difference (more asymmetry in men in studies that focused on sex differences and more asymmetry in women in studies with another main topic), but significance was not reached in either analysis and heterogeneity remained high in both subanalyses. The opposite directions of mean effect sizes for sex differences in these subanalyses

indicate that publication bias may be a moderator of the retrieved sex differences in PT asymmetry.

#### **Language Lateralization, Dichotic Listening**

The meta-analysis on dichotic listening studies showed that there is no sex difference in language lateralization. Handedness of the included subjects showed no correlation with the sex difference, which implies that restricting the sample to right-handed subjects has no major impact on the sex difference in lateralization. When subanalyses were performed on basis of the paradigm applied, a significant sex difference was retrieved by studies that used the CV(-C) task, while meta-analyses of studies that applied digits or rhyme word tasks yielded no sex differences. However, studies applying a CV(-C) task largely overlap with studies that had a main focus on sex differences. Subanalyses of studies that focused on sex differences yielded a significant sex difference, while studies that focused on another topic found no sex difference. To distinguish between the influence of paradigm and that of publication bias, the effect size of the sex difference in language lateralization was calculated from a large data set (Bergen Dichotic Listening Database; courtesy of Kenneth Hugdahl; see also Hugdahl, 2003; Hugdahl et al., 2001) that also applied the CV(-C) task. This database has been accomplished by merging data from several studies that all applied the same paradigm. The sample size of this database was three times larger (1,506 subjects) than the sample size of our subanalysis on published studies applying the CV(-C) task (506 subjects). In the Bergen Dichotic Listening Database, no sex difference was present, indicating that publication bias is probably the most powerful moderator of the results.

Previous reviews on sex differences in dichotic listening studies were partly in line with our current findings. For example, Hiscock et al. (1994) reviewed 114 studies that reported on sex differences in dichotic listening. Of these, 49 studies (34.8%) found at least one significant effect involving the factor sex. Most of these effects, however, involved an interaction between sex and another factor, such as age or task performance. Only 11 studies (10%) reported a main effect for sex. From these, 9 studies found higher degrees of language lateralization in males and 2 studies found higher lateralization in females. Hiscock's review did not include a quantitative analysis, since many studies did not provide enough exact data. Voyer (1996) performed a meta-analysis on perceptual half-field studies in the auditory, visual, and tactile domain. He concluded that there is a modest but significant sex difference in laterality. Voyer noted, however, that his results were not resistant to the file-drawer problem, indicating that the sex difference may have been caused by a publication bias for studies that report a positive effect for sex.

#### **Language Lateralization, Functional Neuroimaging Studies**

In parallel to the results of the (overall) meta-analysis on dichotic listening studies, the analysis on functional imaging studies yielded no sex difference in language lat-

eralization. Subanalyses of studies applying word generation tasks, semantic decision tasks, and listening tasks all produced no sex difference in language lateralization. Subanalyses of studies on language lateralization in adults versus children also produced no sex differences. Finally, subanalyses of studies that did or did not focus on sex difference did not produce a sex difference in either of the analyses. Thus, in contrast to dichotic listening studies, publication bias favoring studies with positive findings may not be a major factor in explaining heterogeneity among functional imaging studies. These findings are in accordance with our earlier meta-analysis on 12 functional imaging studies (Sommer et al., 2004).

### General Discussion

The absence of a sex difference in PT asymmetry and language lateralization observed in all three meta-analyses appears to be a quite consistent finding. Three hypotheses may be considered in the light of these findings. First, there may be a sex difference at the population level, but it is relatively small so that it is only sporadically observed. Were this to be true, studies with larger sample sizes would be expected to report a sex difference in lateralization more frequently than studies with smaller sample sizes, since they have more power to detect subtle differences. On inspection of our data, this appears not to be the case. Furthermore, all three meta-analyses included more than 400 males and females, which renders the chance for three false negative findings very small. Thus, the hypothesis of a true but subtle sex difference in cerebral asymmetry and language lateralization at the population level is not supported by our data.

A second hypothesis to explain the absence of a sex difference in language lateralization is that sex differences may be task dependent. Indeed, there was significant heterogeneity among the studies in our meta-analyses on dichotic listening and functional imaging studies, which may be congruent with this hypothesis. The results of our moderator analysis on dichotic listening studies appeared to support this idea, since a significant sex effect was retrieved only in a subanalysis of studies using the CV(-C) task. However, a much larger (unpublished) database applying the same task showed no sex difference in lateralization, which weakens the argument for a task-specific sex difference. Subanalyses of functional imaging studies according to task did not produce a sex difference in lateralization for any type of task. Thus, the argument for a task-specific sex difference is not supported by our meta-analyses.

The third hypothesis is the null hypothesis; that there is no sex difference in cerebral asymmetry and language lateralization at the population level. If this hypothesis were to be true, the sex differences reported in the small sample studies may reflect biased reporting of chance findings, that is, the file-drawer problem (Rosenthal, 1991). This hypothesis is consistent with the absence of a sex difference in the large unpublished database (Hugdahl). In addition, this hypothesis offers an explanation for the

different results from subanalyses on PT asymmetry and dichotic listening studies that did or did not have sex differences in lateralization as their main topic.

Our data appear to be most consistent with a sex difference in handedness without an associated sex difference in cerebral asymmetry and language lateralization. The increased prevalence of non-right-handedness in males, in the absence of sex differences in asymmetry and lateralization is not easily explained. Several differences between men and women may account for the increased non-right-handedness in males, such as genetic, hormonal, or social influences. It could reflect sex-linked inheritance of the genetic predisposition to develop right-handedness. For example, a gene associated with handedness could be located on the X chromosome (Corballis et al., 1996). Another possibility could be different imprinting in males and females of a gene related to handedness. Indeed, an imprinted gene (LRRTM1, on chromosome 2p12) was found to be associated with handedness (Francks et al., 2007). The suggestion of a genetic cause for the sex difference in handedness is supported by studies that found a higher chance for non-right-handed women to have non-right-handed offspring as compared to non-right-handed men (reviewed by Annett, 1999). However, handedness is associated to brain asymmetry and to language lateralization, and the genetic basis for handedness is supposed to overlap, at least in part, with the genetics of asymmetry and lateralization (McManus, 1991; Annett, 2004). A genetic cause for increased non-right-handedness in males would therefore be expected to be paired with decreased asymmetry and language lateralization in males, which is not supported by our meta-analyses.

Higher antenatal and postnatal levels of testosterone may be another factor to cause more non-right-handedness in males. Studies in patients with abnormal levels of sex hormones appear to support this hypothesis. Schachter (1994) investigated the prevalence of non-right-handedness in a group of women whose mothers had been administered diethylstilbestrol (DES) during their pregnancies. DES is a synthetic estrogen, administered to prevent miscarriage, which affects the fetal brain in a similar fashion as testosterone. The DES-exposed women had a higher prevalence of non-right-handedness than control women. This finding was replicated by Scheirs and Vingerhoets (1995). Another example of the influence of testosterone on handedness is provided by females with the congenital adrenal hyperplasia (CAH) syndrome, whose adrenal glands produce abnormally high levels of testosterone as a by-product of dysfunctional cortisol synthesis. Women with CAH were found to have a higher prevalence of non-right-handedness than their sisters with normal levels of testosterone (Nass et al., 1987). The increased non-right-handedness in women with CAH was replicated by Smith and Hines (2000), but not by Helleday et al. (1994). Though inconsistent and rather anecdotic, these studies lend some support to the idea that higher prenatal testosterone could cause an increased prevalence of non-right-handedness, which may account for the higher prevalence of non-right-handedness

in males as compared to females. The same argument as we made for a genetic cause can also be made against this explanation; why should differences in testosterone cause a sex difference in handedness but not in PT asymmetry or language lateralization? There is indeed some evidence that prenatal testosterone levels do affect language lateralization as well (Grimshaw et al., 1997).

Social influences may be a better candidate to explain the retrieved sex difference in handedness without associated sex differences in asymmetry and functional lateralization. It can be hypothesized that social pressure to use the right hand for unimanual tasks, such as writing and eating, is higher for females than for males. Alternatively, females may be more apt to meet social preferences for using the right hand than males. In support of this hypothesis, women reported significantly more frequently than men that they had been forced to change handedness from left to right (Porac et al., 1986; Porac & Buller, 1990). Porac et al. (1986) suggested that this could explain the overall difference in handedness between the sexes. Interestingly, Annett (2004) noted in her large samples of handedness data that females who use the right hand for writing more frequently use the left hand for other actions scored with a handedness scale, while right-handed males are generally more consistent in their preference for the right hand for all actions. In our meta-analysis, we found that the sex difference in handedness was larger in non-Western as compared to Western samples, which may be indicative of more sex-specific social pressure in non-Western cultures. These findings strengthen the idea that females who are innate left or mixed handed more frequently switch to right-hand use for social activities such as writing and eating than left or mixed-handed males.

## Conclusion

Meta-analysis of handedness studies shows that the prevalence of left-handedness is 25% higher in males than in females. This increase in left-handedness is not associated with a decrease in cerebral asymmetry or language lateralization in males. No significant sex difference could be observed for PT asymmetry nor for language lateralization as measured with either dichotic listening tests or functional imaging techniques.

Several factors may play a role in the increased prevalence of left-handedness in males. There is some support for sex-linked inheritance of a gene predisposing for left-handedness, either through an X chromosomal locus for handedness or through sex specific imprinting. Testosterone also appears to affect handedness and possibly also language lateralization. Higher levels of antenatal testosterone may predict more left-handedness, though evidence is anecdotic. Finally, social pressure to use the right hand may be different for males than for females, which could induce a sex difference in handedness, or perhaps females are more adaptive to social norms to use the right hand. This last hypothesis is supported by higher frequencies of hand switching in

females than in males and by less consistent preference to use the right hand for all unimanual actions in females as compared to males. The social pressure hypothesis is the only hypothesis that can explain the increased left-handedness in men in the absence of a sex difference in PT asymmetry and language lateralization.

### Acknowledgment

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## 11 Laterality and Sleep

Maria Casagrande

Research on functional hemispheric asymmetries in sleep was born in the 1970s on the basis of a merely speculative hypothesis. Many researchers (Galin, 1974; Ornstein, 1972) suggested that the right hemisphere specifically generated dream imagery and, more generally, Bakan (1976) speculated about a specialized role of the right hemisphere in the whole dreaming process. This hypothesis was based on the recognition of some correspondences between the characteristics of dreaming and some features of the cognitive processes ascribed to the right hemisphere. This assumption shares the notion that, since visual imagery is a salient characteristic of dreaming, the right cerebral hemisphere, specifically specialized for spatial information processing, must be the neural structure that contributes most to dream production (for an exhaustive discussion of this issue, see Antrobus & Bertini, 1992). This hypothesis had strong implications for the neuropsychology of sleep. Based on dream research studies, cerebral laterality was addressed to rapid eye movement (REM) sleep, that is, the behavioral state believed to be the dream generator.

The link between right hemisphere and REM sleep was based on early psychophysiological studies on sleep mentation. The first two studies (Aserinsky & Kleitman, 1953; Dement, 1955) examining the relationship between dream reports and sleep reported 74% and 92% vivid dream recall, respectively, when eye movements were present in sleep, and 7% and 0% recall, respectively, when they were absent. The key link to dreaming seemed to be the presence of eye movements. Several subsequent studies (e.g., Dement & Kleitman, 1957; Kales, Hoedemaker, Jacobson, Kales, Paulson, & Wilson, 1967; for a review, see also Herman, Ellman, & Roffwarg, 1978) reported 79% to 81% dream recall from REM awakenings and only 7% recall of dreams following other non-REM (NREM) awakenings. A few years later, the claim of Foulkes (1962) that dreaming was also a property of NREM sleep caused a theoretical upheaval. In view of experimental results which reported higher recall following NREM awakening (up to 74% of NREM dream recall reported by Foulkes in 1962), the idea that dreaming was the exclusive domain of REM sleep was abandoned. Nevertheless, the latter continued to be considered as an elective physiological substratum for the production

of sleep mentation (e.g., Casagrande, Violani, Lucidi, Buttinelli, & Bertini, 1996; Hobson, 1992). This being so, early studies on laterality in sleep aimed to demonstrate a higher activation of the right hemisphere in REM sleep—that is, in the state generating a dreamlike mentation—as compared to both NREM stages and the wake state.

### EEG Asymmetries during Sleep

In order to evaluate cortical hemispheric asymmetries during sleep, quantitative analysis of electroencephalographic (EEG) data recorded by the scalp can be considered a very simple and easy technique. The most common analyses of digitized EEG signals are fast Fourier transforms (FFT), period analysis, autoregression, and coherence analysis. FFT is an analysis in the frequency domain that allows estimation of the power<sup>1</sup> for each EEG frequency; the spectral frequency with the largest power corresponds to the predominant rhythm in the time series. FFT enables an estimation of both total power (e.g., from 0.5 to 35 Hz) and individual frequency bands.<sup>2</sup> On the basis of this EEG analysis, it is assumed that a relatively greater EEG activation corresponds both to a relatively small amplitude and to higher frequencies of EEG signals. Another common technique for EEG quantification is period analysis that provides a direct measure of percent time amplitude of EEG by means of yields EEG power, first derivative, and a zero-cross event<sup>3</sup> estimate (for a review on time series analysis and quantitative EEG analysis, see Gottman, 1981; Ferrillo, 1998). EEG coherence,<sup>4</sup> that is, a measure of the correlation between pairs of EEG signals, has also been frequently used for investigating laterality during sleep (e.g., Nielsen, Abel, Lorrain, & Montplaisir, 1990).

The first studies evaluating cerebral hemispheric asymmetries during sleep compared EEG activity recorded by homologous areas of the two hemispheres during REM and NREM sleep. An early study (Goldstein, Burdick, & Lazslo, 1970), while underlining a predominance of the left hemisphere in waking, only partly confirmed the existence of opposite hemispheric asymmetries in REM and NREM sleep. This study already clearly showed high inter- and intrasubject variability, considered to be one of the factors responsible for the inconsistencies that would characterize the picture of the following neuropsychological results. At variance with previous results, two years later Goldstein and his coworkers (Goldstein, Stoltzfus, & Gardocki, 1972) were the first researchers to observe an EEG asymmetry within sleep, with an amplitude reduction on the left hemisphere during NREM sleep, which shifted to the right during REM sleep. This pioneering study was followed by several others providing conflicting results. Only a few of these studies (Angeleri, Scarpino, & Signorino, 1984; Aviram & Glaubman, 1983; Goldstein, 1979; Hirshkowitz, Turner, Ware, & Karakan, 1979; Hirshkowitz, Ware, & Karakan, 1980; Hirshkowitz, Ware, Turner, & Karakan, 1980; Herman, 1984), however, were able to replicate Goldstein et al.'s findings, although these have

been confirmed by some recent EEG data, revealing a shifting of laterality from wake to sleep. A left prefrontal lateralization on total spectrum amplitude power and a right occipital lateralization in delta activity during waking were found. In contrast, during REM sleep, a right frontal lateralization in theta and beta activities and a right lateralization in occipital delta activity was observed (Bolduc, Daoust, Limoges, Mottron, Braun, & Godbout, 2002; Bolduc, Daoust, Limoges, Braun, & Godbout, 2003). Other studies reported greater right-hemisphere activity in both REM and NREM sleep, compared with waking (Barcaro, Denoth, Murri, Navona, & Stefanini, 1986; Murri, Stefanini, Navona, Dominici, Muratorio, & Goldstein, 1982; Murri, Stefanini, Bonanni, Cei, Navona, & Denoth, 1984; Rosekind, Coates, & Zarcone, 1979; Sockeel, Mouze-Amady, & Leconte, 1987). These results were again considered consistent with Bakan's earlier speculation about the privileged role ascribed to the right hemisphere in the whole dreaming process. In fact, several studies had shown that dream recall could be observed not only in REM sleep but also in all the other NREM sleep stages. Therefore, a different hemispheric pattern between sleep and wake could also be linked to some well-rendered dissimilarities between wake and sleep mentation. At variance with these results, other authors (Benca et al., 1999) reported a rightward shift in alpha power from wake to sleep, particularly in the frontal regions. This increase in alpha power in the right hemisphere was observed in both REM and NREM stages. Since alpha power is usually considered as reflecting decreased brain activation, the results of this study were considered consistent with high left-hemisphere activation during sleep. Due to a greater intersubject variability, mixed results—greater right-hemisphere activity during REM or within all sleep stages only for a few subjects—were also reported (Antrobus, Ehrlichman, & Wiener, 1978; Gaillard, Laurian, & Le, 1984; Goldstein et al., 1970; Herman, 1984; Violani, De Gennaro, & Capogna, 1984). This finding allows many authors to conclude that there is no consistent EEG hemispheric prevalence during sleep (Antrobus et al., 1978; Banquet, 1983; Ehrlichman, Antrobus, & Wiener, 1985; Moffitt, Hoffmann, Wells, Armitage, Pigeau, & Shearer, 1982; Pivik, Bylsma, Busby, & Sawyer, 1982; Rosadini, Ferrillo, Gaspareto, Rodriguez, & Sannita, 1984; Scarpino, Guidi, & Mercante, 1985; Sterman, Smith, Schumme, & Poe, 1988; Violani et al., 1984; Wollman & Antrobus, 1984).

Some studies found asymmetrical activation of the cerebral hemispheres during sleep in some homologous areas but did not confirm a lateral EEG pattern in other cerebral sites (Antrobus et al., 1978; Boivin, Abel, Lapierre, & Montplaisir, 1988; Herman, Rampy, & Hirshkowitz, 1987; Herman, Rampy, & Roffwarg, 1989; Hirshkowitz, Karacan, Thornby, & Ware, 1984; Mercier, Pivick, & Busby, 1985; Murri et al., 1984; Pivik et al., 1982; Reinsel, Antrobus, & Fein, 1989). Furthermore, greater right-hemisphere activity was detected considering some EEG frequencies, with a reverse result (i.e., greater left-hemisphere activity) when other EEG frequencies were considered (Angeleri et al., 1984; Aviram & Glaubman, 1983; Boivin, Cote, Lapiene, &

Montplaisir, 1987; Herman, 1984; Herman et al., 1987; Rosa, Antrobus, & Reinsel, 1989; Reinsel et al., 1989; Sockeel et al., 1987). Finally, greater asymmetries were found in slow wave sleep (SWS) (i.e., stage 3 and stage 4) with respect to both REM and stage 2 sleep (Armitage, Hoffmann, Loewy, & Moffitt, 1988; Armitage, Hudson, Trivedi, & Rush, 1995; Armitage, Roffwarg, & Rush, 1993; Moffitt et al., 1982), a finding also confirmed by late components of auditory evoked potentials during sleep (Campbell, Bell, & Armitage, 1987). By using a nonlinear technique for evaluating interhemispheric EEG asymmetries, Pereda and his coworkers (Pereda, Gamundi, Nicolau, Rial, & González, 1999) found that the right hemisphere appears to be more complex than the left hemisphere during eye-closed wake and sleep stages 1 and 2, and these characteristics reversed during SWS.

Another research strategy that is useful for investigating hemispheric asymmetries during sleep is measuring EEG coherence (see note 4) between homologous areas of the two cerebral hemispheres. Regardless of a greater activation of one cerebral hemisphere with respect to the other, this technique allows evaluation of functional connectivity between brain regions. Thus, analyzing the correspondence of EEG activity recorded from the same locations in the two cerebral hemispheres during wake and sleep can reveal a state-dependent level of cooperation between the two hemispheres.

EEG coherence analysis during sleep again shows contradictory findings. An increase of both EEG coherence and interhemispheric correlation during REM sleep has been found by many authors (e.g., Armitage, Hoffmann, Loewy, & Moffitt, 1989; Barcaro, Denoth, Murri, Navona, & Stefanini, 1986; Dumermuth & Lehmann, 1981; Dumermuth, Lange, Lehmann, Meier, Dinklemann, & Molinari, 1983; Guevara, Lorenzo, Arce, Ramos, & Corsi-Cabrera, 1995; Mann & Roschke, 1997; Nielsen et al., 1990), and these results are consistent with studies on human infants indicating higher EEG interhemispheric coherence during active sleep than in quiet sleep (e.g., Kuks, Vos, & O'Brien, 1987). However, a decrease in the frontal interhemispheric coherence for the alpha frequency from waking to both sleep onset and REM sleep has been shown by other studies (Achermann & Borbély, 1998a, 1998b; Cantero, Atienza, Salas, & Gomez, 1999).

Although there are many discrepancies in results using coherence analysis and interhemispheric correlation techniques, showing that they still have to be properly understood (Guevara & Corsi-Cabrera, 1996), most sleep studies point to interhemispheric coordination increases during REM sleep compared to NREM sleep, suggesting an improved interhemispheric transfer of information during REM.

These conclusions contrast with findings coming from a more direct evaluation of callosal activation during sleep. The only study recording callosal activity during sleep in cats showed a decrease in callosal activity throughout sleep, with a drop in REM (Berlucchi, 1965). Because of the methodological difficulties in measuring callosal

activity, this result was never replicated in human subjects. However, a recent study (Bertini, De Gennaro, et al., 2004) using EEG recordings has shown a decrease in transcallosal activity during awakenings from REM sleep, supporting Berlucchi's finding.

In conclusion, studies using EEG techniques for evaluating cerebral hemispheric asymmetries during sleep yield very conflicting results. This inconsistency may depend on various methodological differences between studies and the meaning ascribed to EEG rhythms during sleep and waking. First, it has been pointed out that it is not so straightforward to compare cerebral asymmetries during sleep and waking since the various studies considered EEG recordings coming from different cerebral areas. There is no reason to expect the same EEG asymmetries when different cortical locations are considered, and this conclusion appears to be well advised with regard to any behavioral state and not only as regards sleep. Taking this remark into account, we may consider another relevant methodological aspect. When EEG recordings are carried out during waking, they are conducted under very controlled conditions: The subjects are in a quiet standing position, and they are required not to move and to be relaxed; their stream of thought has to be calm and stress free; both eye-open and eye-closed recordings are performed; and when EEG recordings are carried out while the subject is involved in a cognitive task, the neuropsychological aspects of the task are well-known to the experimenter, who can easily predict the type of EEG distribution on the scalp. All these conditions simply do not hold when the subject is sleeping. Furthermore, both body and eye movements during sleep are usually artifact sources so that many EEG epochs have to be disregarded from the following analyses.

Other important methodological differences between studies may regard the length of the EEG epoch analyzed, the EEG sampling adopted, and, not least, the type of EEG analysis employed.

An important issue that can account for the many inconsistent results in laterality during sleep concerns the meaning of EEG frequencies. In active wakefulness, alpha activity suppression over specific brain areas has been typically interpreted as an activation index of those cortical regions involved in the information processing of a specific sensory modality. Indeed, a relation between EEG desynchronization and cognitive activation has been shown (e.g., Bradshaw & Nettleton, 1983). To some extent, this seems to also be true during sleep. As a matter of fact, alpha power attenuation over Broca's and Wernicke's area during REM sleep has been observed when subjects report dreams including predominantly expressive and receptive language (Hong, Jin, Potkin, Buchsbaum, & Wu, 1996). Thus, high activation of one cerebral hemisphere with respect to the other appears to depend on the characteristics of sleep mentation. This suggestion could set straight many inconsistent results. In any case, in view of the impossibility of analyzing the type of mental activity occurring in sleep, a right- or left-hemispheric dominance may be due to the nature of the cognitive processes involved during sleep mentation.

Other uncontrolled variables could be important for reconciling the conflicting results in this research area. For example, when we consider the alpha rhythm, we know what it means during waking. This rhythm represents the electrophysiological background of a relaxed eye-closed waking state. Alpha suddenly disappears when the subject opens his or her eyes or when he or she is paying attention to external or internal stimuli. In all these conditions, alpha is replaced by beta rhythm. Thus, alpha and beta rhythms can be considered the EEG background of waking, reflecting an internal relaxation and an arousal state, respectively (Steriade, Gloor, Llinás, Lopes da Silva, & Mesulam, 1990). Based on this view, waking alpha undoubtedly represents a deactivation state as compared to beta rhythm, that is, it replaces high EEG frequencies. The question appears to be whether the same conclusions can be drawn when sleep is taken into account. This does not appear to be the case. Sleep is characterized by the disappearance of alpha activity and by the ensuing emergence of slow EEG rhythms, such as delta and theta. Nevertheless, the alpha rhythm has also been recorded during sleep—above all, during REM, but also in delta sleep and in the other NREM stages. By submitting alpha power spectra recorded from stage 2, stage 4, and REM sleep to principal-components analyses, Corsi-Cabrera and her coworkers (Corsi-Cabrera, Guevara, Del Río-Portilla, Arce, & Villanueva-Hernández, 2000) were able to identify alpha as a band only during wakefulness, a result underlining the difficulty in overlapping EEG rhythms in waking and sleep. Furthermore, two variants of alpha activity with different functional roles are proposed to coexist during REM sleep: (1) an alpha prevalence when rapid eye movements are present and which is dominant in the occipital regions and (2) a spontaneous alpha burst activity showing the same spectral features in tonic and phasic REM, which are considered as microarousals in this brain state. All these data suggest that alpha activity might have different meanings depending on the physiological state in which it is recorded.

In conclusion, sleep appears to be a very multifaceted, complex behavioral state characterized by a very different brain activity during REM, stage 1, stage 2, and SWS, as compared to waking. This varied physiological activity, particularly evident in REM sleep—the paradoxical state defined by the coexistence of a higher cortical arousal and by sensorial and motor inhibition—makes it difficult to delineate a single reliable EEG parameter useful for comparing laterality in waking and sleep.

### **Neuroimaging Studies on Hemispheric Asymmetries during Sleep**

Several techniques are now available to investigate brain functions during any behavioral state. Among these, positron emission tomography (PET) and functional magnetic resonance imaging have been the most used. These methods allow exploration of regional cerebral hemodynamics with a good spatial localization power. Cerebral

blood flow is used as a marker of neuronal activity in both waking and sleep (for a review, see Maquet, 2000).

Chong-Hwa Hong and his coworkers (Chong-Hwa Hong, Gillin, Dow, Wu, & Buchsbaum, 1995) detected a lateralized cerebral glucose metabolism during REM sleep, suggesting a right-hemisphere (frontal eye fields, dorsolateral prefrontal cortex) specialization in saccadic eye movement control during REM sleep. These data are consistent with results by Droste, Berger, Schuler, and Kraus (1993), who found a tendency toward a higher blood flow velocity during REM sleep on the right side than on the left side. However, no hemispherical differences in regional cerebral blood flow (rCBF) during REM sleep have been found in other studies (Braun et al., 1998; Buchsbaum, Hazlett, Wu, & Bunney, 2001; Maquet & Phillips, 1998), except for a greater activation of the left thalamus and right parietal operculum (Maquet et al., 1996).

### **Motor Asymmetries during Sleep**

A noninvasive method for evaluating hemispheric laterality during sleep is, of course, represented by measuring lateral motor activity. The rationale for this approach is based on the neurophysiology of motor control. Indeed, a firm link between handedness and hemispheric dominance in motor functions has been established from the early years of the past century (Kandel, Schwartz, & Jessell, 1985). Since then, human brain imaging studies have confirmed that simple finger movements of the dominant hand are related to an increase in rCBF in the contralateral cortical motor areas, even though rCBF in the primary motor and premotor areas is involved in the control of ipsilateral movements when subjects move their nondominant hand (e.g., Kawashima et al., 1998).

In 1965 Muller-Limroth (cited in Violani, Testa, & Casagrande, 1998) was the first to describe a motor asymmetry during sleep. The author observed that when the nose was tickled during sleep, right-handed people made a defensive movement with the left hand. Later Muller-Limroth's early findings were replicated by a study (Violani, Casagrande, Cinelli, & Testa, 1992) in which tactile stimuli were administered by touching the subject's nose with a paintbrush both during stage 1 and stage 2 sleep and during waking with subjects recumbent on their back with eyes closed and both hands equally free to move. By analyzing the distribution of the electromyographic movements of the hands in both right-handed and left-handed subjects, Jovanovic (1971) found that, during sleep, the nondominant hand was two times more active than the dominant one, regardless of the phase of the REM-NREM cycle. These results are in keeping with data showing a predominance of the left hand during the sleep onset period (SOP) in video-recorded hand movements (Lauerma et al., 1992). In this study, the predominance of the nondominant hand in right-handers was found only

for organized movements (i.e., hand touching the subject's face) depending on cortical structures and involving the somatic-sensitive and prefrontal cortex, while nonorganized movements (i.e., incomplete movements of hand or finger), depending on spinal systems, were symmetrical. Subsequently, when analyzing motor activity recorded by actigraphs worn on each wrist for 13.5 hours, Lauerma and his coworkers (Lauerma, Kaartinen, Polo, Sallinen, & Lyytinen, 1994) found a slight left-sided superiority during sleep as opposed to waking. In a subsequent study (Violani et al., 1998), actigraphic data were recorded for about 56 hours from both wrists and ankles. The results showed a greater motor activity in the right wrist as compared to the left in waking. During sleep, in the first part of the night there was a nonsignificant superiority of the left hand, while in the second part of the night the right hand regained its superiority. No asymmetrical amount of motor activity was detected for ankles in both waking and sleep.

The opposite motor asymmetry found during waking and sleep was usually detected in the first part of the sleep period or during the transition from wakefulness to sleep. This pattern has been interpreted on the basis of a "homeostatic" hypothesis. In this view, as the left hemisphere in right-handed humans should be more engaged in mediating the relationships with both others and the environment, respectively, by means of language and motor activity during waking, it could accumulate a greater sleep debt compared with the nondominant hemisphere, and, therefore, it would cease controlling motor activities in a quicker and more pronounced way than the right hemisphere during sleep. This homeostatic interpretation of behavioral data is consistent with EEG data showing that unilateral activation of the left somatosensory cortex during wakefulness resulted in an increased power density in the delta frequency in the left hemisphere during the first hour of subsequent sleep (Kattler, Dijk, & Borbély, 1994).

However, all data on motor laterality during sleep are also in keeping with results showing that, during the transition from wakefulness to sleep, there is a relative advantage of the right hemisphere, revealed by a stronger impairment of the right hand in reaction time (RT) to auditory stimuli (Casagrande, Violani, De Gennaro, Braibanti, & Bertini, 1995) and in sustaining endogenous motor programs—that is, performing a finger-tapping (FT) task (Casagrande, Violani, et al., 1995; Casagrande & Bertini 2008a, 2008b). The superiority of the right hemisphere during the SOP allows considering the ability of this hemisphere in operating at levels of reduced arousal, suggested by its superiority in sustaining attention (e.g., Heilman & Van Den Abell, 1979; Posner & Petersen, 1990). This issue will be considered in a subsequent section of this chapter.

### **Behavioral Asymmetries upon Awakening from REM and NREM Sleep**

The weakness of the empirical evidence yielded by EEG studies has not discouraged the idea of a functional asymmetry during REM sleep favoring the right hemisphere

with respect to the left one. The possibility of pursuing this research line stems from some experimental data indicating that the process of awakening does not completely cancel all the functional characteristics of the preceding sleep state (see Bertini & Violani, 1992). This psychophysiological phenomenon is known as the "carry-over effect." Originally recognized by Fiss, Klein, and Bokert (1966), carry-over effects were confirmed in several studies that have shown different behavioral responses after awakening from REM and NREM sleep in dreamlike verbalization (Bertini, Torre, & Ruggieri, 1975), in perceptual illusion (Lavie, 1974; Lavie & Giora, 1973; Lavie & Sutter, 1975), and in lateralized cognitive tasks (see Bertini & Violani, 1992). Several recent physiological data have also legitimized the assumption of carry-over effects. As a matter of fact, both PET (Balkin et al., 2002) and blood flow velocity (Hajak et al., 1994) studies have shown that about 30 minutes is needed in order to fully reestablish wake regional brain activity patterns upon awakening from sleep. Moreover, greater negative effects of sleep inertia are detected on performance evaluated after SWS awakenings than REM sleep awakenings (Tassi & Muzet, 2000), and these data are also coherent with the pattern of motor threshold changes in response to magnetic stimuli delivered upon REM and NREM awakenings (Bertini, Ferrara, et al., 2004).

Using spatial tasks upon awakening has revealed a right-hemisphere superiority in REM sleep with respect to wake and NREM sleep (Bertini, Violani, Zoccolotti, Antonelli, & Di Stefano, 1984; Bertini, Violani, Zoccolotti, Altomare, Doricchi, & Evangelisti, 1985; Gordon, Frooman, & Lavie, 1982); however, a consistent left-hemisphere superiority, with no interhemispheric variation across wake, REM, and NREM states, has been found in two studies using lateralized verbal tasks (Bertini et al., 1985; Lavie, 1986). The lack of variation in verbal task performances across the sleep states raised the question of whether improvement of right-hemisphere performances upon REM state awakening reflected a general right-hemisphere activation or whether it was restricted to specific, such as spatial, right-hemisphere tasks. Casagrande and coworkers (Casagrande, Bertini, & Testa, 1995) hypothesized that the absence of interhemispheric variations from wake state to REM and NREM sleep, observed with verbal tasks, could be dependent upon the type of linguistic tasks used. The tasks adopted by both Bertini and coworkers (1985) and Lavie (1986) in their studies required a phonological code, strictly dependent upon a specific left-hemisphere strategy (e.g., Young, Ellis, & Bion, 1984). Concerning this aspect, Levy and Trevarthen (1977) found that the right hemisphere, though comprehending verbal stimuli, could not make phonological transformations. Several clinical and experimental studies have revealed that the left-hemisphere superiority in the processing of verbal stimuli is not absolute and have also pointed out that the right hemisphere exhibits some language processing capacities (e.g., Zaidel, 1985). Several factors may affect the magnitude and direction of hemispheric superiority for language processing. In fact, left-hemisphere superiority is found in the recognition of words, of familiar word fragments, of pronounceable

letter strings (similar to nonsense words), but not of letter strings with low approximation to words (Axelrod & Haryadi, 1977; Young et al. 1984) or of single syllables (Hellige, Bloch, & Taylor, 1988). Based on previous findings (Casagrande, Testa, & Bertini, 1992), showing that the superiority of the left hemisphere was less marked in a consonant recognition task (CRT) as compared to a letter recognition task (consonant and vowel strings), Casagrande, Bertini, and Testa (1995) used the same CRT employed in their previous study and found a left-hemisphere superiority in wake and upon awakening from NREM sleep, but not upon awakening from REM sleep. These results have supported the hypothesis that interhemispheric variations from waking to REM and NREM sleep are not restricted to right-hemisphere tasks.

Behavioral techniques, compared to physiological methods, give more consistent demonstrations about an inversion of brain hemisphere dominance from wake to REM sleep. These findings were all obtained by using cognitive tasks involving spatial or linguistic processes for which a lateral pattern of hemispheric activity is well-known. In a recent study, Casagrande and Bertini (2008b) evaluated the shift from wake to sleep in the laterality pattern by using an FT task, that is, a widely known psychomotor task revealing hemispheric asymmetries in the wake state: a functional superiority of the left hemisphere being indicated by faster responses of the dominant hand in right-handed subjects (Patterson & Bradshaw, 1975). The FT task was applied during an evening wakeful condition, the early and the last part of the SOP, upon experimental awakenings from stage 2 and REM sleep in the first (2nd cycle NREM-REM) and in the second part of the night (3rd and 4th cycle NREM-REM), upon morning awakening, and during a morning wakeful condition. The results showed a significant superiority of the left hemisphere during the two wakeful conditions. At sleep onset, a clear reversal of dominance was observed, and it was followed by steady right-hemisphere superiority upon both REM and NREM sleep awakenings, and upon the morning sleep-wake transition. Therefore, performance in an FT task has shown a repatterning of laterality across wake-sleep-wake states.

Again, the previous findings on the shift of the laterality pattern from wake to sleep were confirmed. Nevertheless, at variance with previous results, no differences between REM and NREM sleep were present. Later results as well as the asymmetrical pattern observed in the two transitional states—from wake to sleep and in morning awakening—have again left the question of the meaning of the laterality shift from wake to sleep unresolved. A clearer conclusion on this issue can be drawn from experimental results collected during the SOP (see the following section) that point to the specialized role of the right hemisphere in vigilance control (e.g., Sturm et al., 1999).

### **Laterality during the Sleep Onset**

The SOP has generally been conceived as a continuous process characterized by gradual arousal variations, detected by EEG changes (Davis, Davis, Loomis, Harvey,

& Hobart, 1937; Rechtschaffen & Kales, 1968) and behavioral responses (e.g., Casagrande, De Gennaro, Violani, Braibanti, & Bertini, 1997; Ogilvie & Wilkinson, 1984). Finer analyses have shown that this slow deactivation occurs with a simultaneous alternating pattern of alpha and theta activity associated with intermittent response failures in performing RT tasks or in sustaining motor performance (Casagrande, De Gennaro, Braibanti, Violani, & Bertini, 1992). This pattern allows evaluation of cerebral laterality during the transition from wakefulness to sleep by means of both EEG and lateralized behavioral techniques.

EEG data have shown that the average amplitude of the left-right hemisphere difference in the beta:delta EEG ratio decreases gradually to zero at 400 seconds after sleep onset (Merica, Fortune, & Gaillard, 1991; Merica & Gaillard, 1992). By analyzing the EEG, other studies have found a decrease in interhemispheric coherence during sleep onset (Boldyreva & Zhavoronkova, 1991; Zhavoronkova & Trofimova, 1997, 1998; Wright, Badia, & Wauquier, 1995), in which all bands except beta reverse to predominate in the right hemisphere (Boldyreva & Zhavoronkova, 1991; Zhavoronkova & Trofimova, 1997, 1998). Furthermore, in the centroparietal 4–8 Hz band, a right-hemispheric predominance in NREM sleep has been described and is particularly prominent in the first hour of sleep (Roth, Achermann, & Borbély, 1999). These results agree with those revealed by nonlinear analysis of the EEG, indicating that the right hemisphere appears to be more complex than the left hemisphere during sleep stages 1 and 2 (Pereda et al., 1999).

On the basis of standard criteria (Rechtschaffen & Kales, 1968), the process of falling asleep is revealed by the occurrence of stage 1 of sleep, characterized by a prevalence of the theta rhythm. By adopting an EEG visual analysis, the latency of theta rhythm appears to be shorter for the left hemisphere as compared to the right (Casagrande & Bertini, 2008a), showing that the left hemisphere falls asleep earlier than the right hemisphere. It is interesting to note that the finding of an asymmetrical theta burst latency agrees with EEG and PET data indicating, in an alert resting state, positive correlations between theta density and cerebral metabolism in right frontotemporal regions, including the right-middle and superior frontal gyri, and the right-middle and temporal frontal gyri (Pizzagalli, Oakes, & Davidson, 2003). EEG data are consistent with behavioral measures. Using this type of technique, it was found that there are systematic variations of hemispheric functioning when falling asleep. A stronger impairment of the left hemisphere both in reacting to external stimuli (auditory RT task; Casagrande, Violani, et al., 1995) and in sustaining endogenous motor programs (FT task; Casagrande, Violani, et al., 1995; Casagrande & Bertini, 2008a, 2008b) was discovered. This pattern was unaffected by the time of night—that is, it did not depend on homeostatic sleep pressure (Casagrande & Bertini, 2008a). Such a result would lead us to suggest that it could be a steady characteristic of the transition from wake to sleep. This conclusion agrees with other data indicating a greater right-sided cerebral

activation during the transition from wake to sleep also when sleep onset occurs during REM sleep (Asenbaum et al., 1995).

Furthermore, by using an FT task performed by normal subjects when attempting to fall sleep during a Multiple Sleep Latency Test (MSLT) procedure (Carskadon & Dement, 1982) reveals a repatterning of the hemispheric asymmetry with respect to the awake state (Casagrande, Violani, & Bertini, 1996b).

Further, during the transition from wakefulness to sleep, the right hand (left hemisphere) stops responding before the left (right hemisphere) both in the RT task and in the FT task (Casagrande, Violani, et al., 1995; Casagrande & Bertini, 2008a). This variation in behavioral hemispheric pattern is in line with the one shown by EEG techniques. Sleep onset happens at different times in the two hemispheres even when considering both EEG (i.e., appearance of visually detected theta rhythm) and behavioral (i.e., stopping of hand responses in a FT task) measures (Casagrande & Bertini, 2008a). The latter result confirms the strong relationship between the FFT and EEG (Anliker, 1963; Casagrande, De Gennaro, et al., 1997). Although both behavioral and EEG measures show that the left hemisphere falls asleep earlier than the right hemisphere, a shorter latency for the FFT as compared to the theta burst latency was found, showing a temporal dissociation between behavioral and EEG sleep, as far as the two indices used in this study are concerned: Indeed, behavioral sleep develops before EEG sleep. This finding confirms previous results (Blood, Sack, Percy, & Pen 1997; Casagrande, De Gennaro, et al., 1997; Ogilvie & Wilkinson, 1984, 1988; Ogilvie, Wilkinson, & Allison, 1989) and is in keeping with the partial independence of the neurophysiological systems that control behavioral and electrophysiological aspects of wake and sleep (Feldman & Waller, 1962). The hemispheric pattern found during sleep onset seems to depend on the handedness of the subjects tested. An asymmetrical hemispheric pattern was found only in right-handers, while left-handers showed only a tendency to a reversed hemispheric pattern. The latter result appears consistent with the greater variability in cerebral organization characterizing the left-handers with respect to right-handers (Casagrande, Curcio, & Bertini, 1999).

In conclusion, EEG and behavioral data obtained from the sleep onset process reveal a greater alerting state in the right hemisphere when the brain is sleepy and is falling asleep. These results are in keeping with data showing the advantage of the right hemisphere in the control of vigilance (e.g., Whitehead, 1991) and in responding to warning stimuli (e.g., Heilman & Van Den Abell, 1979). It is known that a noradrenergic fronto-parietal-thalamic-brainstem network subserving vigilance is located in the right hemisphere (Bench et al., 1993; Deutsch, Papanicolaou, Bourbon, & Eisenberg, 1987; Posner & Rafal, 1987; Raz & Buhle, 2006; Sturm & Willmes, 2001; Sturm et al., 1999; Weis et al., 2000). This right-hemisphere network also seems to be activated when the entire brain is sleepy. In other words, the right hemisphere, as

compared to the left, seems to have greater levels of “wakeability” or “alertness ability” when the vigilance state is very low and the brain is going to sleep.

### Hemispheric Asymmetries Following Sleep Deprivation

There are quite a few studies on the effects of sleep deprivation on human performance. Since the pioneering findings of Patrick and Gilbert (1896), there have been two main aims underlying this research line. Briefly, these refer to (1) the possibility of disambiguating the question of sleep functions and (2) the evaluation of the consequences of low vigilance, due to sleep loss, on human performance and behavior.

As regards the first aim, the earlier studies were interested in evaluating the impairment of cognitive performance, and also behavioral changes with regard to such things as mood and anxiety, as a consequence of sleep loss. On the basis of the extirpation paradigm, finding a specific cognitive or behavioral disease consequent to sleep deprivation could allow inferring the special role of sleep for the correct fulfillment operation of that specific function. In line with this purpose, two kinds of sleep deprivation paradigms were used: selective and total sleep deprivation. Selective sleep deprivation experiments attempt to eliminate sleep stages while having minimal impact on total sleep time. Selective deprivation studies were originally designed as a way to determine the functional role of REM sleep or SWS, which was typically cut short by experimental awakenings or by an arousal procedure, respectively. On the other hand, total sleep deprivation refers to sleep loss that can be considered moderate when it involves only one night without sleep or more severe when the sleep loss is repeated for prolonged periods without sleep for up to about 11 days in humans (Bonnet, 1994).

The second purpose of sleep deprivation research was mainly to evaluate what happens when a subject has to work when his or her vigilance level is very low as a consequence of continuous performance for extended periods of wakefulness, that is, 24 hours without sleep, or when a person undergoes an acute or chronic reduction of sleep, that is, a partial sleep deprivation.

Moderate total sleep loss and partial sleep deprivation, as well as sleep fragmentation, are common forms of sleep loss in the real world. Indeed, total and partial sleep deprivation are frequent conditions in many types of occupations, such as in the military, in road safety and public health, in shift work, and in work performed by civil servants (e.g., Caldwell, Caldwell, Brown, & Smith, 2004; Casagrande, 2002; Dinges, 2004; Hill, 2004; Porcù, Casagrande, & Ferrara, 1999). On the other hand, both partial sleep loss and sleep fragmentation are very common problems for sleep disorder medicine. All these situations can mean accumulating severe sleep debt, leading to dangerous levels of sleepiness, performance decreases, and a lower margin

of safety. These factors can increase vulnerability to accidents in operational settings and in everyday life.

The most apparent effect of sleep loss is sleepiness, which can be inferred from subjective reports, MSLT, EEG changes, and many other measures (Curcio, Casagrande, & Bertini, 2001). In summary, two cardinal features of sleep loss are a decrease in both vigilance and cognitive performance. Performance deficits due to a sleep debt are well documented (e.g., Angus & Heslegrave, 1985; Gillberg & Åkerstedt, 1998), particularly those concerning a decrease in attention (Dinges, 1992; Casagrande, Violani, Curcio, & Bertini, 1997). This impaired behavior is explained by drastic deactivation in many neural networks reported by neuroimaging studies (e.g., Drummond & McKenna, 2009; Thomas et al., 2000; Wu et al., 2006).

Within sleep deprivation research, only a few authors have investigated variations in hemispheric functioning. Many results from this area have come from studies evaluating neural activation while sleep deprived persons were performing tasks of different kinds. In this sphere, the intricate play of deactivation and activation of neural networks interacts with the special role of the right hemisphere in the control of an important attentional function: the ability to prepare and sustain attention in order to process high-priority signals (Posner & Petersen, 1990), namely, the alertness or vigilance system, which is the first to suffer as a consequence of sleep loss.

When subjects are sleep deprived, PET data have shown an increased activation in the prefrontal cortex and parietal lobes, particularly in the right hemisphere (Drummond, Gillin, & Brown, 2001; Szelenberger, Piotrowski, & Justyna, 2005). In line with these data, Ferreira and coworkers (2006) found that EEG activation shifted from the left hemisphere, before sleep deprivation, to the right hemisphere, after sleep deprivation, in all frontal electrode pairs. Lim and coworkers (Lim, Choo, & Chee, 2007) have maintained that the most robust marker of vulnerability to sleep deprivation is the change in the intraindividual variability of RTs. This behavioral pattern result correlated with the drop in left parietal activation from wakefulness pre-sleep deprivation to sleep deprivation. After sleep loss, a deactivation network was found in the posterior cerebellum, right fusiform gyrus and precuneus, and left lingual and inferior temporal gyri; an increased activation was found in the bilateral insula, claustrum, and right putamen. This differential pattern of activation and deactivation was correlated with a worsening of performance (Bell-McGinty et al., 2004).

Following sleep deprivation, performance in a gambling task with higher risk compared to a task characterized by low risk elicited significantly greater activation in the right nucleus accumbens, typically associated with gain prediction (Venkatraman, Chuah, Huettel, & Chee, 2007). At variance with these results, Cote and coworkers (Cote, Milner, Osip, Baker, & Cuthbert, 2008) studied subjects during a week of continuous sleep restriction and found that EEG and event-related potential deficits were more robust in the right hemisphere, which may reflect greater vulnerability to sleep

loss in the nondominant hemisphere. Consistent with these results, a previous study found that the slowdown of RT during a 40-hour period of wakefulness was associated with an increase in the absolute power of the EEG, particularly in the left central cortex (Corsi-Cabrera, Guevara, Arce, & Ramos, 1996). This finding is in line with EEG data showing an EEG frontal right-hemisphere dominance after sleep deprivation (Achermann, Finelli, & Borbély, 2001).

By using near-infrared spectroscopy, it was found that oxygenated hemoglobin concentration both in the ventrolateral part of the frontal lobe and in the upper part of the temporal lobe was negatively correlated with subjective feelings of fatigue and positively correlated with sleep duration in the previous night, but no asymmetrical pattern was evident (Suda et al., 2009).

Contrasting results derived also from the analysis of behavioral responses during sleep deprivation. The superior left-hemisphere processing during a dichotic listening task decreased when subjects were sleep deprived (Johnsen, Laberg, Eid, & Hugdahl, 2002). Analyzing performance in a lateralized consonant recognition task requiring verbal denomination of four vertical capital consonant arrays, randomly presented to the left or right of the fixation point and carried out 96 times, every 15 minutes, during a period of 24 hours of continued wakefulness, did not find a steady asymmetrical pattern, but ultradian variations in hemispheric asymmetries (Casagrande, Violani, & Bertini, 1996a) linked to the basic rest–activity cycle suggested by Kleitman (1963).

A leftward attentional bias, found when subjects were required to judge the relative lengths of the left and right sections of a line, reversed to a rightward shift with sleep deprivation. This result suggests that a diminution of alertness can cause a relative decrease in right-hemisphere activation (Manly, Dobler, Dodds, & George, 2005).

As regards manual RT asymmetries, Barthélémy and Boulinguez (2002)—in a covert orienting task—found shorter left-hand RTs for both neutral and invalid conditions, and no hand difference for valid cues. This indicates that orienting (or reorienting) of attention is slower when responding with the right than with the left hand. These manual RT asymmetries seem to confirm the special role of the right hemisphere in orienting visuospatial attention. At variance with this finding, a covert orienting task during 24 hours of continued wakefulness yielded lower RTs for stimuli in the left visual hemifield as compared to the right (Casagrande, Martella, Di Pace, Pirri, & Guadalupi, 2006). This result supports the hypothesis that both hemispheres are involved in the attentional control of the right visual hemifield (Heilman, 1995; Heilman & Van Den Abell, 1979, 1980; Heilman, Watson, & Valenstein, 1985; Mesulam, 1981; Weintraub & Mesulam, 1987). This finding was confirmed by Fimm, Willmes, and Spijkers (2006), who also observed a specific impairment in the invalid trials—that is, in the reorienting process—in the left visual field.

In conclusion, sleep deprivation research has reported a drastic decrease in cerebral functions; in certain studies this impairment appears to be more severe for the left hemisphere. Other authors have stressed how the deactivation pattern develops equally in the two hemispheres of the brain. Finally, some behavioral studies investigating spatial orienting of attention under sleep deprivation conditions have reported an advantage for the left hemisphere, as compared to the right, that is more pronounced for the reorienting mechanism. The asymmetrical pattern in the orienting system indicates a left-hemisphere superiority when perceptual processing is taken into account but a right hemisphere facilitation when motor responses are considered.

These findings can be interpreted within the complex neural network characterizing sleep deprivation. On the one hand, sleep deprivation causes dramatic cerebral deactivation leading to a strong impairment of alertness, namely in a function subserved by a noradrenergic system, specifically lateralized in the right hemisphere (Raz & Buhle, 2006). This neural network is normally able to sustain performance but seems to falter when an additional effort is required by a cognitive function, such as attentional orienting. Although many neuroimaging studies have supported the existence of different attentional neural networks for alerting and orienting (Raz & Buhle, 2006), these systems may remain independent of one another in some conditions (Casagrande et al., 2006; Fan, McCandliss, Sommer, Raz, & Posner, 2002; Fernandez-Duque & Posner, 1997) and may interact in others (Callejas, Lupiáñez, Funes, & Tudela, 2004, 2005; Fimm et al., 2006; Fuentes & Campoy, 2008; Versace et al., 2006). This interaction may be responsible for the specific impairment found in the right hemisphere, having a special role in mediating attention (Cohen, Semple, Gross, Holcomb, Dowling, & Nordahl, 1988; Deutsch et al., 1987; Pardo, Fox, & Raichle, 1991).

## Conclusions

The many inconsistent results regarding the role of the two brain hemispheres during sleep do not allow us to reach any clear-cut conclusions. The early hypothesis linking right-hemisphere superiority during REM sleep to dreaming is not easy to evaluate. Only one study demonstrated a strong association between dream report characteristics and an asymmetrical pattern in cerebral activation during sleep (Hong et al., 1996). Nevertheless, in that study the distinctive linguistic features of dream reports were related to a higher activation in Broca's and Wernicke's regions of the left hemisphere. This result is very intriguing since it suggests a link between sleep mentation characteristics and cortical network activation, but the link foreshadows a flexible alternating pattern of activation between the two cerebral hemispheres. Based on this idea, one may suggest that some methodological questions in both EEG and

neuroimaging studies, as well as the higher intersubject variability in the activation pattern during sleep, cannot allow us to grasp the laterality of neural networks during sleep.

On the other hand, all the data on motor activity during sleep appear to be more consistent. They suggest the presence of a different homeostatic pressure for the left and right hemispheres of the brain. Finally, the hemispheric pattern recorded from awakenings from REM sleep, in particular, is remarkably consistent, as is the one recorded during the sleep onset process. In both conditions, a clear and stable right-hemisphere superiority has been found. This finding confirms the ability of the right hemisphere to operate at reduced arousal levels (Babkoff, Genser, Sing, Thorne, & Hegge, 1985; Casagrande, Violani, et al., 1995; Dimond & Beaumont, 1971, 1973). These results are in keeping with data showing the advantage of the right hemisphere in the control of vigilance (e.g., Posner & Rafal, 1987) and in responding to warning stimuli (e.g., Heilman & Van Den Abell, 1980).

Lateralization of a function is a marker of increasing complexity in the evolutionary development of biological systems. Thus, the laterality of the sleep onset process might be considered as an important biological requirement for an adequate environmental adaptation that easily allows people to experience the pleasure of dreaming while the right hemisphere maintains greater vigilance that is useful in order to alert people when some environmental stimuli make it necessary to do so, as also shown by RT data recorded during sleep onset (Casagrande, Violani, et al., 1995).

In the same way as dolphins show periods of deep SWS in either the right or left hemisphere alone (Mukhametov, 1987), revealing that—for them—good environmental adaptation requires unilateral sleep, the human brain may require an asymmetrical activation of the cerebral hemispheres during the sleep onset process. In all likelihood, this asymmetrical pattern also remains in the ensuing sleep, as suggested by findings revealing a right-hemispheric predominance in a frequency range (4–8 Hz) close to the theta band and a left-side dominance in the frequency range of sleep spindles (Roth et al., 1999), even if this asymmetrical pattern can be affected by the type of sleep mentation. These results agree with those revealed by nonlinear analysis of the EEG, indicating that the right hemisphere appears to be more complex than the left hemisphere during sleep stages 1 and 2 (Pereda et al., 1999). In addition, it is interesting to note that the finding of an asymmetrical theta burst latency agrees with EEG and PET data indicating, in an alert resting state, positive correlations between theta density and cerebral metabolism in right frontotemporal regions, including the right-middle and upper frontal gyri, and the right-middle and temporal frontal gyri (Pizzagalli et al., 2003).

Data obtained from awakenings from sleep and sleep onset confirm the ability of the right hemisphere to operate at reduced arousal levels (Babkoff et al., 1985;

Casagrande, Violani, et al., 1995; Dimond & Beaumont, 1971, 1973), also in line with other data showing an increased activation in the prefrontal cortex and parietal lobes, particularly in the right hemisphere, following total sleep deprivation (Drummond et al., 2001; Szelenberger et al., 2005).

Nevertheless, total sleep deprivation studies have not reported a stable right-hemisphere superiority; however, these inconsistencies are easier to clear up. Many differences in findings on laterality appear to depend on the type of task adopted in the sleep deprivation paradigm. Finding an increased cerebral activity bilaterally in both the prefrontal cortex and the parietal lobes (Drummond & Brown, 2001) when subjects are performing a verbal learning task does not allow us to draw any conclusions on any asymmetrical pattern following sleep deprivation. Moreover, sleep deprivation data must be considered in the context of other relevant variables that can influence results. One of these, high intersubject variability in the effects of total sleep deprivation (Banks & Dinges, 2007), could, at least partly, account for many incongruent experimental results with respect to total sleep deprivation's effects on performance. Indeed, neurobehavioral deficits from total sleep deprivation vary significantly among individuals and are stable within individuals (Van Dongen, Baynard, Maislin, & Dinges, 2004). Based on a vast review of sleep deprivation research, Banks and Dinges (2007) suggested a traitlike differential vulnerability to sleep deprivation. In line with this hypothesis, it was found that after 48 hours of sleep deprivation, the deactivation of a neural network, including posterior cerebellum, right fusiform gyrus, precuneus, left lingual, and inferior temporal gyri, was effective only in subjects showing an impairment in memory performance, but not in those able to maintain higher performance (Bell-Mcginty et al., 2004). This variability in neural and behavioral responses to total sleep deprivation, in conjunction with the intensity of vigilance decreases produced by total sleep deprivation, could account for many contrasting results in this research area.

Furthermore, under total sleep deprivation, task difficulty leads to cerebral compensatory responses, that is, it facilitates the brain's blood-oxygen-level-dependent responses in those cortical regions that normally underlie task performance (Drummond, Bischoff-Grethe, Dinges, Ayalon, Mednick, & Meloy, 2005; Drummond, Brown, Salamat, & Gillin, 2004). These results allow us to include another variable, that is, task difficulty, as well as other characteristics, like the kind of paradigm design and the length or nature of the task, that should be able to explain some inconsistencies in the sleep deprivation results.

The ability to sustain attention is a necessary prerequisite for most high-level cognitive functions. This capacity can change during sleep since it is geared to the internal flow of thought and information storage. Alertness is certainly compromised during some transitional states, as well as sleep onset and awakenings from sleep, but it is particularly impaired during sleep deprivation.

Finding right-hemisphere superiority when the brain is sleepy could be an important biological requirement for an adequate environmental adaptation. Right-hemisphere superiority during both drowsiness and sleep states may be useful for the cognitive system when it is operating in a relative absence of external input and of voluntary control of the stream of thought. A decrease in left-hemisphere vigilance with respect to the right could enable a hierarchical reorganization of cognitive mechanisms, functional to a mental activity that is different from the one typical of the wakeful condition. That is, a change in hierarchical integration from left hemisphere to right hemisphere could be functional to some internally oriented operations that are more prominent when the brain is drowsy or sleeping.

### Notes

1. Spectral power corresponds to the area of the separate time series curves after the application of a sine–cosine transformation (Ferrillo, 1998).
2. The EEG has usually been described in terms of frequency bands. Six main bands are recognized: delta (0.5–3.5 Hz), theta (4–8 Hz), sigma (12.5–14 Hz), alpha (8.5–12 Hz), beta (13–35 Hz), and gamma (greater than 35 Hz; Casagrande, 1998).
3. “In period analysis, the time interval between successive zero-voltage crossing events is measured for each frequency of EEG activity, yielding percent time zero-cross and power estimates. First derivative values are based on the detection of negative inflections in the EEG signal regardless of whether they cross zero volts, and yield percent time estimates for each frequency band” (Armitage, Hoffmann, & Moffitt, 1992, p. 21).
4. EEG coherence is a quantitative method for analyzing the linear dependency of EEG activity between two brain regions. High coherence between EEG signals recorded at different sites on the scalp allows the supposition of a prominent functional interplay between the underlying neuronal networks. The coherence function is obtained by cross-spectral analysis, derived from EEG spectral analysis, which allows quantification of the relationship between different EEG signals. Coherence values lie within a range from 0 to 1: 0 means that corresponding frequency components of both signals are not correlated; 1 means frequency components of the signal are fully correlated with constant phase shifts, although they may show dissimilar amplitudes. Since background noise may occur in one or both signals, new frequency components may add on the signals, modifying their amplitude. Therefore, coherence can also be interpreted as a measure for phase stability between the same frequency components of two simultaneously recorded EEG signals. Thus, high coherence between two EEG signals means high cooperation and synchronization between underlying brain regions within a certain frequency band (Weiss & Mueller, 2003).

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## V Asymmetry of Perception



## **12 Auditory Laterality: Recent Findings in Speech Perception**

**Patricia E. Cowell**

Contemporary research into speech laterality in humans is deeply rooted in several areas of study within the behavioral neurosciences. First were the experimental and neuropsychological studies showing lateralized processing of syllables and words by way of dichotic listening (Kimura, 1967; Studdert-Kennedy & Shankweiler, 1970). Second were neuroanatomical and neuropsychological investigations of temporal lobe asymmetries in relation to language (Geschwind & Levitsky, 1968; Wada et al., 1975) and developmental language disorders (Galaburda et al., 1985). Finally were the studies of auditory and perceptual asymmetries in animal communication (Heffner & Heffner, 1984; Petersen et al., 1978).

Each of these research strands played a critical role, shaping the theoretical cornerstones of current thinking about functional and structural asymmetries in speech perception. Dichotic listening provided behavioral scientists with a paradigm,<sup>1</sup> sensitive to the most subtle of experimental manipulations, for exploring lateralized processing of auditory input as the basis for syllable and word processing. The research of clinicians and psychologists working in the area of anatomical and functional lateralization in developmental language disorders was vital in establishing the neurobiological basis of dyslexia. Given the potential for human language to be shaped by cultural factors (social and linguistic), findings from other species, which revealed lateralized systems for auditory perception and communication input processing, provided crucial support to the biological case for asymmetry in human speech perception.

The core ideas generated by the work reviewed above continued to receive support as scientists applied new approaches and technologies to investigate perceptual speech asymmetries. For example, functional neuroimaging allowed a closer look at the lateralized neural systems underlying dichotic listening effects (Hugdahl et al., 1999), lateralized speech perception more generally (Zatorre et al., 1992; Zatorre et al., 1996), and the variations in speech processing asymmetries that characterize dyslexia (Temple et al., 2003). Animal models continued to provide important evidence for neural asymmetry of lateralized communication-related auditory processing across the animal

kingdom (Cynx et al., 1992; Ehret, 1987; Ehret & Riecke, 2002; Fitch et al., 1993; Gannon et al., 1998; Gannon et al., 2005).

Against this background, recent research has explored in more depth the lateralization of auditory signal processing and speech perception. This chapter will focus on several exciting new developments in this area. The first section will explore recent work into the biology of speech lateralization with a focus on humans and with reference to key supporting studies in other species. The second section will look at linguistic and cultural factors that impact laterality of speech perception. A third section will consider clinical research into patterns of speech lateralization in neurodevelopmental language disorders.

Two important themes emerge from the research of the past 10 years. First, the degree and direction of lateralization in speech perception involve a rich interplay between biological and experiential influences; this has taken scientific inquiry beyond the search for "main effects" and more deeply into the study of multifactorial interactions (Cowell & Denenberg, 2002). Second, the nature of the stimuli that evoke lateralized neural and behavioral responses in speech perception is more complex than originally believed; thus, lateralized speech processing appears to involve a range of functions from the processing of acoustic input to the processing of integrated input such as words and phrases. Connections between lower and higher order levels of lateralized perceptual speech processing undoubtedly exist (Obleser et al., 2007). However, the complete nature and role of neurofunctional asymmetries within such a network is not entirely clear.

The aim of this chapter is to review the studies that best capture the complex constellation of elements that shape what Petersen et al. (1978) so aptly referred to as the "functional lateralization of conspecific sounds" in communication-based perception. In humans, the interactions of biology (e.g., age, sex, neurodevelopmental language disorders) with experience (e.g., stimulus properties, linguistic context) will be considered in relation to perceptual speech asymmetries at the behavioral and neurobiological levels.

## **Biological Basis and Individual Differences**

### **Introduction and a Broad Cross-Species View**

Structural and functional asymmetry is a fundamental feature of the auditory perceptual systems of many species. Lateralized auditory perception which plays a role in communication has been documented in birds (Cynx et al., 1992; Nottebohm et al., 1990), rodents (Ehret, 1987; Ehret & Riecke, 2002), and nonhuman primates (Hopkins & Fernandez Carriba, 2002). When such asymmetries are involved in communication function, cross-species comparisons become directly pertinent to the understanding of human speech. Early studies showed, in the Japanese macaque, that discrimination

of "coo" sounds used during affiliative contact-seeking behavior was perceptually lateralized to the right ear (Petersen et al., 1978) and neurofunctionally lateralized to the left auditory cortex (Heffner & Heffner, 1984). More recently, progress has been made in understanding the specific conditions that favor lateralization of communication perception in female (Hauber et al., 2007) and male song birds (George et al., 2002, 2005).

Although more likely to be evolutionary analogues than homologues,<sup>2</sup> particularly in comparisons involving avian and rodent species, there remains a strong scientific case for looking to animal models to provide insight into human communication (Kuhl, 2003). A comparative approach allows one to study communicatively relevant lateralization in systems free from the influence of human culture. In such a preparation, biological factors can be isolated, with the caveat that the social context of the nonhuman species under study will pose limits to the full extent to which results can be generalized. However, work in humans, at the sensory-perceptual levels of speech processing, suggests that these considerations may be less of a constraint than initially appeared to be the case. Evidence is mounting that there are multiple lateralized components of human speech perception asymmetry: (1) those that operate at a lower order input level of acoustic feature processing, (2) those that operate at a higher order level of integrated acoustic features (i.e., combined sounds such as syllable or word forms), and (3) those that operate at a level where perceptual input is fully networked with higher order cognitive functions that enable communication (i.e., links to memory and speech production systems; Rimol et al., 2005; Tzourio-Mazoyer et al., 2004; Zaehle et al., 2008). Rimol et al. (2005) neatly demonstrated the existence of multilevel input systems. Lateralized temporal lobe activation was more marked when right-handed men (with a right-ear advantage for dichotic listening) listened to the first 70 milliseconds of syllables compared to the whole syllables. Although leftward asymmetry in temporal cortex was present at both the syllable and subsyllabic levels, it was more marked for the subsyllables.

Rimol et al.'s (2005) results are important for two key reasons. First, they indicate different degrees of left-hemisphere asymmetry for the acoustic features (first 70 milliseconds) and the assembled features (entire 500-millisecond segment) from the same set of consonant-vowel (CV) syllable stimuli. Thus, the results call into question one of the tenets of traditional psycholinguistic thinking that leftward lateralization of function in perisylvian cortical regions is index linked to the degree to which stimuli are inherently speech based. A second and related implication of Rimol et al.'s (2005) partial dissociation between isolated and combined features of speech signals suggests that there are asymmetries specific to lower order speech perception systems in humans which may be examined in more direct comparison to similar systems in other species. Thus, results from earlier studies in monkeys, rodents, and birds may be reviewed in a new light. Animal studies of lateralized auditory perception in communication were

often presented as models for the fully integrated set of lateralized human speech and language processing systems. However, it currently seems more appropriate to consider work in nonhuman species to understand how lateralization is involved in processing the auditory feature input, and possibly feature integration, of communication signals.

### **Recent Work in Human Perceptual Asymmetry**

Asymmetries in speech perception have been examined in relation to many biological factors. These include studies of individual and group variation in healthy participants as well as clinical and treatment-based investigations. This section will focus on a hotly debated area of individual differences in the field of speech and language lateralization, sex differences, and will examine recent findings that look at males and females across the life span.

The past several decades of sex differences research in the language lateralization domain have provided researchers with some basic principles from which to build a seemingly stable consensus. Regarding sex differences in lateralized speech perception function, neuroanatomical correlates, and neurocognitive activations, the general picture that emerges is one of leftward hemispheric lateralization which is expressed more strongly in males, right-handed males in particular. Challenges to this model have been made through reviews and meta-analyses (Hiscock et al., 1994; Sommer et al., 2004). Far from reducing the importance of sex effects in the lateralization of speech perception, the controversy stimulated a deeper search for the source of variation in neurocognitive expressions of sex differences. Indeed, some scientists understood the lack of consistent main effects as confirmation that more research was needed to investigate the multifactorial interaction effects that shape interhemispheric relationships (Cowell & Denenberg, 2002) and, more specifically, lateralized speech perception (Cowell & Hugdahl, 2000). Thus, the lack of consistent main effects of sex provided the necessary catalyst for a new wave of research into the hormonal mechanisms that shape lateralized speech perception. The work concentrated on identifying the factors that differentiate asymmetries between the sexes and, perhaps even more importantly, factors that differentiate asymmetries *within* the sexes.

In a recent study, Foundas et al. (2006) examined dichotic listening in young healthy adults with roughly equal samples of right- and left-handers. They reported important handedness-by-attention-condition effects, but no sex differences at the level of main effects or in interactions with handedness, attention condition, and ear (i.e., laterality). This is consistent with recently reported overlaps in the range of dichotic listening asymmetry scores for healthy young men and women (Dos Santos Sequeira et al., 2006; Wadnerkar et al., 2008) and in healthy adult samples taken from a wider age range (Hugdahl, 2003). However, sex differences can be highlighted in two specific contexts that involve variation in female hormone levels. First, sex differences were enhanced after the age of 50 in right-handed adults (Cowell & Hugdahl,

**Table 12.1**

Means and standard errors for dichotic listening asymmetry scores measured from the nonforced condition

Cowell and Hugdahl (2000)	n	Laterality index	Wadnerkar et al. (2008)	n	Laterality index
Men 20–44 years	11	0.18 ± 0.09	Men 20–25 years	20	0.36 ± 0.04
Women 20–44 years	5	0.19 ± 0.09	Women 20–25 years, midluteal phase	25	0.31 ± 0.04
Women 45–64 years	13	0.08 ± 0.06	Women 20–25 years, menstrual phase	25	0.16 ± 0.04

Note: Data from Cowell and Hugdahl (2000) have been divided by age, as a function of a median split of the sample age range from 35 right-handed men and women. Scores for men and women in the menstrual cycle study were originally presented in a composite form averaged across attention conditions (Wadnerkar et al., 2008). Laterality indices were computed using the difference between correct right-ear (RE) and left-ear (LE) responses divided by the total right plus left-ear responses, that is,  $(RE - LE)/(RE + LE)$ . In the Cowell and Hugdahl (2000) study, younger men and women showed similar scores, whereas older women showed lower asymmetry. In the Wadnerkar et al. (2008) study, younger men and women at the midluteal phase (ovarian hormones are high) showed similar scores in contrast to the lower asymmetry observed in the same women during the menstrual phase (ovarian hormones are low). Within both studies women in the “low-hormone” condition were less lateralized than men or women in the “high-hormone” condition.

2000). Second, sex differences were greater when comparisons were made between men and women assessed during the phase of the menstrual cycle when ovarian hormone levels are low (Wadnerkar et al., 2008). Examination of data presented in table 12.1 show a consistent, within-study pattern of males having a right-ear advantage (positive laterality index) equivalent to that seen in women with higher ovarian hormones. In addition, both women with higher hormone levels and men had right-ear advantage scores that were double in magnitude to those of women with lower hormone levels. Convergent data in children come from a study of dichotic listening in 10- to 11-year-olds. Girls from same-sex twin pairs, but not opposite-sex twin pairs, were less lateralized than boys (Cohen-Bendahan et al., 2004). This indicates that in typical development, that is, females not exposed to male hormones in utero, comparisons between the sexes should yield a pattern of greater male asymmetry. Taken together, these studies suggest that sex differences in perceptual asymmetry for CV syllables are highly plastic and vary as a function of age- and hormone-related changes.

In light of the reports presented above, one would only expect to observe sex differences in young adults when female participants were studied at the low-hormone

phase of the menstrual cycle. Looking across a wider age span, sex differences could also be expected when males are compared to females with lower circulating levels of ovarian hormones, such as before menarche or after menopause. This line of reasoning supports the premise that left-hemisphere functional lateralization of speech perception, as measured by a right-ear advantage in dichotic listening of syllables or words, is both state and trait dependent. Differences between the sexes illustrate variation in laterality traits, and the within-subject differences in women across the menstrual cycle illustrate variation across laterality states. In summary, females' dichotic listening performance is less lateralized than that of males, but only at points in the life span and menstrual cycle when ovarian hormones are low. More systematic research is needed to confirm this interpretation and to elaborate on the specific mechanisms by which male and female hormones affect perceptual asymmetry. Of particular interest is the hypothesis, based on observations reviewed above, that while male hormones appear to modify lateralization in early life (Cohen-Bendahan et al., 2004; Friederici et al., 2008), female hormones continue to impact lateralization through the reproductive phase of healthy adulthood. Similar patterns of hormone action have been documented in the development of the corpus callosum in rodents (Fitch & Denenberg, 1998).

### **Recent Work in Human Brain Asymmetry**

Not all components of the auditory perceptual system show clear-cut right-left differences (Binder et al., 2000; Lutz et al., 2007). Even well-documented asymmetries in speech perception and related language functions are not always lateralized in the same direction or to the same extent across individuals (Tzourio-Mazoyer et al., 2004). For components that are lateralized, in particular those linked to speech perception, differences occur as a function of two primary sets of factors: (1) the neurobehavioral system or subsystem under consideration (neurofunctional domain including stimulus type) and (2) the characteristics of the individuals or groups being studied (life span development, sex, handedness, neurodevelopmental language status).

A large literature documents left-hemisphere asymmetries for speech perception, and their structural-neurofunctional correlates (Tervaniemi & Hugdahl, 2003). The general consensus, as mentioned in the previous section, was that males had more lateralized brain systems linked to speech and language processing, and that this asymmetry was most prominent in healthy right-handers (Harasty et al., 1997; Kulynych et al., 1994; Phillips et al., 2001). A similar controversy arose, parallel to that in the behavioral speech lateralization literature, showing a lack of consistent sex differences (Sommer et al., 2004). Likewise, the revised approach to sex differences beyond the search for main effects has now evolved into a search for multifactorial interactions that influence the way that gonadal hormones shape lateralized speech perception systems. The new picture emerging is that the basic template for male-greater-than-

female lateralization has many manifestations. The objective of this section is to review recent reports which show how neuroanatomical and neurofunctional asymmetries in the speech perception system vary both between and within the sexes. The focus is on research in healthy males and females that examines factors also shown to impact speech laterality at the behavioral level, such as handedness, age, and sex hormones.

In their meta-analysis of sex differences in language lateralization, Sommer et al. (2004) stated that “the putative sex difference may be absent at the population level, or may be observed only with some as yet not defined, language tasks” (p. 1845). However, an increasing number of recent studies tell a more complex and multifactorial story about sex differences in the neural correlates to speech perception laterality. For example, Dos Santos Sequeira et al. (2006) showed that while a leftward asymmetry in planum temporale (PT) volume characterized their whole study sample, the degree of laterality varied as a function of interactions between sex, handedness, and speech perception asymmetry. Consistent with dichotic listening studies (Cowell & Hugdahl, 2000; Foundas et al., 2006), the main effects of sex and handedness accounted for less variation than the higher order interactions. Specifically, degree of leftward asymmetry of the PT was greatest in right-handed men with a right-ear advantage and in left-handed women with a right-ear advantage as measured by dichotic listening performance (Dos Santos Sequeira et al., 2006). However, this leftward asymmetry was associated with greater left planum size in right-handed men in contrast with smaller right planum size in left-handed women.

The Dos Santos Sequeira et al. (2006) study highlights the importance of between- and within-sex comparisons in the characterization of lateralization of speech perception systems. The authors specifically emphasize the need to embrace multifactorial interactions of sex, handedness, and speech lateralization to overcome past inconsistencies in the field. Their message resonates with conclusions drawn from related research on sex and handedness effects in regional corpus callosum anatomy (Cowell et al., 1993). There, a multifactorial approach was also recommended to transform the field from one that could merely detect inconsistent main effects (Bishop & Wahlsten, 1997) to one that could sensitively harness the complexity of biological variation in regional corpus callosum size (Cowell, 2003).

Recent work using diffusion tensor/magnetic resonance imaging to study the brains of healthy right- and left-handed men and women provided further support for a cortical speech and language system whose patterns of laterality and interhemispheric connectivity are different between and within the sexes (Hagmann et al., 2006). Hagmann et al. (2006) showed that male right-handers had greater intrahemispheric connections between the temporal and frontal speech–language processing cortices of the left hemisphere compared to the right. In left-handed men, and women of both handedness types, within-hemisphere links between anterior and posterior language

regions were similar in the right and left hemispheres. In addition, interhemispheric links varied as a function of sex and handedness with male right-handers and women showing strong callosal links for both anterior and posterior language regions in contrast to left-handed males whose anterior connectivity was much greater than posterior connectivity between the hemispheres. This work confirms earlier reports showing sex differences in the intra- and interhemispheric cortical language systems (Shaywitz et al., 1995; Wood et al., 1991) but goes one step further in specifying the effects in terms of handedness groups and specific neuroanatomical pathways.

A neurofunctional account for hormonally state-dependent variation in speech perception asymmetry has only started to emerge. Precursors in related areas include the study of menopause, hormone effects, and menstrual cyclicity on neurobehavioral systems that are likely to be involved in or closely related to the lateralization of speech perception (Bayer et al., 2008; Dumas et al., 2008; Hausmann et al., 2006). Indeed, considerable work on sex differences and hormone effects has been conducted for lateralized and interhemispheric language functions in adults that involve processing of word meaning and verbal memory (Bayer et al., 2008; Craig et al., 2008; Craig et al., 2009; Fernández et al., 2003; Konrad et al., 2008; Mordecai et al., 2008; Weis et al., 2008). None of these adult studies have specifically addressed lateralization in speech perception. However, there is evidence from the investigation of speech perception in early neurodevelopment that testosterone mediates differences within and between the sexes. Using event-related potential and mismatch detection in 4-week-old infants listening to speech syllables, Friederici et al. (2008) showed a sex difference in cortical activation patterns between females and males with lower testosterone levels. In females, mismatch detection was associated with activation bilaterally in anterior and posterior sites. In males, a left-greater-than-right activation pattern was present. This sex difference is consistent with work in children and adults where greater asymmetry for speech perception has been shown in males. In addition, a source for inconsistencies within males and, in particular, in relation to individuals with possible speech delays was shown; male infants with higher testosterone levels at 4 weeks did not show a strong response to detection of mismatched syllables, nor did they show a pattern of leftward asymmetry in cortical activation. Consistent with Cohen-Bendahan et al.'s (2004) study of dichotic listening in children, Friederici et al. (2008) showed that leftward lateralization of speech processing varied as a function of between-sex differences as well as early within-sex exposure to male hormones.

Convergence across a number of recent large-scale studies points to a lateralized perisylvian cortical system involved in speech perception in healthy adults that is characterized by an interplay of factors which includes sex, handedness, and anterior-posterior regionality. Probes at the behavioral (Cowell & Hugdahl, 2000; Foundas et al., 2006; Wadnerkar et al., 2008) and neurobiological (Dos Santos Sequeira et al.,

2006; Hagmann et al., 2006) levels support this claim. Studies examining the neurobehavioral basis of speech lateralization in children and infants provide developmental evidence for between- and within-sex differences (Cohen-Bendahan et al., 2004; Friederici et al., 2008).

### **Asymmetries in Integrated Input Systems and the Input–Output Complex**

An inherent feature of laterality in speech perception is its association with other lateralized functions, in particular, those involving the frontal cortex. For example, lateralized frontal lobe function has been implicated in relation to dichotic listening performance (Hugdahl, Bodner, et al., 2003; Thomsen et al., 2004). Connections have also been highlighted through neuroimaging activation studies that examine performance on a range of tasks requiring higher order analysis and basic discrimination of speech sounds.<sup>3</sup> Regions of left frontal cortex, including Broca's area, were shown to be involved in the phonetic segmentation of words (Démonet et al., 1994; Zatorre et al., 1996) and some forms of rhyming discrimination (Shaywitz et al., 1995). In an experiment based on functional anatomical frameworks for sound-to-motor representations (Hickok & Poeppel, 2007; Scott & Wise, 2004), Zaehle et al. (2008) showed the spectrotemporal analysis of speech and nonspeech sounds was a bilateral, though leftward lateralized, function of the superior temporal cortex. In addition, they found that the inferior frontal gyrus and parietal operculum of the left hemisphere were involved in discriminating both speech and nonspeech sounds on the basis of temporal but not spectral features. Zaehle et al.'s (2008) findings suggest at least some of the lateralized functions involved in speech processing may actually be co-opting or building upon the asymmetries of more general auditory perceptual processing systems. At a higher order level of processing, Tzourio-Mazoyer et al. (2004) showed enhanced leftward lateralization of, as well as interhemispheric connectivity between, temporal, frontal, and parietal cortical regions during covert verb generation to auditorily presented nouns. Based on their findings, the authors proposed that the networked complex of perisylvian cortices, which provides the basis for integrated language functions, has its own lateralized "mode" of functioning (Tzourio-Mazoyer et al., 2004). Lateralization of speech perception can be examined in experimental isolation. However, it is important to remember that in ordinary human communication speech perception operates within a broader set of lateralized processes and functional states.

Consideration of asymmetries in related communicative and cognitive processes has particular importance in the study of state-dependent laterality, where shifts may occur not only within speech perception but in relation to coherence between speech perception and production. For example, we recently showed that females at the midluteal phase of the menstrual cycle had higher right-ear advantage on dichotic listening of CV syllables (Wadnerkar et al., 2008) as well as more precise speech pro-

duction as measured by voice onset time (Wadnerkar et al., 2006; Whiteside et al., 2004).<sup>4</sup> Speech production, like perception, is lateralized to the left hemisphere (Bohland & Guenther, 2006; Riecker et al., 2005). Our conjoint results drawn from the same sample of women (Wadnerkar et al., 2006; Wadnerkar et al., 2008) suggest that increases in ovarian hormones across the menstrual cycle impact the lateralization of individual functions related to speech perception and production. The findings also raise the possibility of greater coherence between speech input and output functions within the left hemisphere during the higher hormonal state in women. What remains unclear is whether the ovarian hormone-mediated lateralized state in women's language cortices functionally mirrors, in any way, the early testosterone-mediated trait of greater lateralization observed in right-handed men (with rightward ear asymmetry on dichotic listening). New evidence from the study of across-field advantages in semantic letter type matching (the Banich-Belger task) showed that interhemispheric processing varies as function of menstrual cyclicity (Bayer et al., 2008). Bayer et al. (2008) demonstrated that interhemispheric integration during performance on the semantic task was significantly reduced for women in the low-hormone phase of the menstrual cycle. Further experiments are needed to systematically test hypotheses relating to intra- and interhemispheric integration in relation to lateralized speech perception processing.

Lateralization in the auditory perception of communication signals has been well documented in birds at the individual and population levels. For example, in contrast to tones and noise, conspecific whistles played to male starlings elicited lateralized neural responses from field L neurons in the right hemisphere in some birds and the left in others (George et al., 2002). More recent and detailed work has shown state-dependent patterns of lateralization with consistent left-sided specialization in the vocal control nucleus (HVC) for perceptual processing of song sequences which may be involved in preparation for motor responses and vocal output (George et al., 2005). A right-sided specialization in the same nucleus was observed for processing informational complexity in other whistle and warble classes. A cautious approach would limit cross-species comparisons in the processing of communication signals to (1) the lower levels of auditory input and perceptual integration and (2) our closest evolutionary relatives among the great apes (Gannon et al., 1998; Gannon et al., 2005). However, there may also be interesting cross-species parallels at the level of signal input–output integration in humans and songbirds. The work of George et al. (2005) on leftward laterality in the avian HVC may have relevance, by way of general processing frameworks, to asymmetries in cortical networks that are activated when perceptual processing of speech serves as the input for a speech production sequence (Hickok & Poeppel, 2007; Scott & Wise, 2004). As in humans, there is evidence that lateralization in birds varies between the sexes (Hauber et al., 2007). Lateralization in song perception and production in birds also varies within sex, as a function of hormonal state, although

variation occurs in relation to seasonal changes in the male (Nottebohm et al., 1990). Thus, comparisons between humans and birds are also important for understanding basic mechanisms of hormonally regulated plasticity in lateralized communication functions. In general, cross-species comparisons may provide a valuable framework for developing theories about the environmental and social demands (George et al., 2005) which invoke lateralization as a means to increase neurobehavioral capacity and efficiency in communication systems (Rogers, 2002).

### **Acoustic and Linguistic Factors: The Sounds That Drive Lateralized Speech Perception**

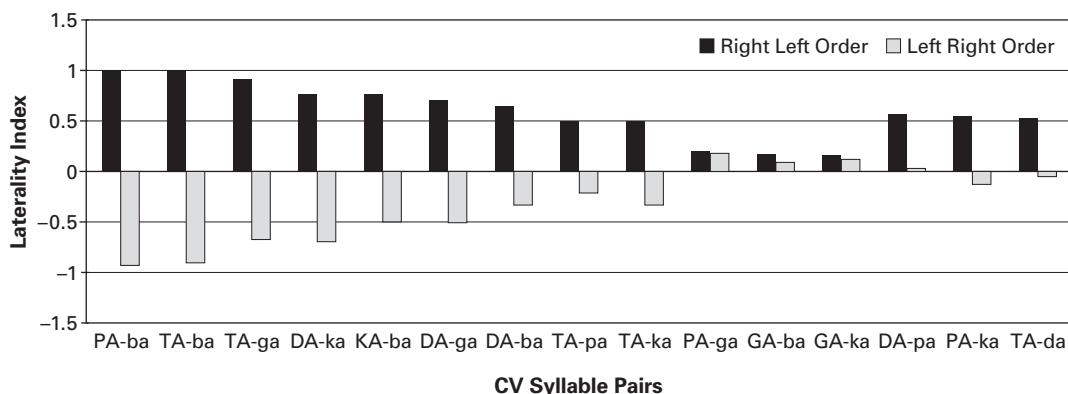
Until recently, there has been less focus on mechanisms of neurofunctional plasticity in the auditory cortex when compared to other systems such as visual and somatosensory cortices (Rauschecker, 1999). This represented a significant gap in contemporary understanding of human communication, given the importance of auditory cortical plasticity in the organization and adaptability of speech perception. Recent findings in relation to biologically based plasticity, both in shaping lateralized traits and states of speech perception, were discussed in the previous section. The aim of the current section is to explore recent research into the environmentally and experientially mediated aspects of auditory plasticity with particular focus on lateralized speech perception systems.

The impact of particular speech sounds on perceptual asymmetry has long interested psychologists. Early work documented the degree to which various speech sounds led to a larger or smaller right-ear advantage (Darwin, 1971; Hugdahl & Andersson, 1984). Research in this area was often driven by the theoretical debate over the salience of acoustic versus linguistic properties of speech in the organization of language function and its lateralization (Shankweiler & Studdert-Kennedy, 1967; Studdert-Kennedy & Shankweiler, 1970); a modified version of this debate can still be detected in contemporary research (Shtyrov et al., 2005; Zaehle et al., 2008). This debate was further fueled by controversy as to the source of speech processing impairments in children with neurodevelopmental language disorders (Denenberg, 1999; Mody et al., 1997; Tallal et al., 1996). Research stimulated by these theoretical arguments yielded findings important for the field of speech perception asymmetry. Indeed, a recent union between the fields of acoustic phonetics and cognitive neuroscience has provided fascinating insights into how lateralized speech perception varies as a function of the properties of communication signals.

In 1980, Schwartz and Tallal published a report that retains its scientific currency to date. They showed that dichotic listening scores were affected by the formant transition durations of CV syllables. For syllables with formant transition durations in the natural speech range, participants showed a right-ear advantage. This asymmetry was reduced when the formant transitions of the same syllables were extended from 40 to

80 milliseconds. This modification translates roughly to an extension of the time over which some of the most spectrotemporally dynamic information of the CV syllables is conveyed, that is, a temporal “dilution” of the speech stimuli. More recent findings substantiate the principle that the lateralization of speech perception varies as a function of the richness of acoustic signal dynamics over time. Rimol et al. (2006) tested healthy adults using dichotic listening, and investigated the contribution of voice onset time (VOT) to the perceptual asymmetry. Speech stimuli were CV syllables with either a short VOT (/ba/-/da/-/ga/) or a long VOT (/pa/-/ta/-/ka/) in Norwegian. Thus, all speech sounds contained naturally occurring variants of the temporal feature voicing. Results showed that the largest right-ear advantage occurred with stimulus pairs that presented syllables with long VOT to the right-ear and syllables with short VOT to the left ear (Rimol et al., 2006). A similar result in English was recently documented in my laboratory (Wadnerkar, 2008). CV syllables with long VOT are characterized by an initial phase of aperiodic noise between the release of the plosive and prior to the onset of voicing. This adds another dynamic element to the signal, differentiating it from CV syllables with short VOT, such that long VOT syllables are relatively richer in terms of the complexity of spectrotemporal change. Thus, the VOT findings are consistent with the formant transition findings of Schwartz and Tallal (1980) if one considers the relative acoustic parallels between the CV syllables with the shorter versus extended formant transitions and CV syllables with long versus short VOTs. That is, both the shorter formant transition and the longer VOT add complexity to the signal.

In both studies, a key component of speech perception asymmetry was dynamic change in the acoustic signal (Rimol et al., 2006; Schwartz & Tallal, 1980). Rimol et al. (2006) were able to define this more specifically as a voicing-based contrast of right- and left-ear input. Preliminary research from my laboratory examined the impact of all stimulus pairs on the laterality of healthy adults ages 20 to 72 years who were administered the English version of the dichotic listening test (Cowell & Hugdahl, 2000). The total number of right-ear and total number of left-ear responses for each dichotic pair were computed across the sample of 61 healthy adult participants. From this, sample-level laterality indices were computed and are displayed in figure 12.1. From these data, it is apparent that the syllable pairs contribute to asymmetry in a number of ways. Some pair combinations contribute very little in total to the overall laterality. For example, the pair “PA-right ear with ba-left ear” resulted in a perfect right-ear advantage; however, the opposite pair of “BA-right ear and pa-left ear” resulted in near perfect left-ear advantage. Thus, the net contribution of these syllable pairs to overall sample asymmetry was close to zero. In contrast, some syllable pair combinations yielded a higher net contribution to the overall asymmetry. For example, the pair “DA-right ear with pa-left ear” resulted in a moderate right-ear advantage, whereas the opposite pair of “PA-right ear and da-left ear” resulted in a nearly sym-

**Figure 12.1**

Laterality indices of dichotic listening for a sample of healthy adult men and women ages 20 to 72 years. Coefficients are plotted for each of the 30 consonant-vowel (CV) syllable pairs that comprise the English version of Hugdahl's dichotic listening test (Cowell & Hugdahl, 2000). Syllable pairs are arranged in combinations that reflect the balanced presentation of each syllable to the right and left ear. For example, the laterality index for "PA to the right ear with ba to the left ear" is plotted in the first dark bar, and the laterality index for "BA to the right ear with pa to the left ear" is plotted in the adjacent light bar. See further explanation in the text.

metrical score. This preliminary analysis indicates that even within the limited stimulus set of six CV syllables, there is sufficient range of acoustic complexity in the combined pairs to warrant further analysis of how stimulus features contribute to laterality of speech perception. Additional analysis will also be required to determine the stability of these psychoacoustic properties across the sexes and age groups.

Such studies are important for describing the features of speech stimuli that enhance lateralization. Although they provide details as to the necessary characteristics of stimuli that induce asymmetry, they do not disentangle a number of other stimulus features and, thus, may not fully describe both the necessary *and* sufficient stimulus properties. For example, the spectrally rich, rapidly changing, long VOT CV syllables /pa/-/ta/-/ka/ are also fairly frequent in both English and Norwegian as parts of words. Moreover, for the British English speakers tested in my laboratory in Sheffield, the syllable /ta/ is a frequently used expression for "thank you" and thus has a quasi-lexical status. Such is the status of other items in the English and Norwegian six-CV-syllable sets. Shtyrov et al. (2005) probed this issue by systematically contrasting the acoustic properties and the phonemic status of sounds as stimuli in a cortical activation study using MEG and a passive oddball test paradigm. They inserted the same sound /t/ into different contexts so that participants' perceptually activated hemispheric responses could be compared when the sound was a part of nonword noise bursts, part of words

(nouns and verbs), or part of pseudowords. Shtyrov et al. (2005) recorded left-hemisphere-greater-than-right-hemisphere response amplitudes from the superior temporal gyrus that were significant only in the condition where /t/ was part of words (both nouns and verbs). Response activations were leftward lateralized but not significantly so when /t/ was embedded in nonwords and pseudowords. In an integrated system it is difficult to discern whether the lower order processing of physical features or a higher order processing of integrated features (i.e., frequently occurring speech items) drives the asymmetry. Results from Rimol et al.'s (2005) study of CV syllables and subsyllabic components and Shtyrov et al.'s (2005) study of sounds in different contexts both suggest that in right-handed adults these lower and higher order levels are semi-independent, sharing direction but not necessarily degree of asymmetry.

Research in birds and primates supports the premise that perceptual processing is lateralized for acoustic communication signals produced by conspecifics (George et al., 2005; Heffner & Heffner, 1984; Petersen et al., 1978). Hauser and Andersson (1994) studied rhesus monkeys' turning bias to calls in the wild and found a right turning preference, but only for vocalizations from their own species' repertoire. A later study showed that this was the case for natural, but not temporally modified, call signals (Hauser et al., 1998). By taking a broad, cross-species view in light of data from human studies it seems unlikely that there is either a single continuum of physical feature properties or a strict acoustic–semantic delineation that evokes asymmetrical speech processing. Rather, an optimal set point is reached for acoustically complex, communicatively relevant stimuli. At the acoustic level, richness of the spectral dynamics and rapidity of the temporal features both play a role determining laterality. Obleser et al. (2008) showed left auditory cortical response to word comprehension was more sensitive to temporal variations, in contrast to right auditory cortical response which was more sensitive to spectral variations. At the integrated feature level, phonemic or other meaning-based aspects may also influence laterality. Together, the work of Shtyrov et al. (2005) and Rimol et al. (2005) shows that these levels of lateralized processing coexist. Under certain conditions, these semi-independent elements, comprised of left-hemispheric cortical language regions, may work together as part of a network of asymmetries, becoming engaged in an integrated fashion (Obleser et al., 2007; Tzourio-Mazoyer et al., 2004; Zaehle et al., 2008). At all levels, whether working independently or together, direction and degree of asymmetry will be modulated by the biological characteristics of the organism (sex, age, hormone status) and, as will be discussed below, the specific environmental context (e.g., exposure to the stimuli in communication).

What we know about laterality in speech perception is limited to a fairly small subset of speech sounds. Many studies have used CV syllables constructed from the plosive consonants /p/-/t/-/k/-/b/-/d/-/g/ combined with the vowel sound /a/. Another frequently used stimulus set is digit or number words. The full possible set

of speech sounds is limited only by the structure and function of the human vocal-perceptual and neural apparatus, subsets of which are represented differently within each spoken language. The sounds that comprise the speech signals are language specific. Yet the studies reviewed in preceding sections of this chapter, which reflect research in English print over the past 40 years, involved the testing of English, German, Norwegian, Finnish, and Swedish speakers. From a global perspective, these languages are first or primary languages for a relatively small proportion of human beings. Therefore, work is needed to catalog more comprehensively the properties of speech sounds that stimulate lateralized perceptual processing across a wider range of world languages. This will allow for greater understanding of how a common neurobiological substrate in humans responds in a lateralized fashion to the wide variety of cultural variants that exist for speech sounds.

A well-known phenomenon in the auditory processing literature is the right-hemisphere asymmetry for musical, pitch, and tone processing (Hugdahl et al., 1999; Mead & Hampson, 1996; Zatorre et al., 1992; Zatorre et al., 1994). However, the literature on dichotic listening in speakers of tonal languages presents an interesting twist on this finding. In tonal languages, such as Mandarin, word meaning may be differentiated by variation in the rising and falling of tonal inflections. Thus, an item such as /ma/ has the same lexical meaning regardless of tonal quality in English, where tonal inflection is primarily used to denote emotional or syntactic emphasis. However, in Mandarin /ma/ has at least four meanings, depending on which tone is used. When presented with speech stimuli from tonal languages, participants for whom English is the first and primary language showed no asymmetry (Wang et al., 2004; Wang et al., 2001). However, when native Mandarin speakers were presented with the same speech stimuli, they showed a clear right-ear advantage (Wang et al., 2004; Wang et al., 2001). It is difficult to account for these findings using either a purely acoustic or purely phonemic-based model that fits both tonal and nontonal languages. A similar comparison was found in an earlier study of click consonants from the Zulu language, which elicited a right-ear advantage in Zulu and Xhosa language speakers but not English speakers (Best & Avery, 1999). The results of these cross-linguistic experiments are consistent with Shtyrov et al.'s (2005) report that the same sound can elicit different degrees of leftward activation in temporal cortex depending on the specific language-based context in which that sound is perceived. Indeed, Norwegian speakers showed a right-ear advantage for the tonal variants of their native language (Moen, 1993) but not for tonal speech stimuli from Mandarin (Wang et al., 2004). Thus, an effective model may have to consider the intersection between the system's exposure to a range of acoustic stimuli with the potential to stimulate auditory asymmetry *and* the system's emergence within a particular language context.

The presence and development of lateralized speech perception may even differ depending on the specific acoustic element involved. At 4 weeks, typically developing

male infants in Friederici et al.'s (2008) study showed lateralized cortical activation when discriminating variants of the sound /ba/ in German. In contrast, Minagawa-Kawai et al. (2007) studied the acquisition of vowel duration discrimination, which is lateralized in native Japanese speakers. They showed that while younger infants could discriminate vowel duration at 6 to 7 months, the developmental shift to a left-lateralized activation in temporal cortex did not occur until 13 months. Evidence suggests that these acoustically and linguistically based asymmetries may be sexually dimorphic (Hsu et al., 2009; Obleser et al., 2001), mediated during development by hormonal exposure (Cohen-Bendahan et al., 2004; Friederici et al., 2008) and affected by the presence of neurodevelopmental language delay (Friederici et al., 2008). A new frontier in the lateralization of speech processing will be to study the interface between these linguistic and biological factors.

### **Speech Perception Asymmetries in Neurodevelopmental Language Disorders**

Lateralized speech perception is impacted by both biological and environmental factors in healthy humans across the life span. This makes it difficult to conceive of a firm basis from which to compare differences between individuals who are affected or not affected by neurodevelopmental language disorders. However, there is a need to document and understand these phenomena in relation to conditions such as dyslexia and specific language impairment, where lateralized speech perception is related to the development of reading and language skills (Asbjørnsen & Helland, 2006; Helland et al., 2008; Hugdahl & Andersson, 1987). This section will briefly review some of the recent studies that document these complex phenomena in light of the biological and experiential factors reviewed in the preceding two sections. It is not an exhaustive review but rather a selective look at behavioral, neuroanatomic, and neurofunctional findings that expose the subtle and intricate variations in speech perception asymmetry present in children and adults with neurodevelopmental language disorders.

Differences in the lateralized processing of speech at the behavioral level in neurodevelopmental language disorders have proven to be surprisingly elusive. For example, the direction of the asymmetry for dichotic listening with CV syllables in children with dyslexia was the same as nonaffected children in terms of direction of the right-ear advantage (Hugdahl, Heiervang, et al., 2003). An equal proportion of children in both groups showed the typical rightward pattern. Small, nonsignificant differences were present in the degree of asymmetry, with fewer right-ear responses from the dyslexia group (Hugdahl, Heiervang, et al., 2003). In addition to demographically based factors that affect laterality in typical development, clinical factors add an additional layer of heterogeneity to speech perception asymmetries in neurodevelopmental language disorders. Helland et al. (2008) showed that the clinical

severity of dyslexia was a key factor in determining direction of asymmetry in dichotic processing of CV syllables. Their study compared children with a diagnosis of dyslexia who had relatively stable educational and reading progression to children with more persistent difficulties. Perceptual asymmetry for the children with more persistent difficulties differed from that of unaffected controls; the less affected children with dyslexia showed a pattern of right- and left-ear scores that was virtually identical to that of controls. Differences in the more severely affected dyslexia group were due to a reduced right-ear score, the component of dichotic listening performance that correlated with speech, language, and literacy test scores (Helland et al., 2008). Together, these studies suggest that clinical severity or symptomatology, rather than presence of dyslexia per se, is a defining variable in behavioral measures of speech asymmetry. In addition, research in adults free from neurodevelopmental language disorders indicates that selection of the comparison group should also be carefully considered on grounds of differences in dichotic listening asymmetries between right- and left-handed males and females (Cowell & Hugdahl, 2000; Foundas et al., 2006).

Atypical asymmetry of the PT and associated areas of temporal cortex, as originally reported by Galaburda et al. (1985), have not been consistently found (e.g., see Robichon et al., 2000). This situation parallels that observed for perceptual asymmetries in speech at the behavioral level. In reports where differences have been found, degree, rather than direction, of asymmetry differentiated measures of PT size in dyslexia (Hugdahl, Heiervang, et al., 2003; Leonard et al., 2001). In light of the literature reviewed in the first section of this chapter, inconsistencies would be expected given the sensitivity of anatomical laterality in speech processing regions of temporal cortex to factors such as sex, handedness, and perceptual speech asymmetry (Dos Santos Sequeira et al., 2006). Variations in laterality based on the interactions among these factors could affect, or even obscure, differences in comparisons between people with neurodevelopmental disorders and controls. Recent evidence suggests that the gray and white matter composition and morphology of the left hemisphere are different between girls and boys with dyslexia. Girls with dyslexia were more affected than boys; they showed higher gray-matter-to-white-matter ratios and greater convolutions of the gray matter-white matter border compared to a control sample of nonaffected girls (Sandu et al., 2008). Thus, even if individual studies carefully match their comparison and clinical samples, variations in sample demographics across studies in either or both groups may lead to differences in experimental outcomes. Geschwind and Galaburda's original hypothesis focused on the role of testosterone in the neurodevelopment of temporal lobe asymmetries in dyslexia (Geschwind & Galaburda, 1985a, 1985b); this has received recent support in relation to typical and disordered speech perception development (Cohen-Bendahan et al., 2004; Friederici et al., 2008). The work of Sandu et al. (2008) suggests that a new framework will be

needed to account for the development of neuroanatomical characteristics in females with dyslexia.

In addition to the perceptual, the attentional–executive components of dichotic listening have also been implicated in neurodevelopmental language disorders (Asbjørnsen et al., 2003; Niemi et al., 2003). Motor-speech difficulties have also been identified in dyslexia and related neurodevelopmental language disorders (Jäncke et al., 2007; Lalain et al., 2003). Therefore, it is not surprising that neuroanatomical investigations of laterality have revealed effects in frontal cortices. An atypical degree of rightward asymmetry has been reported in the size of Broca's area in adults with dyslexia (Robichon et al., 2000) and in the prefrontal volumes of dyslexic adults with specific phonologic processing deficits (Zadina et al., 2006).

As with typical asymmetries in speech perception processing, research on the left-hemisphere cortical network between frontal and temporal regions is important for understanding the basis of neurodevelopmental language disorders and their treatment. This is exemplified by Temple et al. (2003), who reported lower left-hemisphere activation of frontal and temporal language regions during a rhyming task in children with dyslexia. Increased activity in an overlapping constellation of left-hemisphere cortical regions was observed in the brains of these children after remediation for speech sound processing. The profile of aberrant left-hemisphere activations in the untreated children from Temple et al.'s (2003) functional study is consistent with more recent work studying the anatomical connectivity between temporal and frontal regions in a related neurodevelopmental language disorder. Jäncke et al. (2007) showed that white matter density was reduced in left-hemisphere frontotemporal cortical networks of children with phonologic–syntactic disorders. Given the interactive impact of sex and handedness on lateralized intrahemispheric temporal and frontal cortical connections in adults (Hagmann et al., 2006; Shaywitz et al., 1995), future work on cortical speech processing networks in dyslexia may benefit from more in-depth investigation on the basis of these demographic factors.

In addition to biological factors, a range of acoustic factors and related culturally contextualized linguistic experiences have been shown to mediate lateralized speech processing in typical development (Minagawa-Kawai et al., 2007; Rimol et al., 2006; Schwartz & Tallal, 1980; Shtyrov et al., 2005). Recent work in French-speaking adults with a history of developmental dyslexia showed differences in VOT-processing asymmetries to the speech sounds /pa/ and /ba/ in auditory cortex (Giraud et al., 2008). Auditory-evoked potentials yielded typical patterns of left-greater-than-right activation in controls, but atypical patterns of asymmetry were observed in adults with a history of dyslexia. Consistent with dichotic listening findings (Helland et al., 2008), direction and location of differences in laterality varied between dyslexia subgroups as a function of the persistence of their reading difficulties into adulthood (Giraud et al., 2008). Models of rapid speech processing have played a prominent role in the

field of dyslexia research (Gaab et al., 2007; Tallal et al., 1996; Temple et al., 2003). This underscores the need for more detailed work on the acoustic properties of speech sounds that invoke lateralized processing in typical development but fail to do so in neurodevelopmental language disorders.

Together with the behavioral findings from speech perception asymmetry, recent neuroanatomical and neurofunctional evidence points to a system which is sensitive to clinical subtype and severity of neurodevelopmental language disorder, sex differences, and the spectrotemporal dynamics of speech sounds. The individual differences and plasticity that characterize the lateralized temporal and frontal speech network have profound implications for understanding and successfully treating dyslexia and other neurodevelopmental language disorders (Gaab et al., 2007; Simos et al., 2007; Temple et al., 2003).

### **Conclusions**

Recent research in speech perception asymmetries has made progress in several key areas over the past decade. These are summarized below with comment on future directions and challenges for the field.

With respect to biological factors, sex differences research has moved beyond the investigation of main effects and now applies a more multifactorial approach. This has uncovered new findings about the particular circumstances that define between-sex differences, and the hormonal factors that affect early development and the fluctuation of within-sex laterality states. The future of research in this area will be to improve understanding of the biological factors that regulate both traits and states of lateralized speech perception. Systematic application of this approach to the study of neurodevelopmental language disorders has recently emerged and holds great promise. A primary challenge faced by scientists in this area is that large sample sizes are required to achieve satisfactory statistical power, particularly for laterality differences that commonly show small and medium effect sizes. The correlated nature of right and left neurobehavioral measures reduces this problem for within-subject comparisons, but for between-groups studies, recruiting and testing the large numbers of participants required to analyze multiple biological and clinical factors remains a formidable limitation for many laboratories.

A resurgence in interest regarding the acoustic properties of the speech signal has underpinned recent progress in the understanding of lateralized speech perception. In particular, the microacoustic features of speech and the emergence of lateralized response to particular features in early development comprise some of the most exciting new findings in the field. Great strides have also been made in relation to the culturally based linguistic effects that mediate lateralized responses to speech stimuli; this work includes studies of different contexts within language as well as studies of

the same speech sounds tested across speakers of different languages. The challenge for future research in our increasingly linked global community will be to put greater emphasis on cross-linguistic studies. Work is required from a wider range of the world's most frequently spoken (e.g., Mandarin and Spanish) and rapidly increasing (e.g., Hindi-Urdu and Arabic) languages (Graddol, 2004). This will promote understanding of laterality in human speech perception and provide a broader base from which to consider the interface between culturally determined language-specific factors and the common human neurobiological substrate. Future work in this area will be particularly salient for applications to clinical populations.

Research into the factors that govern lateralized processing of acoustic perception and production in animal communication continues to provide valuable insights into parallel systems in human speech. Currently, human speech perception research remains relatively isolated from the influence of findings in other species. This has not been the case for other areas of behavior and cognition, such as vision, motor function, and memory, which have benefited tremendously from a cross-species approach. Indeed, many studies of lateralization that examine auditory communication perception in animals make specific reference to other species, including humans. Yet very few studies of human speech perception do the same. A challenge for future research is to remove the barriers that isolate human research from the rich literature on neurobehavioral asymmetries in other species' communication. A shift toward using human language as a means to understand communication systems more widely across the animal kingdom has been suggested: "Human language provides an opportunity to study the interface between systems that control the acquisition of complex behavioral repertoires in natural social settings" (Kuhl, 2003, p. 9646). Even with their ethological limitations and evolutionary uncertainties, cross-species comparisons bring into sharper focus the contrast between elements of lateralized speech processing which are grounded in biologically versus culturally based factors. In turn, more systematic application of cross-species comparisons should add greater clarity to our understanding of the mechanisms that govern the neurobiological and cultural interface inherent in human speech perception.

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## Notes

1. Dichotic listening was originally used to test attention and short-term memory input; for example, see Treisman (1960).
2. The issue of evolutionary homologues to human speech and language systems remains a hotly debated area, particularly in comparisons involving higher order primate species such as the great apes (Chance & Crow, 2007; Taglialatela et al., 2008).
3. Activations were present in studies that elicited performance by auditory and visual stimulus media.
4. Both perception and production tasks focused on the plosive consonants /p/t/k/b/d/g/ in English.

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## **13 Processing Asymmetries in the Visual System**

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The left and right hemispheres of the human brain make complementary contributions to visual information processing. The present chapter reviews our current state of knowledge regarding this visual asymmetry. The chapter begins with a brief discussion of visual asymmetries across species and across evolutionary time to set the context for considering visual laterality in contemporary humans. This is followed by a discussion of hemispheric asymmetry for processing spatial relations; specifically, left- and right-hemisphere specialization for processing categorical versus coordinate spatial relations, respectively. This is followed by a discussion of hemispheric asymmetry in processing high versus low ranges of visual spatial frequency and how this relates to the processing of categorical versus coordinate spatial relations. With these sections as a backdrop, we then discuss asymmetries of object recognition and consider how asymmetries in the processing of spatial relations may relate to asymmetry of object recognition and object classification. From these discussions emerges a picture of the left and right hemispheres' making complementary contributions to various aspects of visual information processing. The final section of the chapter builds on this knowledge of hemispheric asymmetry to consider interhemispheric interaction in visual processing with a view to understanding how unified visual perception emerges from the asymmetrical brain and how the two hemispheres interact to increase the brain's computational power.

### **Visual Asymmetries across Species and across Evolutionary Time**

The present chapter focuses on hemispheric asymmetry for visual information processing in contemporary humans. It is, nevertheless, instructive to consider human asymmetries within the context provided by our knowledge of visual asymmetries in other species and the likely implications for the evolutionary history of those asymmetries.

Many examples of visual asymmetry in other species are provided in books edited by Rogers and Andrew (2002) on comparative vertebrate lateralization and by Hopkins (2007) on the evolution of hemispheric specialization in primates (see also Halpern,

Güntürkün, Hopkins, & Rogers, 2005; Hopkins & Cantalupo, 2008; Vallortigara, 2000; Vallortigara & Regolin, 2006; Vallortigara, Rogers, & Bisazza, 1999). Rogers and Andrew note sufficient similarity to propose that all vertebrate groups have inherited a basic pattern of laterality from a common chordate ancestor. Whether aspects of laterality are homologous in this way or are the product of convergent evolution remains a controversial topic (for discussion, see the references cited earlier as well as Corballis, 2007; Crow, 2004; Rogers, 2004). Nevertheless, there is sufficient similarity across species to make it likely that humans emerged from ancestors whose brains were already asymmetrical in significant ways. While no simple generalization captures the wide variety of visual asymmetries that have been documented, based on a review of findings from many vertebrate species, Rogers and Andrew (2002) describe the results as showing "complementary" visual specializations, with right-hemisphere dominance for "diffuse or global attention, spatial analysis and no special involvement in control of response" and with left-hemisphere dominance for "focused attention, recording of local cues and control of response" (p. 96; for similar statements regarding visual laterality in primates, see Hopkins, 2007; Hopkins & Cantalupo, 2008). As we will see in subsequent sections of the present chapter, this description bears striking similarity to generalizations about the nature of visual laterality in contemporary humans.

Visual asymmetries in humans and other species tend to be subtle rather than all-or-none. That is, both sides of the brain typically have at least some competence to perform a visual task or to engage in a specific visual process, though one side may be superior or dominant. For example, the right and left hemispheres are generally superior for processing global configuration and local detail, respectively, but both hemispheres can process both types of information to a reasonable extent. In addition to being subtle in the way just described, visual asymmetries can also be described as complementary in the sense that each side is superior for different and sometimes contradictory aspects of a task or process. This is illustrated in later sections of the present chapter in terms of asymmetry for processing what have been called coordinate versus categorical aspects of visual spatial relationships, for processing global versus local aspects of visual patterns, and for processing information carried by low versus high ranges of visual spatial frequency.

These properties of subtlety and complementarity are consistent with the idea of the brain's being characterized by "weak modularity" (see Kosslyn, 1994, 2006; Kosslyn & Koenig, 1992) or "nearly decomposable systems" (Simon, 1981) and suggests that there exists an optimal balance between extreme lateralization and the absence of lateralization. Weak modularity or incomplete separation between processing subsystems would still be mainly characterized by specialization within the brain into specific processing subsystems but, differently from "strong," Fodorian modularity (cf. Fodor, 1983), these processing subsystems would show some degree of mutual "penetrability"; that is, modules could constrain each other's output so as to achieve a

graded level of functional interdependence. Moreover, a subsystem may compute independently of another subsystem and the two could be separated neuroanatomically, but their computations could nevertheless be intimately related, especially when one subsystem's output normally provides optimal input for the other subsystem. In the latter case, the subsystem downstream in the processing flow could influence the processing of the upstream subsystem via feedback connectivity.

In discussions about the evolution of laterality, there is a long-standing idea that hemispheric specialization is advantageous because it permits more abilities to be packaged into the brain than would be the case if the two hemispheres were functionally identical. To be sure, there is likely to be pressure for symmetry of certain basic sensory processes like stimulus detection, as organisms must be sensitive to visual stimuli coming from both sides (see Corballis, 1991). However, beyond this early sensory level, the advantage of lateral specialization may outweigh any advantage of symmetry. Within the domain of visual processing, optimal performance (with the survival advantage that it provides) depends on the ability to quickly and efficiently engage in specific processes that are contradictory in a computational sense. For example, both coordinate and categorical information are important to locate objects in space, and both global configuration and local detail are useful to identify visual objects. It is likely that the precise computational network that is optimal for one half of a complementary pair is not optimal for the other half. Consider, for example, neural network computer simulations created by Kosslyn, Chabris, Marsolek, and Koenig (1992) to process coordinate and categorical aspects of spatial location. Certain aspects of these simulations will be discussed in more detail in a subsequent section of the present chapter. Of particular relevance at the moment is their finding that networks which were split so that some of their hidden units contributed to a coordinate judgment and others contributed to a categorical judgment performed better than unsplit networks in which all hidden units contributed to both types of judgment (see also Kosslyn & Jacobs, 1994). Findings such as this indicate that there are computational advantages to segregating the two types of spatial processing. When combined with other evidence that tasks tend to interfere with each other less when they are performed by different hemispheres than when they compete for resources from the same hemisphere, these simulations suggest that it is advantageous for complementary processes to be segregated into opposite hemispheres so as to reduce maladaptive cross talk.

From the foregoing perspective, it is interesting that lateralization in the domestic chick enhances the ability to perform two complementary tasks simultaneously: discriminating grains of food from small pebbles, for which there is typically left-hemisphere superiority, and being attentive to visual cues associated with a predator flying overhead (silhouette of a hawk), for which there is typically right-hemisphere superiority (e.g., Rogers, Zucca, & Vallortigara, 2004; see also Sovrano, Dadda, &

Bisazza, 2005, for indications that lateralized fish perform better than nonlateralized fish in spatial reorientation tasks). In a study of individual differences in humans, Hirnstein, Hausmann, and Güntürkün (2008) report an effect in the opposite direction (simultaneous face–nonface and word–nonword discrimination decreased with increased lateralization for the two tasks), but the results are difficult to interpret in view of the fact that the same relationship to the degree of lateralization was found for each of the two tasks performed alone, which was not the case in the animal studies. Furthermore, other studies in humans have found increases in cognitive ability with increasing strength of laterality, at least as measured by handedness (e.g., Leask & Crow, 2001; Nettle, 2003). Strength of handedness also appears to be related inversely to the size of the corpus callosum and to the extent of interaction between the two hemispheres (see Christman, Propper, & Dion, 2004; Christman, Propper, & Brown, 2006).

Segregating complementary processes into left- and right-brain hemispheres may confer computational advantages that operate at the level of individual organisms but would not require that individuals within a species be lateralized in the same direction. In fact, in other species there are many examples of robust left–right differences for individuals without an overall population bias as well as examples of population-level asymmetry (for examples and review, see Hellige, 1993, 2006; Hopkins, 2007; Hopkins & Cantalupo, 2008; Rogers & Andrew, 2002; Vallortigara & Rogers, 2005). It is, therefore, important to consider factors that might favor moving from individual to population-level asymmetry.

A particular left–right asymmetry may have been determined largely by chance when it first appeared, yet a genetic bias for direction as well as the presence of an asymmetry may have been passed on to the lateralized individual's offspring. On this view, population-level asymmetry would emerge in a straightforward way (for discussion, see Hopkins & Cantalupo, 2008). In addition, some aspects of functional laterality depend on asymmetries that unfold during the course of embryological development and that may, therefore, produce population-level laterality because they codevelop with the asymmetry of other internal organs or even of certain key proteins (e.g., Hamada, Meno, Watanabe, & Saijoh, 2002; McManus, 2002; Rogers, 2002). It has also been hypothesized that some population-level asymmetries emerged because lateral consistency within a population benefits group-level or social behavior, perhaps by making behavior of members of the group more predictable. Consistent with this hypothesis, population-level asymmetry is more characteristic of “social” fish species that school to protect themselves from predators than of fish species that do not do so (Vallortigara, 2000; Vallortigara & Regolin, 2006; Vallortigara & Rogers, 2005). The evolutionary hypothesis also proposes that, within a species, the specific distribution of left–right differences for the population is an evolutionarily stable strategy of the sort discussed by Maynard-Smith (1982; see also Ghirlanda & Vallortigara, 2004; Vallortigara & Rogers, 2005).

Regardless of how population-level asymmetries first emerged, it is important to note that an existing asymmetry is likely to constrain the direction of other asymmetries that emerge only later, via a kind of “snowball” mechanism. That is, in organisms whose brains have already become asymmetrical, it is likely that some of the subsequent evolutionary adaptations that are favored by future environments will be implemented more efficiently on one side or the other. This is the case precisely because the two sides are already different from each other to some extent. The result in some of these cases would be to increase the extent of functional asymmetry and thereby set the stage for still more lateralization as evolution proceeds. Once this process begins, laterality could increase over evolutionary time even if the environment did not specifically favor laterality per se.

Thus far we have argued that the existence of so many visual asymmetries in other species makes it likely that the visual hemispheric asymmetry we see in contemporary humans is rooted in our distant evolutionary past. At the same time, there are clear differences between laterality in humans and in other species, including our closest primate relatives. For example, though there are population-level hand preferences in some other primate species, this is not always reported, and even when it is, the proportion of right-handedness does not approach that of humans. With respect to visual processing, there is clearer evidence of hemispheric asymmetry for processing coordinate versus categorical spatial information in humans than in other primates, though the primate evidence is sparse in this regard (e.g., Postma & Laeng, 2006; Vauclair, Yamazaki, & Güntürkün, 2006). Consequently, it is important to consider factors that may have contributed to the continuing evolution of asymmetries that were already present in our distant ancestors. These are likely to have included such things as an upright walking position, tool use, the emergence of language, lateralization of mirror neuron systems, evolution of the corpus callosum, and extended postnatal immaturity. Though detailed discussion of these factors is beyond the scope of the present chapter, we will briefly note how some of them may have influenced asymmetry for the sort of visual processes we consider later.

In considering the ontogenetic development of visual asymmetries, Previc (1991) has suggested that right-hemisphere superiority for certain visuospatial processes arises from asymmetrical shearing forces on the developing otolith organ as the mother walks during pregnancy. Such asymmetrical shearing forces are dependent on the mother's walking upright and may reflect one way in which bipedalism influenced the further evolution of visual asymmetry in humans. Though tool use and language may have had more direct influence on such things as handedness and language asymmetry than on visual processes, to the extent that aspects of laterality are intertwined, there are likely to have been influences on visual processing as well. For example, increasing left-hemisphere dominance for a variety of language-related functions may have accelerated pressure for greater right-hemisphere involvement in

certain spatial and visual processes. Of course, to the extent that certain right-hemisphere superiorities were already present, this may have also favored a disproportionate role for the left hemisphere in the evolution of language.

Rizzolatti, Fadiga, Gallese, and Fogassi (1996) discovered individual neurons ("mirror neurons") in monkey brains that respond to specific reaching and grasping movements made by the animal but also respond when the monkey sees those same movements made by other monkeys or even humans (for a review, see Arbib, 2005; Rizzolatti & Craighero, 2004). Thus, the mirror neuron system provides a link between perception and action. Though the mirror system in monkey is typically described as bilateral, in humans the mirror system for linking the perception of reaching and grasping with the production of reaching and grasping has been associated with an area of the left hemisphere that generally corresponds to Broca's area. There is also some indication that mirror systems within the two hemispheres of humans came to be specialized for linking different sorts of actions and perceptions. For example, there is functional imaging evidence for a right-hemisphere mirror neuron system in humans that responds in the same way to passive viewing of facial expression as it does to the imitation of facial expression (Leslie, Johnson-Frey, & Grafton, 2004), perhaps providing a neural substrate (and right-hemisphere superiority) for understanding the emotional experience of others or identifying the emotional expression shown on a face.

In order for complementary hemispheric specialization to be successful, there must be both sufficient isolation of the complementary computational processes and sufficient communication of the computational results between the two hemispheres. It has even been suggested that it was the evolution of the corpus callosum that enabled hemispheric specialization to develop (e.g., Gazzaniga, 2000). While this is unlikely in view of so much laterality in species that do not have a corpus callosum, it may well be that the continued evolution of laterality was interwoven with the emergence and continued evolution of the corpus callosum. The relationship between these two is likely to have been complex because the corpus callosum in humans permits mutual inhibition between the hemispheres in addition to enabling the transfer of information from one hemisphere to the other (for discussion, see Hellige, 2006; Zaidel & Iacoboni, 2003). Furthermore, as noted by Hopkins and Cantalupo (2008), relative to other primates, human beings have a very large brain for their body size and a small corpus callosum size relative to brain size. This may lead to greater isolation between the two hemispheres of humans relative to other primates, making functional asymmetries easier to observe in neurologically intact individuals. Thus, the continuing evolution of the corpus callosum and its relationship to brain size may have added to the evolutionary advantage of segregating complementary or mutually incompatible processes into opposite hemispheres. In any case, the fact that the corpus callosum of humans mediates a variety of interactions between higher cortical areas of the two

hemispheres means that understanding hemispheric asymmetry for visual processing requires understanding the manner in which the two hemispheres interact to process visual information.

There is evidence that homologous areas of the left and right hemispheres mature at different rates, beginning in utero and continuing through at least the first few years of human life. At least in humans, certain areas of the right hemisphere develop earlier in utero than do homologous areas of the left hemisphere, leading to the suggestion that the earlier developing right hemisphere is initially more influenced by the sort of impoverished information that the developing brain encounters before and for a short time after birth (for examples, see Hellige, 1993, 1995, 2006). It may be the case that the consequences for functional laterality are magnified to the extent that the brain undergoes more of its development after birth, as this would provide opportunity for greater interaction between the developing nervous system and the environment. From this perspective, it is interesting that, relative to other primates, humans are characterized by a prolonged period of postnatal immaturity. In the case of vision, the earlier developing right hemisphere might be more influenced by the sort of global properties of the visual world to which the visual pathway of newborns is sensitive (see de Schonen & Mathivet, 1989; Fritzsch, 2003; Turkewitz, 1988), setting the stage for right-hemisphere dominance for such properties and, perhaps, making the right hemisphere a less suitable substrate for processing the higher quality visual information that is received later, as the visual system matures.

Even this brief review makes it clear that hemispheric asymmetry for visual processing is ubiquitous across contemporary species and quite likely emerged early in our evolutionary history. It is against this backdrop that we now examine visual asymmetry in contemporary humans.

### Categorical and Coordinate Spatial Relations

It is common parlance among visual neuroscientists to refer to major divisions between neural streams with the use of interrogative pronouns, like "what" versus "where" systems. Schneider (1967) apparently coined the catchy phrases "What is it?" and "Where is it?" (Ingle, 2002), and the terminology was later adopted by Mishkin, Ungerleider, and Macko (1983) in describing "two cortical visual systems" (a ventral visual stream that mediates object identification and a dorsal visual stream that mediates localization of objects in space). Neither the "what" nor "where" cortical visual systems are nowadays identified with functional specialization of a specific hemisphere of a specific animal. Instead, both systems are duplicated in each hemisphere, so that one must consider at least four cortical visual systems that are potentially distinct. Indeed, there are reasons to believe that each hemisphere is concerned with

different aspects of the “What is it?” and “Where is it?” questions. We will begin our discussion with a review of each hemisphere’s contribution to answering the “where” question.

A primary function of vision is to provide a sense of location. Primitive eyes that cannot focus on an “image” that is detailed enough to contain information about the form of an object can still provide basic spatial information (e.g., cardinal directions as up–down based on sunlight; detecting a motion path or distances by use of optic flow; Ings, 2007). However, most of our knowledge on the cerebral laterality for different spatial abilities derives from studies of humans. This research has revealed that the right hemisphere has a relative superiority to the left hemisphere at assessing “analogue” spatial relations (e.g., the distance between two objects). Instead, a complementary superiority in assessing “digital” spatial relations (e.g., whether two objects are attached to one another or above or below the other) has been attributed to the left hemisphere.

According to Stephen Kosslyn (1987, 2006), each of the two lateralized networks within the dorsal system performs different types of computation on the same input, so that, in turn, each produces as output a representation of a different kind of spatial relation. Kosslyn’s terminology distinguishes “coordinate relations” that occur within a “metric” space, so that coordinate relations allow the perception and expression of space in a quantitative sense (object A and object B are about 10 meters apart), which would be suitable, for example, for navigation. In addition, a qualitatively different mode of perception does not “measure” but “categorizes” space. That is, locations are grouped to define an equivalence class so as to delineate regions and boundaries or limits separating or connecting patches of space. In Kosslyn’s terminology, this type of spatial information is therefore defined as “categorical.” These representations are abstract (i.e., they do not locate an object exactly) compared to the “coordinate” ones and would seem to represent spatial relations in a manner similar to that expressed in every language by use of different prepositions (e.g., “above,” “alongside,” “around,” “behind,” “between,” “inside,” “left,” “on top of,” “opposite,” “south,” “toward,” “underneath,” etc.; cf. Kemmerer, 2006; Pinker, 2007).

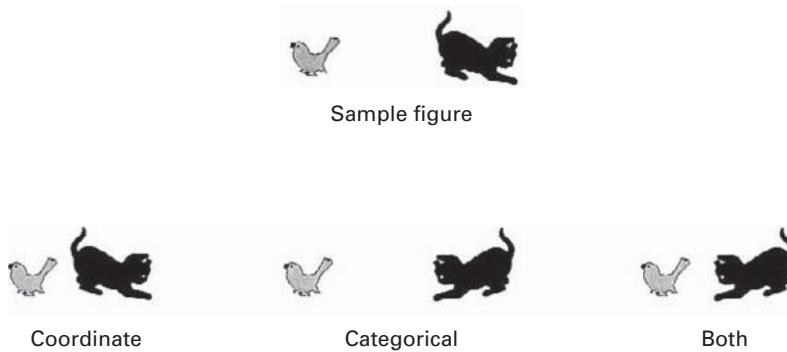
As for other hemispheric asymmetries, there exist individual variations in both the strength and directionality of complementary lateralization for categorical–coordinate spatial relations, but there is clearly a large amount of regularity. An impressive number of studies, using a variety of research methods and paradigms, have converged in showing that, in groups of right-handers, the left hemisphere is more efficient with categorical spatial relations whereas the right hemisphere is more efficient with coordinate spatial relations (for reviews, see Hellige, 1995; Jager & Postma, 2003; Laeng, Chabris, & Kosslyn, 2003).

An initial body of evidence consisted in interactive effects observed in divided-visual-field studies (e.g., Hellige & Michimata, 1989), where subjects were faster and

more accurate in judging metric relations of stimuli ("Is a dot within 1 centimeter of a line?") presented in the left visual field (or to the right hemisphere initially; LVF-RH trials) and faster and more accurate in judging categorical relations ("Is a dot above or below a line?") when stimuli were presented in the right visual field (or to the left hemisphere initially; RVF-LH trials). Most studies (e.g., Hellige & Michimata, 1989; Kosslyn, Koenig, Barrett, Cave, Tang, & Gabrieli, 1989; Laeng, Peters, & McCabe 1998; Roth & Hellige, 1998; van der Ham, van Wezel, Oleksiak, & Postma, 2007) have used simple geometrical figures (e.g., a dot at variable distances either above or below a line; a dot either on or off a circle or in various positions within a circle's quadrants) but other studies (e.g., Laeng & Peters, 1995) have generalized the results to naturalistic figures (e.g., drawings of animals), where a more variable or complex set of both categorical and coordinate spatial relations can be used. Some authors (e.g., Wang, Zhou, Zhuo, & Chen, 2007) have pointed out that the conceptual distinctions of categorical and coordinate spatial relations have strong similarities to different types of geometries (e.g., "topological" vs. "Euclidean" or "affine" geometries; cf. Saneyoshi, Kaminaga, & Michimata, 2006). Wang and colleagues (2007) presented evidence that an inside–outside judgment (i.e., a topological or categorical judgment) results in a robust left-hemisphere advantage, whereas judging the orientation of angles (i.e., an Euclidian property or coordinate judgment) results in the opposite right hemisphere's advantage.

Typically, measured visual field differences in response times tend to be rather volatile (e.g., Cowin & Hellige, 1994; Hellige & Cumberland, 2001; Kosslyn et al., 1989; Laeng, Shah, & Kosslyn, 1999; Roth & Hellige, 1998), and, when they are observed, they also tend to be rather small: One meta-analysis (Laeng, Chabris, & Kosslyn, 2003) of 24 such studies showed that the left hemisphere is about 8 milliseconds faster than the right hemisphere in making categorical judgments, whereas the right hemisphere is about 14 milliseconds faster than the left hemisphere in making coordinate judgments. However small these absolute differences might look, they are highly significant (combined  $Z$  value = 6.93,  $p < .0001$ ), and the overall effect size for this interaction is  $d = 0.47$ .

Perhaps a clear manner to appreciate the relevance of hemispheric differences in the normal brain—that at first glance would seem rather weak or even negligible—is to observe the outcome of damage to each hemisphere in human patients when they perform perceptual or memory spatial tasks. Laeng (1994) documented a "double dissociation" between two types of deficits: a failure to notice changes in categorical spatial relations versus a failure to notice changes in coordinate spatial relations. For example, patients ( $N = 60$ ) with unilateral damage may fail to notice that a picture showing a cat and a bird side by side was different from another picture showing the same cat and a bird side by side but in the former display the cat was oriented toward the right and in the latter toward the left (see figure 13.1). When groups were split by

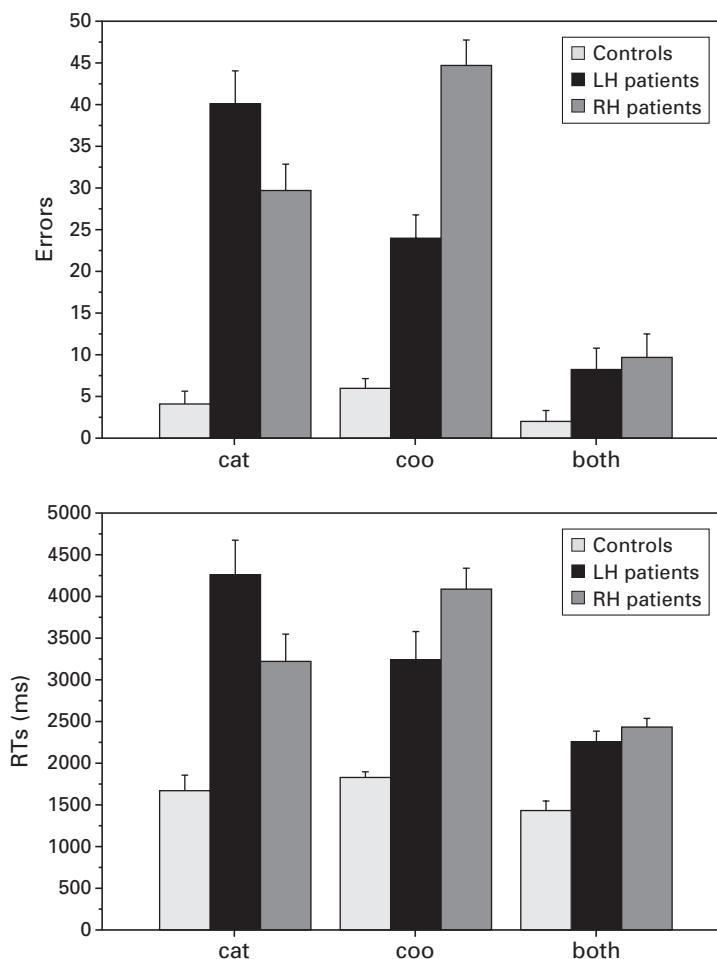


**Figure 13.1**

Perceptual categorical-coordinate test. (Top) Sample figure. (Bottom) Spatial transformations (from left to right: coordinate, categorical, and both coordinate and categorical spatial transformations).

side of lesions, it was clear that that type of error was significantly more common in patients with unilateral lesions to the left hemisphere; in contrast, these same left-damaged patients had considerably less difficulty in noticing that in two subsequent pictures the distance between the cat and the bird had either increased or decreased. In contrast, the group with unilateral damage to the right hemisphere showed a difficulty in noticing a change in distance or angle between two animals, whereas they had less difficulty noticing a change of relative orientation (e.g., left vs. right) between animals. Figure 13.2 illustrates the performance of patients with unilateral lesions ( $N = 20$ ) in a second clinical study by Laeng (2006), which also closely replicated the findings of the original study (Laeng, 1994). This second clinical study also revealed that the patients would make characteristic errors in spatial construction tasks (e.g., patterns made of matchsticks; cf. Benson & Barton, 1970), so that mirror reversals of elements of a pattern would be more common after left-hemisphere damage whereas distortions in reproducing the angle between two elements would be more common after right-hemisphere damage.

A third clinical study by Palermo, Bureca, Matano, and Guariglia (2008;  $N = 22$  unilaterally damaged patients) revealed that those with left-hemisphere damage had difficulty visually imaging whether a dot shown in a specific position would fall inside or outside of a previously seen circle but they had less of a problem in visually imaging whether a dot shown in a specific position would be nearer or farther apart from the circle's circumference than another dot previously seen together with the same circle. Patients with right-hemisphere damage showed the (expected) reverse pattern of deficits. Thus, there appears to be high consistency in the effects of lateralized damage in patients on each type of spatial ability.

**Figure 13.2**

Categorical–coordinate test. Columns show the performance of the controls, left-handed (LH) patients, and right-handed (RH) patients when spatial relations among the items—categorical (cat), coordinate (coo), or both—were transformed; bars show 95% confidence intervals. (Top) Errors. (Bottom) Response times (RTs) in milliseconds.

Neuroimaging has also been used to specifically test the anatomy of spatial functions with the specific intent to map areas engaged by either categorical or coordinate information considered relevant to the solution of the task. These studies have revealed variable patterns of cortical activations within a frontoparietal network that has often (in other unrelated studies) been implicated for spatial encoding and indexing, spatial attention shifting and tracking, and spatial working memory. Perhaps the most consistent finding of these brain imaging studies is precisely that of laterality, and, for most of these studies, the relative specialization of each hemisphere has been rather consistent with the laterality pattern shown in patients' studies or divided-visual-field studies of normal subjects (e.g., Baciu, Koenig, Vernier, Bedoin, Rubin, & Segebarth, 1999; Kosslyn, Thompson, Gิตelman, & Alpert, 1998; Slotnick & Moo, 2006; Trojano, Grossi, Linden, Formisano, Goebel, & Cirillo, 2002).

However, laterality effects are not invariably found in these neuroimaging studies (e.g., Martin, Houssemand, Schiltz, Burnod, & Alexandre, 2008). Nevertheless, variability in brain imaging results is to be expected since peak activations are subject to the influence of several processes, some of which are functional to the task and some of which are likely to be epiphenomenal. In addition, there are reasons to believe that cognitive functions, although separable in terms of cognitive architecture, may often have overlapping neural representations (Logothetis, 2008). An example of overlapping neural representation that is most relevant for the present discussion is that the cognitive system responsible for spatial attention shifts and the cognitive system responsible for computing coordinate spatial relations may use the same neural substrate within the right parietal areas that underlies the spatiotopic representation of locations in the field of vision (Kosslyn, 1994; Culham, Brandt, Cavanagh, Kanwisher, Dale, & Tootell 1998). Thus, it may not be surprising that a robust finding of all these neuroimaging studies is the strong activation within the posterior regions of the right hemisphere in the coordinate spatial task and, sometimes, also in the categorical spatial task (Martin et al., 2008). For example, Kosslyn and colleagues (1998) used an above–below versus near–far judgment of an X in relation to a bar and found the expected pattern of hemispheric activations when each decision was compared to the control task. However, direct comparisons between the categorical and coordinate conditions revealed only a greater right-hemisphere engagement in the coordinate task.

Another likely source of variability in brain imaging findings (Kosslyn et al., 1998) derives from the fact that the blood-oxygen-level-dependent (BOLD) response may occur at subthreshold levels when a task is too easy and only the more processing-challenging tasks can reveal peak activity in the cortex. Since in most studies the categorical spatial task requires easier decision making than the coordinate spatial task (as indicated by differences in accuracy rates and response times), it is not surprising that categorical spatial processing has been harder to image with the BOLD response

than coordinate spatial processing. Martin and colleagues (2008) specifically argue that task difficulty is the prevailing factor behind laterality effects (see also Banich & Federmeier, 1999; Monaghan & Pollmann, 2003; Reese & Stiles, 2005; van der Lubbe et al., 2006), and they only found significant activation for a difficult categorical spatial task (i.e., a spatial working memory task within a display with a very irregular grid) in the right hemisphere. However, it is possible that increasing the difficulty of the categorical task would also (1) decrease the likelihood that a categorical coding strategy is preferred to a coordinate coding strategy since the former may become ineffective to solving the task (e.g., there may be a limit to the number of boundaries, regions, and categorical relations that can be mapped simultaneously), as well as (2) increase the likelihood that multiple spatial attention shifts are required during the task. Both effects would likely result in the increased engagement of the right hemisphere. Bullens and Postma (2008) have specifically suggested that failures to replicate a left-hemisphere advantage for categorical spatial judgments in divided-visual-fields studies may also be due to avoiding a categorical coding strategy of locations when this proves to be too difficult.

Finally, a few studies (Slotnick, Moo, Tesoro, & Hart, 2001; Trojano, Conson, Maffei, & Grossi, 2006) used the method of repetitive transcranial magnetic stimulation (rTMS) applied to the left or right parietal areas during categorical-coordinate tasks. Slotnick and colleagues (2001) used perceptual categorical and coordinate tasks and obtained a pattern of laterality that was, overall, consistent with the expected interactive effects, especially when task difficulty was sufficiently high. Trojano and colleagues (2006) used a spatial imagery task (using hands positioned as in clock faces; see also Michimata, 1997) and found that performance in the categorical version of the task was disrupted more after left-sided stimulation than right-sided stimulation, whereas the reverse effect of lateralized stimulations was observed with the coordinate version of the task. Thus, results from the rTMS method, which provokes a temporary “lesion” effect in intact brains, have been clearly consistent with the pattern of laterality effects revealed in studies of patients with actual unilateral brain damage.

In conclusion, about 20 years of research on the lateralization of categorical versus coordinate processing has supported the processing dichotomy originally proposed by Kosslyn in 1987 (see also Kosslyn, 2006). If separate and lateralized categorical and coordinate spatial relation representations exist, then what remains unclear is what causes the observed pattern of lateralization.

### **Spatial Frequency Processing**

Why is the typically observed lateralization profile a left-hemisphere specialization for categorical (digital) spatial relations and a right-hemisphere specialization for coordinate (analogue) spatial relations? Such a functional asymmetry profile was originally

predicted by Kosslyn (1987) on the basis of two parallel but independent hypotheses. The first is that the brain seeks optimality by separating computations of representations that can potentially interfere with one another (e.g., Kosslyn et al., 1992; Jacobs & Kosslyn, 1994). As mentioned earlier, an efficient way to separate cerebral functions in the vertebrate brain may be through hemispheric specialization. Note that the above hypothesis only predicts that there should be separation of function (e.g., lateralization) but cannot make predictions about a regular pattern of directionality in every individual. Such a prediction derives from a second hypothesis that there is a preexisting “seed” for neural development, which is identical in the majority of human individuals, so that an optimal wiring of functional area would bias in a predictable manner one particular subsystem to a specific side of the brain.

There have been several proposals, in a time period of about 20 years, on the most likely candidates for such an evolutionary seed or “snowball” mechanism. The first proposal was that the presence of language specialization in the left hemisphere (of the great majority of individuals) would specifically bias the localization of an input system that represents space in a categorical manner to the same side of the brain (since the left-sided language system would benefit from categorical perceptual distinctions like left-right, above-below; cf. Tranel & Kemmerer, 2004). Although the left-lateralized linguistic functions as a “seed” might explain (in part) the human profile of laterality, it fails to explain how a similar asymmetry for categorical spatial relations could have originated at the group level in other animals (e.g., in Guinea baboons; Dépy, Fagot, & Vauclair, 1998; see Vauclair, Yamazaki, & Güntürkün, 2006, for a review). Moreover, finding hemispheric advantages for categorical spatial relations in other animals strongly supports the argument that such laterality cannot be simply explained away as the reflection of a verbal mediation or preposition-based coding of positions. In fact, one could reverse the causality and hypothesize that the foundation of categorical relation processing and abstraction in the left hemisphere might have been a precursor for the evolution of language (Postma & Laeng, 2006). Thus, a more general evolutionary “seed” would be preferable, since it would satisfy one of the most sought-after goals in any scientific account: that of providing a unified theory of all phenomena. Therefore several researchers have looked for general evolutionary seeds in perceptual “primitives,” like the response properties of cortical cells within the low-level visual areas of the brain.

In this respect, it is important that the two hemispheres seem to have different preferences in spatial frequency processing (Ivry & Robertson, 1998). Specifically, Sergent (1983a, 1983b) has first proposed that, at some level of processing beyond the visual cortex, the left and right hemispheres are dominant for processing visual information carried by channels tuned to relatively high and low spatial frequencies, respectively. This spatial frequency model has been tested by use of hierarchical stimuli (Sergent, 1983a, 1983b), by frequency filtering methods such as blurring

(Jonsson & Hellige, 1986; Michimata & Hellige, 1987), and by use of sinusoidal gratings (Kitterle, Christman, & Hellige, 1990; Christman, Kitterle, & Hellige, 1991; Kitterle, Hellige, & Christman, 1992). These studies have generally supported the model, though the experiments using simple grating stimuli (sine wave, square wave, Gabor patches) have not always been replicated (for an extensive review, see Grabowska & Nowicka, 1996).

Kosslyn et al. (1992) suggested that the hemispheric asymmetries for categorical and coordinate spatial relations could be linked to the asymmetries in processing of spatial frequency. Using neural network simulations, they found that networks that receive input from smaller receptive fields, which efficiently encode higher frequencies, computed categorical spatial information efficiently. In contrast, networks that receive input from larger overlapping receptive fields, which efficiently encode lower frequencies, computed coordinate spatial information efficiently via a *coarse coding* mechanism. Thus, they hypothesized that the left hemisphere is predisposed toward efficient use of higher spatial frequency and, hence, efficiently processes categorical spatial relations. In contrast, the right hemisphere is predisposed toward efficient use of lower spatial frequency and, hence, efficiently processes coordinate spatial relations.

This hypothesis has been tested by Okubo and Michimata (2002, 2004) in divided-visual-field studies using categorical and coordinate tasks patterned after those used by Hellige and Michimata (1989). In both studies, the conventional visual-field-by-task interaction (RVF-LH advantage for the above–below categorical task and LVF-RH advantage for the near–far coordinate task) was found when the stimulus patterns were composed of small, clear bright dots. However, the use of stimulus patterns that were constructed using contrast-balanced dots that were devoid of low spatial frequencies selectively eliminated the right hemisphere's advantage for the coordinate task (Okubo & Michimata, 2002), and the use of low-pass-filtered stimuli that were devoid of high spatial frequencies selectively eliminated the left-hemisphere's advantage for the categorical task (Okubo & Michimata, 2004). These results suggest strongly that spatial frequency plays a role in hemispheric asymmetry for the processing of spatial relations.

### Object Recognition

Thus far we have focused on hemispheric asymmetry for processing the “where,” or location, of visual stimuli. The left and right hemispheres also make complementary contributions to the “what” of visual stimuli. For example, the left hemisphere is hypothesized to be superior for processing the local details of visual stimuli and for recognizing whether or not a visual stimulus belongs to a category, whereas the right hemisphere is hypothesized to be superior for processing the global or configural

properties of visual stimuli and for discriminating among the exemplars within a category. In this section, we review evidence for these asymmetries and consider how hemispheric asymmetry for object recognition can be understood in terms of categorical and coordinate properties that are important for the different aspects of recognition. It is important to understand at the outset that by relating hemispheric asymmetry for processing categorical versus coordinate aspects of spatial location to hemispheric asymmetry for aspects of object recognition, we are not suggesting that the dorsal visual stream mediates hemispheric asymmetry for object recognition. It is possible, however, that hemispheric asymmetry in both ventral and dorsal visual streams derives in part from underlying hemispheric attentional biases in monitoring responses from cells with different size receptive fields or spatial frequency tuning.

Intuitively, between-categories discrimination (e.g., cups vs. pots) would seem to require the use of categorical spatial relationships among the parts. For example, all coffee cups preserve basic categorical properties such that a curved cylinder is attached to the side of a main cylinder. In contrast, distinguishing among objects within the same category (e.g., this cup vs. that cup) would seem to require the use of precise metric spatial relationships among the parts, as well as metric figural features of the parts such as the length and curvature. For example, different coffee cups can be distinguished by metric properties such as the length of the main cylinder or the size of the curved cylinder (for relevant discussion, see Marr, 1982; Biederman, 1987; Cooper & Wojan, 2000). As already discussed, there is evidence that categorical and coordinate (metric) spatial relationships are most efficiently processed by the left and right hemispheres, respectively. Thus, it has been hypothesized that between-categories object discriminations would show a left-hemisphere processing advantage whereas within-category object discriminations would show a right-hemisphere advantage. In fact, several behavioral studies have provided evidence supporting this hypothesis (e.g., Marsolek, 1999; Laeng, Zarrinpar, & Kosslyn, 2003; see also Laeng, Carlesimo, Caltagirone, Capasso, & Miceli 2002).

With this hypothesis in mind, Saneyoshi et al. (2006) conducted a functional magnetic resonance imaging (fMRI) experiment to examine cortical activation patterns associated with between- versus within-category object discrimination. One advantage of their experiment over the previous studies was that they systematically manipulated the metric properties of objects, so that the tasks had clear figural feature processing demands. Stimuli were photos of everyday objects (six categories; chair, cup, etc.), with five members for each category. Members of the same category differed in metric properties (see figure 13.3 for examples). During the experiment, participants judged whether the two successive stimuli were same or different (one-back matching). Neurologically normal, right-handed participants performed two object-matching tasks in separated experimental blocks. For the between-categories task, they judged whether the two successive objects belonged to the same category. For the within-

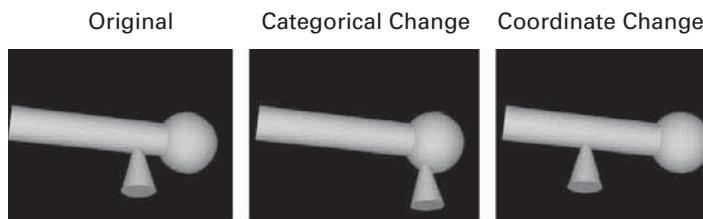


**Figure 13.3**

Examples of stimuli used in a functional magnetic resonance imaging experiment by Saneyoshi, Kaminaga, and Michimata (2006). See text for explanation.

category task, they judged whether the two successive objects were physically identical. During the between-categories task, the left precuneus, the left superior parietal lobule, and the left inferior parietal lobule (IPL) were activated, with left-IPL activation being significantly higher than right-IPL activation. During the within-category task, the right precuneus, the right superior occipital gyrus (SOG; with right-SOG activation being greater than left-SOG activation), the bilateral IPL, the left fusiform gyrus, and the left medial frontal gyrus were activated. Overall, these results are consistent with relatively greater left- and right-hemisphere contributions to between-categories versus within-category discrimination, respectively.

In addition, Saneyoshi and Michimata (2009) have extended investigation in a behavioral experiment using nonnameable multipart three-dimensional objects consisting of “geons” (cf. Biederman, 1987). Combinations of three geons formed a set of



**Figure 13.4**

Examples of stimuli used by Saneyoshi and Michimata (2009), showing an original stimulus, an alternative with a categorical change in the arrangement of parts, and an alternative with a coordinate change in the arrangement of parts.

original gray-scale pictures of novel objects (e.g., a sphere connected to the side of a cylinder and a cone connected to bottom of the cylinder, etc.; see figure 13.4 for examples). Two types of transformation were introduced to create comparison stimuli. The stimulus set for the categorical task consisted of the original and the categorically transformed objects, in which geon A originally connected to geon B moved in the transformed object to be connected to geon C. In contrast, the stimulus set for the coordinate task consisted of original and coordinately transformed objects, in which geon A remained connected to geon B but moved to a different position on geon B. The degree of transformation was adjusted so that the two tasks were equally difficult. For each object, two different views were created by rotating the object around the vertical axis. In both tasks, the two objects (original and transformed) were presented one after another, and right-handed participants judged whether they were the same or different, ignoring the view. The reaction time data revealed a significant visual-field-by-task interaction, with no main effect of the task. For the categorical task, reaction time was shorter on RVF-LH trials (795 milliseconds) than on LVF-RH trials (809 milliseconds), with the visual field effect being reversed for the coordinate task (RVF-LH = 778 milliseconds, LVF-RH = 760 milliseconds).

Taken together with others in the literature, the studies by Saneyoshi et al. (2006) and Saneyoshi and Michimata (2009) suggest that hemispheric differences for making between- versus within-category judgments of visual stimuli depend on the computational demands made by different tasks—specifically, on the extent to which a task requires attention to categorical versus coordinate spatial relationships among the parts of an object. This may be particularly true for the processing of complex multi-part objects, most especially when those objects are novel or seen in challenging novel conditions (e.g., unusual perspectives or contorted poses; Laeng et al., 1999). This is consistent with the possibility that hemispheric asymmetry in both ventral and dorsal visual streams derives in part from underlying hemispheric attentional biases in monitoring responses from cells with different size receptive fields or spatial frequency

tuning. We next consider briefly how these same biases may relate to hemispheric asymmetry for processing local versus global aspects of hierarchical stimuli and for face recognition.

### Global–Local Processing

Visual patterns can be thought of as containing various levels of information, ranging from the overall or global configuration to smaller, local details. This is particularly clear for hierarchical patterns for which a large, global pattern (e.g., a large letter H) is composed of many small, local patterns (e.g., the letter J repeated many times; e.g., Navon, 1977). Evidence from a variety of sources indicates that the left and right hemispheres have an advantage for processing local and global levels of visual information, respectively (Sergent, 1983a; Kimchi & Merhav, 1991; Robertson, Egly, Lamb, & Kerth, 1993; Fink, Halligan, Marshall, Frith, Frackowiak, & Dolan, 1996, 1997; Yamaguchi, Yamagata, & Kobayashi, 2000). The most consistent findings come from studies of patients, which indicate that damage to the left versus right superior temporal gyrus disrupts local versus global processing, respectively (for reviews, see Hellige, 1993; Ivry & Robertson, 1998). Support also comes from divided-visual-field studies, which generally show an RVF-LH advantage for identifying local patterns and an LVF-RH advantage for identifying overall global patterns (for review and meta-analysis, see Van Kleeck, 1989; also Hübner, 1998; see Hübner & Studer, 2008, for a study using naturalistic stimuli; see also Hopkins, 1997, for evidence that chimpanzees show right-hemisphere superiority for global processing combined with no significant asymmetry for local processing). However, the visual field advantage in such studies depends on a variety of attention-related factors—for example, continuous attention to only one level versus monitoring both levels simultaneously. Functional brain imaging studies have also found asymmetries related to processing global versus local levels of visual information, but the results are more variable than the results of clinical studies in terms of both the presence of asymmetry and the specific areas of asymmetrical activation (e.g., Fink et al., 1996, 1997; Han, Weaver, Murray, Kang, Yund, & Woods, 2002; Heinze, Hinrichs, Scholz, Burchert, & Mangun, 1998; Sasaki, Hadjikhani, Fischl, Liu, Marrett, Dale, & Tootell, 2000). At least some of this variability is likely related to specific task demands and to some of the issues discussed earlier with respect to the BOLD response.

There are indications that, like the visual asymmetries discussed earlier, hemispheric asymmetry for processing local versus global information is related to the range of spatial frequency that is relevant for processing local (relatively high-frequency) versus global (relatively low-frequency) information. Certainly, the spatial frequency contained in hierarchical patterns systematically influences processing (for discussion, see Hellige, 1993, 1995). For example, eliminating low spatial frequencies

from a hierarchical pattern eliminates asymmetrical global interference (the tendency for the global pattern to interfere more with identifying local stimuli than vice versa; Hughes, Fendrich, & Reuter-Lorenz, 1990). A similar effect occurs when the hierarchical pattern is presented on a red background, which attenuates processing of the magnocellular visual system with its focus on low spatial frequencies (Michimata, Okubo, & Mugishima, 1999). Furthermore, spatial frequency filtering influences the pattern of hemispheric asymmetry in appropriate ways (e.g., Han et al., 2002; Yoshida, Yoshino, Takahashi, & Nomura, 2007).

### Face Recognition

There are indications that the two hemispheres make complementary contributions to face processing, with the hemispheric advantage depending on a number of task requirements (i.e., discriminating faces from nonfaces, individual identification, same-different matching, identifying emotional expression etc.). Among other things, right- and left-hemisphere advantages seem to be associated in part with processing the configural aspects of faces versus processing local facial features, respectively (e.g., Hellige, 1993). Based on behavioral studies that compared facial characteristics that are important for face identification versus face–nonface discrimination, Cooper and Wojan (2000) concluded that face identification involves processing of configural, metric, or coordinate information whereas basic-level categorization of a stimulus as belonging to the face category involves categorically coded spatial information. Thus, the right hemisphere's advantage for face identification may be related to its advantage for processing coordinate, metric spatial relationships.

It has been suggested that a portion of the fusiform gyrus has a special role to play in face processing, so much so that it is frequently referred to as the fusiform “face” area (FFA). The role of the FFA in face processing and in object processing more generally remains a matter of some debate, as does the idea that face processing is somehow “special” (for examples and discussion, see Gauthier, Tarr, Moylan, Skudlarski, Gore, & Anderson, 2000; Hasson, Avidan, Deouell, Bentin, & Malach, 2003; Steeves, Culham, Duchaine, Pratesi, Valyear, Schindler, Humphrey, Milner, & Goodale, 2006; Yue, Tjan, & Biederman, 2006). Nevertheless, there is some indication that the left and right FFAs play different roles in face processing. For example, Rossion, Dricot, Devolder, Bodart, Crommelinck, de Gelder, and Zoontjes (2000) had participants perform delayed face-matching tasks in two conditions while undergoing positron emission tomography. In the *whole* condition, they judged whether two faces were identical to each other, requiring attention to the configural or metric relationships among the parts. In the *part* condition, they judged whether a particular feature (the eyes in one scan or the mouth in another scan) were identical in two faces. They found greater activation in the right FFA during the *whole* condition and greater activation

in the left FFA during the *part* condition, consistent with the idea that hemispheric asymmetry for face processing may, in part, be related to hemispheric asymmetry for such things as high versus low spatial frequency, spatial relations processing, and processing of global versus local characteristics.

### Interhemispheric Interaction in Visual Processing

Unified visual perception of the world around us emerges from a brain in which the left and right hemispheres make complementary contributions to such things as stimulus localization and stimulus identity. Lateralization of complementary processes to opposite hemispheres may minimize the extent to which those processes interfere with each other and thereby maximize processing efficiency. At the same time, unified perception requires that the specialized processes of the two hemispheres be integrated with each other. From this perspective, it is important to consider the various ways in which the two hemispheres interact to increase the brain's computational power.

There is rather precise division of visual projection fibers along the visual midline such that information from each visual half-field projects to opposite cerebral hemispheres. Thus, when we fixate the middle of an object, the left and right portions of the object project to the right and left hemispheres, respectively. As a result, some amount of interhemispheric collaboration is required to fuse sensory information across the cortical midline. In fact, it has been hypothesized that the initial evolutionary pressure for development of the corpus callosum had more to do with the need for sensory integration than with the need for communication between cortical areas that are involved in higher order visual processing (e.g., Aboitiz, Ide, & Olivares, 2003). However, the corpus callosum of contemporary humans mediates a variety of interactions between higher cortical areas of the two hemispheres. As well as enabling the transfer of information between the two hemispheres, the corpus callosum may permit mutual inhibition between the two hemispheres and thereby serve to reduce interfering cross talk between computations performed by homologous regions of the two hemispheres. Thus, the fact that the left and right hemispheres play different roles in processing visual stimuli has additional implications for the role of interhemispheric interaction beyond simple integration across the visual midline. This section explores aspects of such interhemispheric interaction.

As reviewed earlier, the right and left hemispheres are dominant for processing global and local aspects of visual stimuli, respectively. It is reasonable to hypothesize, therefore, that interaction of global and local information depends on efficient transfer of information between the two hemispheres. On this view, efficient interhemispheric interaction would facilitate performance when global and local information must be integrated to produce a single response but impair performance when global and local information must be kept separate. With this in mind, Robertson, Lamb,

and Zaidel (1993) compared the performance of neurologically intact individuals and commisurotomized, or split-brain, individuals in a task that required identification of either the global letter or the local letters contained within hierarchical letter patterns. They found that, when the global and local letters were different from each other, neurologically intact individuals (whose interhemispheric transfer was efficient) showed interference from incongruent information at the global level when trying to identify the local letter, but commisurotomized patients (whose interhemispheric transfer is eliminated or impaired) did not (see David, 1992, for similar results using individuals with agenesis of the corpus callosum). Christman (1995, 2001) compared performance for right-handers and left-handers, with the logic being that, relative to right-handers, left-handers both are less lateralized and show greater callosal connectivity (presumably leading to more efficient interhemispheric interaction). Observers performed tasks that either required them to integrate global and local dimensions (e.g., indicating whether the global and local letters match) or to keep them separate (e.g., identifying the local letter while ignoring the global letter). Relative to right-handers, left-handers were superior at integrating the two dimensions and impaired at keeping them separate. Similar results were obtained for Stroop-type color-word stimuli, which is interesting in view of a clear left-hemisphere superiority for word identification and hypothesized right-hemisphere superiority for color identification (e.g., Barnett, 2008). (See also Singh & O'Boyle, 2004, who used global-local processing tasks to study enhanced interhemispheric interaction in mathematically gifted adolescents compared to average-ability adolescents and college students.)

The fact that the corpus callosum and related structures permit interhemispheric interaction at many levels does not mean that such interaction occurs without cost or that it is always useful to involve both hemispheres in processing. Consider, for example, the effect of presenting redundant information to the two cerebral hemispheres. In a typical experiment of this sort the relevant visual stimulus is projected to only one visual field-hemisphere on unilateral trials. On redundant bilateral trials, two copies of the same stimulus are projected simultaneously, one to each visual field and hemisphere. To the extent that both hemispheres engage in task-relevant processing, performance should be better on redundant bilateral trials than on unilateral trials. In fact, previous visual laterality experiments show that stimulus identification is frequently better on redundant bilateral trials than on unilateral trials, suggesting contributions from both hemispheres (e.g., Baird & Burton, 2008; Hellige, 1993; Hellige & Adamson, 2007; Marks & Hellige, 1999, 2003; Mohr, Pulvermüller, & Zaidel, 1994; Roser & Corballis, 2003). One interpretation of this bilateral redundancy gain is that it reflects a race between the independent processing of the two stimuli. While versions of such a race model can account for some instances of bilateral gain, such models have a difficult time accounting for the fact that the bilateral gain is more often observed for familiar stimuli than for unfamiliar stimuli; for example, for words

but not for nonwords in a lexical decision paradigm (e.g., Mohr et al., 1994) and for familiar faces but not for unfamiliar faces (e.g., Baird & Burton, 2008; Mohr, Landgrebe, & Schweinberger, 2002). Such findings suggest that the two hemispheres collaborate to process familiar visual stimuli, perhaps because familiar (but not unfamiliar) visual stimuli come to be represented in interconnected cell assemblies that are distributed across both hemispheres, with these transcortical cell assemblies being activated more efficiently if both hemispheres are stimulated simultaneously than if only one hemisphere is stimulated (e.g., Pulvermüller & Mohr, 1996).

Recent experiments have shown that bilateral redundancy gain for familiar visual stimuli does not require physical identity of the two bilateral stimuli, though physical identity may increase the magnitude of the gain. In one such experiment, Marks and Hellige (2003) required observers to identify the numerical quantity represented by either digits or dice-like dot patterns, two stimulus formats that may lead to the same abstract numerosity code while engaging somewhat different cortical pathways along the way. They included two types of bilateral trials: same format (two identical digits or two identical dot patterns) and different format (a digit to one visual field and the corresponding dot pattern to the other visual field). Bilateral gain was robust for both format conditions, suggesting that much of the interhemispheric collaboration occurred at the level of an abstract numerosity code. At the same time, however, there was significantly less bilateral gain on different-format trials than on same-format trials, suggesting that beneficial effects of interhemispheric collaboration also occur at the level of less abstract, format-sensitive visual codes. Similar findings have been reported using identical versus different images of familiar faces on bilateral trials (Baird & Burton, 2008). Based on the fact that most callosal fibers connect homologous regions of the two hemispheres (e.g., Zaidel & Iacoboni, 2003), such results may indicate that bilateral redundancy gain is greatest to the extent that the two redundant visual stimuli are processed in homologous areas of the two hemispheres.

In order to examine the costs and benefits of interhemispheric interaction, it is also instructive to compare performance of the same task under conditions that demand interhemispheric collaboration and conditions that do not. Consider a task that requires observers to indicate that two simultaneously presented visual stimuli match each other according to some criterion. The critical comparison involves trials on which the two matching stimuli are presented to the same visual field and hemisphere (within-hemisphere trials) versus trials on which the two matching stimuli are presented to opposite visual fields and hemispheres (across-hemispheres trials). Note that on within-hemisphere trials it is possible for the single hemisphere that receives the two stimuli to determine that a match has occurred. On across-hemispheres trials, however, neither hemisphere receives sufficient information to determine that a match has occurred, necessitating interhemispheric collaboration. An important conclusion to emerge from such studies is that distributing the processing across the two

hemispheres becomes more beneficial as tasks become more complex or demanding. That is, for very simple tasks (e.g., determining whether two uppercase letters are physically identical), performance is typically better on within-hemisphere trials than on across-hemispheres trials, suggesting that the costs of interhemispheric transfer outweigh the benefits of interhemispheric interaction. In contrast, when tasks become more complex (e.g., determining whether two letters of different case have the same name), performance is typically better on across-hemispheres trials than on within-hemisphere trials, suggesting that the benefits of spreading processing across both hemispheres outweigh the costs of interhemispheric transfer (for examples and reviews, see Banich, 2003, 2004; Bayer, Kessler, Güntürken, & Hausmann, 2008; Hellige, 1993; Welcome & Chiarello, 2008; Weissman & Banich, 2000; Weissman & Compton, 2003). Dividing relevant input between the two hemispheres is also advantageous if it permits the two hemispheres to engage in mutually inconsistent visual processes (e.g., one hemisphere must match upright letters while the other must match inverted letters; e.g., Liederman, Merola, & Hoffman, 1986). Additional indications that it becomes advantageous to spread processing across both hemispheres when a task overloads the processing resources of a single hemisphere come from both computer simulations and fMRI investigations (see Monaghan & Pollmann, 2003).

Evidence reviewed earlier suggested that interference between global and local levels of hierarchical visual stimuli is generated by interhemispheric interaction. While this may be true when a single stimulus is presented separately, under appropriate conditions interference between the two levels can be reduced by spreading processing across both hemispheres. For example, Weissman and Banich (1999; see also Banich, 2003) required observers to indicate whether two hierarchical visual stimuli were identical at a specific, attended level (e.g., the global level). They varied whether the two matching items were identical at both the attended and unattended levels (consistent trials) or matched at the attended level but not at the unattended level (inconsistent trials). Global-local interference was measured as the difference in reaction time between consistent and inconsistent trials. Global-local interference measured in this manner was significantly reduced when the two matching items were presented one to each hemisphere compared to when they were both presented to the same hemisphere. Given that the matching task is more difficult for inconsistent stimuli than for consistent stimuli, these results provide another indication that spreading processing across both hemispheres is more beneficial as tasks become more difficult.

Though across-hemispheres advantages generally become more likely with increases in task complexity and task difficulty, neither complexity nor difficulty per se determines completely whether a task will sufficiently overload the resources of a single hemisphere so as to produce an across-hemispheres advantage. This is demonstrated clearly by experiments that mix stimulus formats that are processed via different cortical routes, even within a single hemisphere. For example, Patel and Hellige (2007)

required observers to indicate whether two visual stimuli represented the same numeric quantity. Matching stimuli consisted of two digits, two dice-like dot patterns, or a digit and a dice-like dot pattern (mixed-format condition). In spite of the added difficulty and complexity, the mixed-format condition produced a significant within-hemisphere advantage rather than the across-hemispheres advantage that would be expected for a task that, like name matching of different-case letters, cannot be performed on the basis of physical identity. In a second experiment, Patel and Hellige required observers to indicate whether two nonidentical matching stimuli fell into the same magnitude category: small (1, 2), medium (3, 4), large (5, 6). When the two stimuli were presented in the same visual format (both digits or both dot patterns), there was an across-hemispheres advantage for performing this abstract, magnitude category task. However, the counterintuitive within-hemisphere advantage persisted for the mixed-format condition, even though the task required a more difficult and complex decision. In considering their results, Patel and Hellige refer to the fact noted earlier that digits and dot patterns are processed via different cortical routes, even when the two stimuli are presented to the same cerebral hemisphere. This may reduce the extent to which the stimuli compete for resources on within-hemisphere trials, limiting the extent to which the benefits of spreading processing across both hemispheres outweigh the costs of interhemispheric collaboration.

Similar within-hemisphere advantages have been obtained mixing other visual formats that are known to be processed along different cortical pathways. For example, Koivisto and Revonsuo (2003) required observers to indicate whether two visual stimuli referred to objects from the same semantic category (e.g., both items of clothing). Stimuli could be either words or pictures. Of particular interest was a condition in which the two items that matched referred to different exemplars from the category (e.g., a coat and a shoe), so that there was never an opportunity to match the stimuli on the basis of physical identity. When the two stimuli came from the same visual category (both words or both pictures), there was a significant across-hemispheres advantage of the sort that has come to be expected for a complex task. However, when one stimulus was a word and the other was a picture, there was a significant within-hemisphere advantage. Similar results have been reported by Hellige, Patel, Kim, and George (2007) in experiments that required observers to indicate whether two visual stimuli referred to the same emotion, with the matching stimuli being words or cartoon faces. In the same-format condition, the matching stimuli were either two words that differed in letter case (e.g., SAD, sad) or two different cartoon faces that depicted the same emotion (e.g., two different sad cartoon faces). As expected for tasks that cannot be performed on the basis of physical identity, there were across-hemispheres advantages for these same-format conditions. In contrast, there was a within-hemisphere advantage for a mixed-format condition in which one stimulus was a word and the other was a cartoon face. As with digits and dots, there is evidence that words

versus pictures and words versus cartoon faces are processed along different cortical routes, even though they may converge on the same abstract semantic or emotional category. Thus, the extent to which multiple visual stimuli presented to the same hemisphere must compete for the same cortical route appears to be a critical factor in determining the relative costs and benefits of interhemispheric interaction. At least in the visual modality, the division of labor among more areas within a hemisphere can increase the processing capacity of that hemisphere.

### **Concluding Comments**

Research on perceptual asymmetry has a long history, at least since John Hughlings Jackson's (1874/1915) speculation that the right hemisphere is specialized for visual perception. Evidence and theoretical models for hemispheric specialization continue to expand, and interest in hemispheric specialization has not abated, even with the advent of neuroimaging techniques. On the contrary, researchers continue to find (often serendipitously) differences in activity between homologous areas of the two hemispheres for the same perceptual task or stimuli. In fact, it is clear more than ever that the two hemispheres are not simply copies or mirror images of each other, either anatomically or functionally.

It has also become clear from a growing body of animal studies and systematic findings with humans that hemispheric specializations are not the epiphenomenal result of the inability of biological systems to create perfectly symmetrical bodies and organs. In fact, hemispheric specializations are likely to have been shaped by evolutionary processes so as to promote a modular organization of perceptual and cognitive functions. Adaptive design does not, however, deny the influence of various epigenetic factors, and, as we discussed, several hemispheric specializations may have originated from developmental "seeds" that predispose, channel, or bias, more than they determine, a final design for the neural architecture.

Science has an ambivalent attitude toward dichotomies. Many theoretical accounts pit one of two things against the other, only later to complain that the endeavor was too simplistic (cf. Allan Newell; see Kosslyn, 2006). The history of research on hemispheric specializations has been particularly dominated by dichotomies, and, indeed, many of them have turned out to be too simplistic, too vague, or just not supported by the data. Nevertheless, some of the left-right dichotomies have endured the scrutiny and have appeared to capture some underlying differences in hemispheric function that are reliable and robust. For example, the distinction between categorical and coordinate spatial functions offers an excellent example of a perceptual asymmetry that is replicable at the empirical level and theoretically grounded (in cognitive and computational accounts) without simply being a redescription (in "technical" terms) of the very results.

In the end, our prediction is that research on hemispheric specialization and interhemispheric interaction will continue to thrive, despite the fact that current neuroimaging techniques allow functional localization on a spatial scale that is so precise that the distinction in left-right function may simply look too coarse to be of any neurobiological meaning. The reason we eschew such a skeptical view is simply that, no matter how small or precisely we will define any neural functional structure, there will always exist a basic neurobiological fact: Any patch of neural tissue exists necessarily in two versions, one in the left and one in the right hemisphere, and their functions turn out to differ with too much frequency and reliability to be ignored.

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## **14 Integrating Auditory and Visual Asymmetry**

**Heikki Hämäläinen and Fia Takio**

In this chapter we propose that the spatial perceptual and attentional capacity of a normal, healthy human is biased to the right. This phenomenon is seen in its severest form as hemispatial neglect and/or extinction after right parieto-temporo-frontal disorders/lesions. We present tentative evidence that this bias is multimodal, covering at least the auditory and visual space, and that it is mainly present in childhood and in old age, but not in young adulthood and middle age, when the frontal executive functions work at their best. Thus, we propose that the early developing asymmetry in cognitive abilities is balanced by later developing executive functions, or cognitive control. The asymmetry again becomes evident in old age with the decline of executive functions (cf. Hugdahl, Westerhausen, Alho, Medvedev, Laine, & Hämäläinen, 2009).

### **Asymmetry and Age**

#### **Development of Asymmetry**

Is hemispheric asymmetry hardwired with predetermined maturation, or does it develop as a function of nature and/or nurture? The steps of the development of asymmetry in our cognitive skills are still far from being well described and even further from being understood. Boles, Barth, and Merrill (2008) present three different viewpoints on maturation and development, the nature versus nurture discussion about hemispheric asymmetry. According to the invariant viewpoint, lateralization emerges in the same way for every normally developing individual and is complete by the end of infancy. Thus, lateralization according to this view is “fixed” rather than “progressive” (Bryden 1982). The progressive viewpoint states, in contrast, that lateralization develops over time. According to Lenneberg (1967), the hemispheres are equipotential in infancy but are lateralized by age 11 to 14. As a new viewpoint, Boles et al. (2008) propose the modular view, according to which brain lateralization is subject to modification by both experience and maturation and can take different courses in different individuals, thus producing individual differences in lateralization.

The brain develops on a modular basis, with some processes lateralizing at later developmental periods than others. The timing of this development follows the maturation and plasticity of the corpus callosum during development (Boles et al., 2008).

Boles et al. (2008) propose that “the relation between lateralization and performance, while orderly, is complex” (p. 124). Empirical data on this question are also sparse. The modularity hypothesis by Boles et al. (2008) claims that individuals differ in the timing of the maturation of their corpus callosum, and this is reflected in the lateralization. The corpus callosum and its impact on interindividual differences in dichotic listening (DL) have recently been thoroughly discussed by Westerhausen and Hugdahl (2008).

### What Is Asymmetrical?

#### Head Turn and Involuntary Attention

We are born asymmetrical at least in terms of our head-turn preferences. If human newborns are placed in a supine position, approximately 80% exhibit a head-turning preference to the right (Turkewitz, Gordon, & Birch, 1965). Ginsburg, Fling, Hope, Musgrave, and Andrews (1979) demonstrated, first of all, that 69 of 88 infants tested during the first 2 to 8 weeks of life exhibited a right-head-turning preference. In the second study, they showed that 60 of 78 full-term neonates showed a consistent directional preference when tested during the first 48 hours after birth, and in further tests on 54 showing consistent preference, 37 showed a preference to turn the head to the right and 17 to the left. This finding has since been confirmed at least by Rönnqvist and Hopkins (1998), who found the same preference in newborns in a quiet awake state and without any interfering stimuli.

What is being measured with the head turn by the infants? The head-turn method applied by Ginsburg et al. (1979) and many others detects the turning of the head as a consequence of an unexpected event in the environment evoking involuntary attention. Therefore, we may conclude that involuntary, stimulus-driven attention mechanisms are already biased to the right in the newborn infants. It is very interesting that the disorders of apparently the same mechanism, the parietofrontal stimulus-driven attention mechanism (Corbetta & Shulman, 2002; Corbetta, Patel, & Shulman, 2008), allowing involuntary attention focusing to unexpected alerting events in the environment, manifests itself at later stages as unilateral (left) neglect following brain injury.

#### Motor Biases

Motor biases have been targeted in the series of studies by some research groups. Corbetta and Thelen (1996, 1999) report on a follow-up study of four infants during the first year of their lives: No stable pattern of preference in spontaneous movements or reaching was to be observed, but all infants showed a short period of right-sided

preference during the first year. These temporary right-side biases were found to be matched with a right-sided preference at 3 years of age (Corbetta & Thelen, 1999). Rönnqvist and Domellöf (2006) conclude that motor biases to prefer the right arm in reaching can be observed early, but this only later develops into hand preference via the developing of contralateral neural mechanisms for motor control. Domellöf, Rönnqvist and Hopkins (2007) studied the stepping responses in newborns via kinematic registrations. The findings suggest that asymmetries in newborn stepping responses are present in terms of spatiotemporal parameters and intralimb coordination. No evidence of a lateral preference in terms of frequency of the first foot moved was found. Therefore, it may be concluded that a functional asymmetry exists at a more proximal body level during early stages of development, which then develops, according to the early preference, into a finer-tuned right-side preference, emerging in right-handedness (Domellöf et al., 2007).

### **Spatial Perception**

Concerning cognitive skills related to auditory and visual space, there are relatively few studies on these more cognitive functions involving cognitive control. Boles et al. (2008), in their important review on emergence of asymmetry and development of performance level, proposed that auditory linguistic (dichotic) skills show the first signs of asymmetry already during the first few years after birth (see Hiscock, 1988). Thereafter, visual spatial quantitative processes seem to develop early, the first signs of asymmetry being seen at the age of five, when planar categorical processes also begin to show signs of asymmetry. In contrast, spatial positional processes including spatial working memory (WM), seem to develop far later (see Boles et al., 2008, for a review). At brain level the asymmetry is just developing in the sense that the asymmetry of the different functions is not yet hardwired. To summarize, it is evident that many involuntary and voluntary functions show emerging asymmetry. Interestingly, both involuntary attention (head turn) and DL already show asymmetry very early, whereas motor reactions and simple visuospatial tasks take longer to show signs of asymmetry, and finally, more difficult tasks requiring WM develop, also asymmetrically, far later.

### **Asymmetry of Perception and Attention Observed in Adults**

There are no reports on the lateral bias and asymmetry of capacity of young, healthy adults in spatial auditory and visual (nonlinguistic) perception. In tactile modality and body scheme, there are some examples of lateralization of stimulus detection in the left or right hemispace, and usually related to motor response to the detected stimulus. Bradshaw, Nathan, Nettleton, Pierson, and Wilson (1983) showed that indeed it is not the limb but the position of the limb in the personal hemispace that matters. In healthy dextrals, there is no difference in simple reaction times (RTs) between the two

hands in general (pressing a button with the thumb when feeling a vibration transducer on the adjacent finger). However, RTs of either hand were, on average, 9 milliseconds faster when the hand was in the right hemispace. This right-side advantage (RSA) appeared to be dependent on head and body coordinates (Bradshaw et al., 1983). Eimer, Cockburn, Smedley, and Driver (2001) demonstrated, with event-related potentials (ERPs), an interesting cross-modal interaction between spatial attention and "common external locations" (hands crossed or noncrossed) instead of hemispheric projections. More severe examples of the significance of the hemispace, where, for example, the upper limb is positioned, come from neurological patients with hemispatial neglect (Pierson-Savage, Bradshaw, Bradshaw, & Nettleton, 1988; Smania & Aglioti, 1995; Aglioti, Smania, & Peru, 1999), who show improved tactile sensitivity of the neglected left hand when crossing the arm to the right hemispace. Spinelli and Di Russo (1996) have also shown in left hemispatial neglect patients that trunk rotation to the left shortened the previously lengthened P100 latencies of visual-evoked potentials to left visual field stimulation.

The most dramatic examples of the asymmetry of perceptual–attentional–awareness systems are unilateral neglect and extinction (see Driver & Vuilleumier, 2001, for a review). The neglect may cover the patient's own body and/or near and far space (Robertson, 1999; Lindell, Jalas, Tenovuo, Brunila, Voeten, & Hämäläinen, 2007), and on many occasions it covers more than one modality (visual, auditory, tactile; Hämäläinen, Pirilä, Lahtinen, Lindroos, & Salmelin, 1999). Its core mechanism is located within the right parietotemporal junction (Vallar, 1998) and right ventral frontal areas (Corbetta et al., 2008). Studies applying ERP measurements have indicated that the basic mechanism disturbed in neglect is the arousal–alertness system underlying involuntary attention switch (Hämäläinen et al., 1999; Deouell, Hämäläinen, & Bentin, 2005; Robertson, Mattingley, Rorden, & Driver, 1998). Consequently, the hemispheric asymmetry in attention mechanisms has been demonstrated by virtual neglect produced by transcranial magnetic stimulation (TMS), with special reference to left-frontal stimulation as modulator of unilateral extinction (e.g., Oliveri, Rossini, Traversa, Cicinelli, Filippi, Pasqualetti, Tomaiuolo, & Caltagirone, 1999). Recently, the right hemisphere parietofrontal network responsible for involuntary attention switch has been described (Corbetta & Shulman, 2002; Corbetta et al., 2008). This system seems to be essential for stimulus detection and awareness, and disturbances of this system, either by natural lesions or virtual lesioning via TMS, will cause perceptual abilities to be limited to the right hemispace in a total (neglect) or in a bilateral stimulus condition (extinction).

### **Executive Functions: Slow Early Development and Equivocal Late Decline**

As a function of the parallel cognitive and neural development in childhood and adolescence, improving performance in, for example, visuospatial WM tasks

has been documented in several studies (Hale, Bronik, & Fry, 1997; Gathercole, Pickering, Knight, & Stegmann, 2004). The performance on WM tasks requiring simple maintenance of visuospatial information shows rapid development until the age of 8 years, after which the development up to 11 to 12 years of age is slower. However, the executive WM takes a longer time to develop (Gathercole, 1999). Thus, the functional maturation of basic perceptual and sensorimotor skills in WM takes place earlier, whereas the neurocognitive maturation of more complex aspects of WM function takes a longer time (Luciana, Conklin, Hooper, & Yarger, 2005).

Age-related development of WM has been connected to changes in, for example, the capacity of processing, storage, and attentional functions (Hulme, Thomson, Muir, & Lawrence, 1984; Gathercole, 1999). Cumulative evidence from recent neuropsychological studies indicates that the development of WM continues to adolescence, and a mature level of complex WM function is reached approximately at the age of 15 to 19 years (Luna, Garver, Urban, Lazar, & Sweeney, 2004; Luciana et al., 2005; Huizinga, Dolan, & van der Molen, 2006). Finally, the age-related increase in WM capacity was associated with increased activity in the prefrontal cortex and in the posterior parietal cortex (Klingberg, Forssberg, & Westerberg, 2002). These areas constitute the right-hemisphere visuospatial attention system involved in visuospatial WM (Kwon, Reiss, & Menon, 2002).

The dominant theory of cognitive aging in the 1980s proposed the general slowing of information processing in the brain as the core reason for deficits in memory and reasoning (e.g., Cerella, 1985; Salthouse, 1985). Thereafter, the focus has been on the role of frontal-executive processes in explaining the cognitive changes with age (e.g., West 1996). The frontal lobe theory of aging proposes that early, localized changes in the frontal lobes of the brain are associated with deficits in executive control processes (Mittenberg, Seidenberg, O'Leary, & DiGiulio, 1989; West, 1996; Troyer, Graves, & Cullum, 1994). The key issue is that the effects of aging should parallel the effects of focal frontal damage. In general, patients with frontal lobe damage tend to show deficits in executive functions, working memory, emotional control, and behavioral self-regulation (Stuss & Levine 2002).

However, there is relatively little evidence that neural changes in the frontal lobes correlate with executive decline in old age. As a matter of fact, the recent review by Hedden and Gabrieli (2004) states that cognitive changes are related to their neural substrates, including structural and functional changes not only in the prefrontal cortex but also in the medial temporal lobe regions and in the white matter tracts. Longitudinal comparisons (Schaie, 1996; Zelinski & Burnight, 1997) reveal that age-related changes in cognition from ages 20 to 60 are almost nonexistent, with speed of processing showing the largest change. However, changes after the age of 60 show a more rapid decline (Schaie, 1996; Zelinski & Burnight, 1997). Thus, there is a need

to substitute the general frontal hypothesis with a more refined analysis of changes in subregions within the prefrontal cortex (Tisserand & Jolles, 2003).

A recent study by Thomsen, Specht, Hammar, Nytingnes, Ersland, and Hugdahl (2004) demonstrated that the old (53–63 years of age), in contrast to the young (19–34 years of age) participants, failed to monitor voluntarily, that is, to attend to the left-ear stimuli in the Bergen DL test (Hugdahl & Andersson, 1986). This decline in voluntarily attending to the left-ear syllables, and thus being able to repeat them, was further shown to correlate with left prefrontal structural and functional changes in the old participants and was interpreted as reflecting a decline of frontal executive functions (Thomsen et al., 2004), that is, cognitive control (Hugdahl et al., 2009).

### **Findings from Dichotic Listening Studies**

The DL task, widely applied in studies of hemispheric asymmetry, in its present form is based on consonant–vowel syllables (e.g., BA, DA). This means that it is a linguistic task, and it can be described as interaction between bottom-up and top-down processes. The right-ear advantage (REA) in the nonforced (NF) condition can be interpreted as a stimulus-driven, bottom-up process due to the direct projection of the right-ear stimulation to the auditory and speech areas of the left hemisphere (see Hugdahl et al., 2009, for a review). When the participant is asked to actively monitor the right ear in the forced-right (FR) condition (Hugdahl et al., 2009), the bottom-up (stimulus-driven) and top-down (executive) processes work synergistically, producing a stronger REA than in the neutral NF condition. However, when the subject is asked to monitor the left ear in the forced-left (FL) condition, the bottom-up and top-down processes are in contradiction, the top-down process trying to resist and redirect the bottom-up process, that is, the REA. In young adults this results in an REA decrement and even a slight left-ear advantage (LEA). The LEA is not a mirror image of the REA seen in NF or FR, however, because of the aforementioned contradiction between stimulus-driven processes and executive functions (see Hugdahl et al., 2009).

As shown by Thomsen et al. (2004), the ability to resist the REA and voluntarily monitor the left ear declines with age because of the changes in top-down cognitive control mechanisms (Hugdahl et al., 2009). Interestingly, the performance of the seniors in the FL condition drops back to the level typical for children (Hugdahl et al., 2001; Hugdahl, 2003), and more careful comparisons have recently shown that the performance of 59- to 79-year-old seniors is at the level of 10- to 11-year-old children (Takio et al., 2009). As a matter of fact, the DL task and especially the FL condition have been shown to be a sensitive measure of neurocognitive plasticity. It has been demonstrated to be sensitive to, for example, interindividual differences induced by early blindness (Hugdahl, Ek, Takio, Rintee, Tuomainen, Haarala, & Hämäläinen, 2004) and special spatial auditory skills (Milovanov, Tervaniemi, Takio, & Hämäläinen, 2007), reflecting the usage and training of the spatial auditory system.

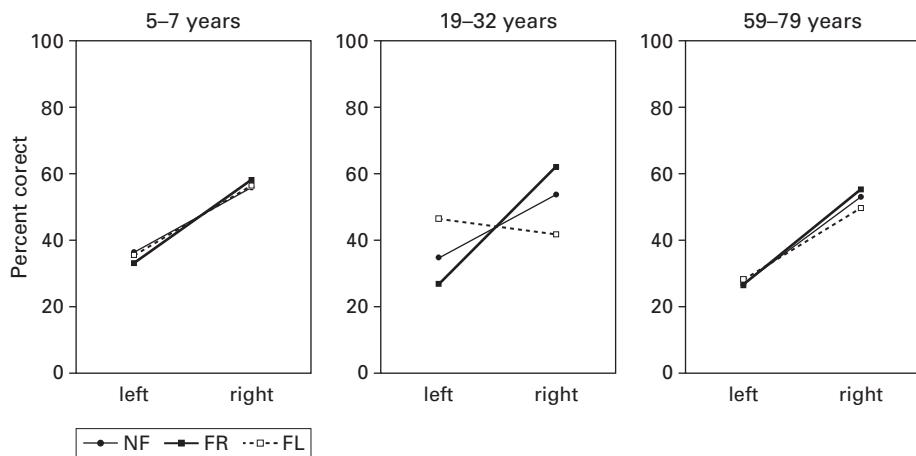
### Effect of Age on Auditory and Visual Spatial Perception

We here describe some results of a series of studies targeting the DL, as well as further linguistic and nonlinguistic auditory and visual spatial perception–attention abilities of different age groups. The groups participating in the studies are 5- to 7-year-old children ( $N = 29$ ) at the preschool stage, young adults of 19 to 32 years of age ( $N = 50$ ), and seniors of 59 to 79 years of age ( $N = 40$ ). Our aim is first of all to demonstrate the effect of a DL performance, that is, the early development and late decline of the ability to resist REA in the FL condition (the relative strength of the top-down process over the bottom-up stimulus-driven process; Hugdahl et al., 2009) in our different age groups (Takio et al., 2009). Thereafter, we show that among the same three age groups, mainly the children and the old adults show lateral bias in their performance in the auditory linguistic and nonlinguistic spatial perception–attention tests, this lateral bias also being detected in corresponding visual tasks. Furthermore, we demonstrate that this bias is evident as a tendency toward a right stimulus detection/response preference in a bilateral stimulus condition, mimicking the neglect-related extinction-type bias in normal, healthy participants. This result is interpreted as reflecting the prewired RSA in humans, balanced by the late developing executive (prefrontal) functions, which again deteriorate as a function of aging. This series of studies forms the doctoral dissertation of Fia Takio, the results presented being based on DL results (Takio et al., 2009) and preliminary analyses of part of the auditory and visual spatial performance data to be published.

#### Dichotic Listening

The Finnish version (Tallus et al. 2007; Takio et al., 2009) of the DL test (the original “DLCV-108” DL test by Hugdahl & Andersson, 1986) was applied. All three groups showed clear-cut REA in the NF and FR conditions (see figure 14.1; for details, see Takio et al., 2009), but the older adult participants had fewer correct left-ear responses in the NF condition than the other groups. Interestingly, for the children and the older adult participants, the REAs found in the FR condition were not modified by attention. The young adults were the only ones who were able to strengthen the REA with attention in the FR condition, as the number of right-ear correct responses increased and the number of left-ear correct responses decreased. Moreover, there was a distinct difference between the young adults and the other groups in the FL condition. Only the young adults were able to monitor the left-ear stimuli to some degree.

The typical response patterns are also demonstrated by the scatter plots (see figure 14.2). In the FL condition, the children as well as the old participants showed the same kind of response pattern as in the NF and FR conditions, even though they were instructed to focus their attention toward the left ear. Only the young adults were able to reverse the response pattern according to the instruction in the FL condition:



**Figure 14.1**

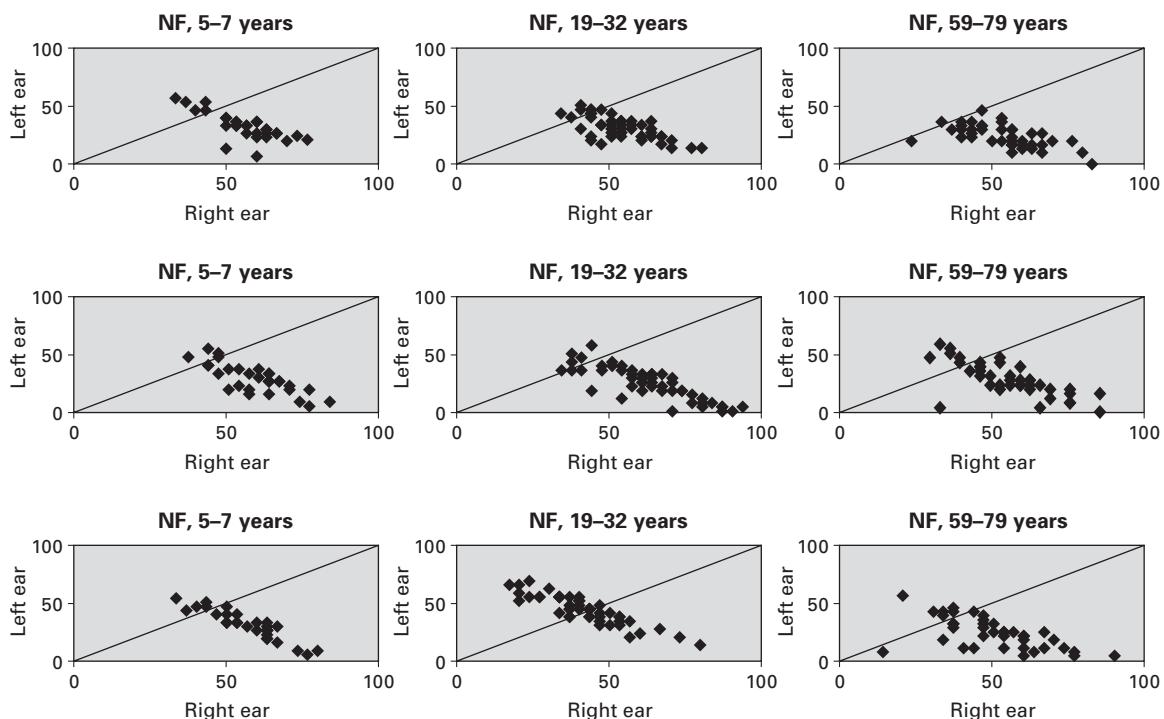
Dichotic listening task. Percentage of correct reports to the left- and right-ear stimuli in nonforced (NF), forced-right (FR), and forced-left (FL) attention conditions by the different age groups.

They were able to report numerically, though not significantly, more correct reports from the left ear (46%,  $SD = 11.69$ ) than from the right ear (42%,  $SD = 13.18$ ). Thus, they were the only group able to focus the attention to the left-ear stimuli and/or inhibit the stimuli delivered to the right ear, thus reducing the REA. This response pattern was not the mirror image of the NF or FR conditions (see, e.g., figure 14.2, the scatter plot diagram), thus indicating the strength of the bias to catch the right-ear stimuli even in this situation.

#### Auditory Spatial Selective Attention

Voiced digits from 1 to 9 for the adults and the names of nine different animals for the children were presented via standard headphones randomly to the left, the right (nondichotic), or both ears (dichotic) simultaneously. The difficulty level of the tasks was controlled by varying the number of target digits and the interstimulus interval (ISI). The participant's task was to press the Z and X keys of the computer keyboard as fast as possible with the left and/or right forefinger, respectively, when he or she perceived the target as coming to the left or right ear, or both ears simultaneously. We report here the results from the selective attention task with an ISI of 200 to 1,000 milliseconds and four targets condition. The data were statistically evaluated by a general 3 (age groups: 5–7, 19–32, 59–79)  $\times$  3 (ear: right, left, both) analysis of variance (ANOVA).

The number of correctly detected targets (see figure 14.3a) was highest in all groups when stimuli were delivered monaurally, and the best overall performance was found

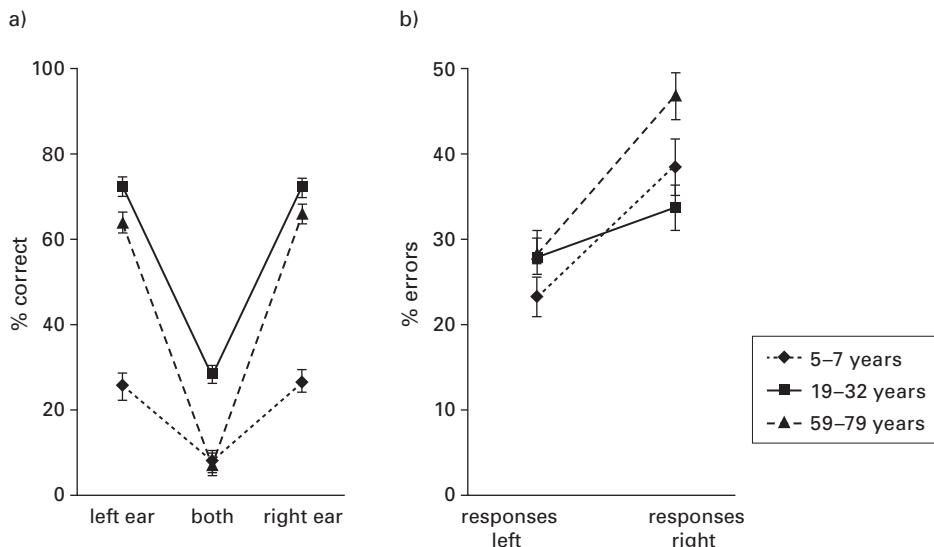


**Figure 14.2**

Dichotic listening task. Distribution of individual performances in the three age groups, separated according to the three attention conditions: nonforced (NF), forced-right (FR), and forced-left (FL). In the scatter plots, right ear stands for the percentage of right-ear correct responses and left ear stands for the percentage of left-ear correct responses. The dots represent the performance of individual participants. The dots below the diagonal trajectory represent a right-ear advantage, and those above the diagonal trajectory represent a left-ear advantage.

among the group of young adults. The performance by the seniors was at a clearly lower level than that of the young adults, while the poorest performance was obtained by the children. No lateral bias was found in children and young adults. In contrast, the old participants' group detected best (hits) the right-ear targets, then the left-ear, and worst the bilaterally presented targets ( $p < .05$ ). In other words, the older participants preferred the right side in unilateral target conditions. The performance of the seniors and the children in the bilateral (dichotic) stimulus condition was at the same level.

When further analyzing the errors (see figure 14.3B) made by the participants in the bilateral-dichotic stimulus condition, that is, when responding only with a left or right button press instead of pressing both simultaneously, a curious phenomenon



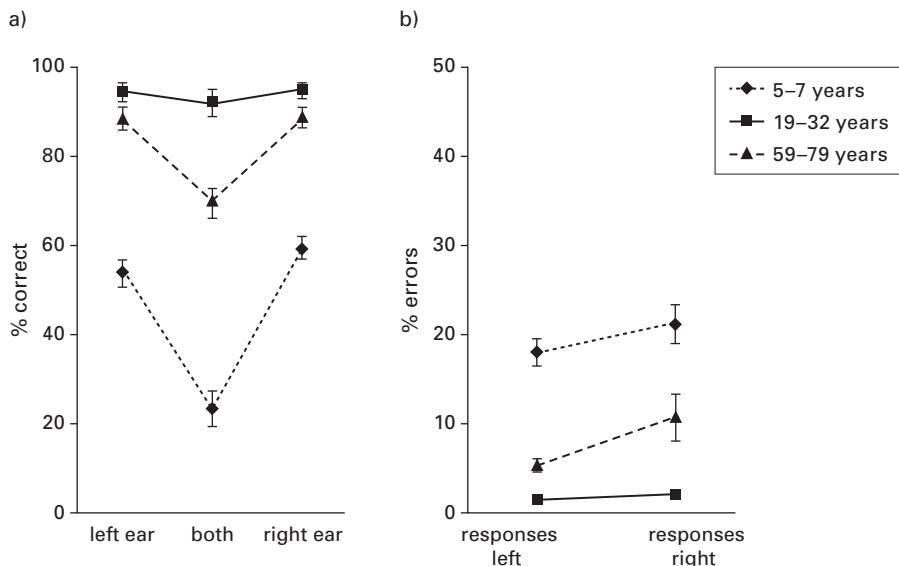
**Figure 14.3**

Auditory selective attention task (interstimulus interval = 200–1,000 milliseconds, four targets). (a) Percentage of correct reports to the left ear, the right ear, and the binaural stimuli by the different age groups. (b) Binaural stimulus condition. Percentage of errors made in binaural stimulus condition (i.e., responses only with right or left button) by the different age groups. The vertical bars represent the standard error of the mean.

emerged. All age groups preferred to more often press the right button only as their response. Furthermore, there was a significant difference between the two adult groups. As shown in figure 14.3b, the old participants preferred responding with the right-side button more than did the young adults ( $p < .005$ ; left:  $p = \text{n.s.}$ ). There was no difference between the children and the young adults. In other words, all age groups tended to show signs of extinction, that is, biased detection of the right-side stimuli in this linguistic task when stimuli were presented bilaterally, but this bias was strongest in the old participants.

#### Auditory Spatial Divided Attention

The auditory spatial divided attention test was the same for children and adults: sinusoidal tone pips were presented via standard headphones to the left, the right, or both ears simultaneously. The task consisted of two difficulty levels, determined by the ISI. The procedure was otherwise the same as in the auditory spatial selective attention tasks. We report here the results from the 1,000-millisecond ISI condition. The data were statistically evaluated by a general 3 (age groups: 5–7, 19–32, 59–79)  $\times$  3 (ear: right, left, both) ANOVA.



**Figure 14.4**

Auditory divided attention task (interstimulus interval = 1,000 milliseconds). (a) Percentage of correct reports to the left ear, the right ear, and the binaural stimuli by the different age groups. (b) Binaural stimulus condition. Percentage of the errors made in binaural stimulus condition (i.e., responses only with right or left button) by the different age groups. The vertical bars represent the standard error of the mean.

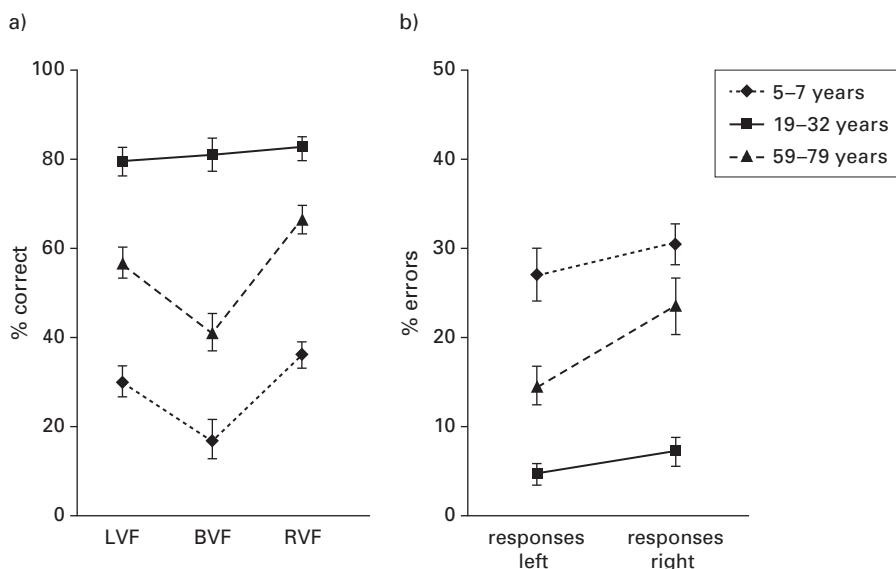
The young adults were the most accurate group (over 90% correct detections for the hits to the left, right, and binaural stimuli), and no difference in this simple, nonlinguistic divided attention task was seen between detection of monaural or binaural stimuli (see figure 14.4a). The older group's performance was poorer than that of the young adult group, and the children's performance was the poorest compared with the other two age groups ( $p < .001$ ). Furthermore, only children performed differently in the three stimulus conditions. The children had the most hits to the right-ear stimuli, then to the left-ear stimuli, and the least to the binaural stimuli ( $p < .05$ ). In other words, in the auditory spatial divided attention task with nonlinguistic stimuli, the young children showed a lateral bias toward the right side.

The error analysis (see figure 14.4b) of the binaural stimulus condition revealed that all age groups more often pressed only the right button when making a wrong response to the binaural stimuli. This side difference was significant ( $p < .05$ ) for all age groups, with the 5- to 7-year-olds making the most errors and the 19- to 32-year-olds making the fewest errors.

### Visual Spatial Selective Attention

The visual spatial selective attention test mimicked the corresponding auditory paradigm: Digits from 1 to 9 for the adults and pictures of animals for the children were presented with a data projector to the left (LVF) and/or right (RVF) visual fields on a dark background. A single digit-animal figure was projected at a horizontal visual angle of 30° to the right and/or left of the fixation point measured from the center of the fixation point to the nearer edge of the stimulus. The difficulty level of the tasks was varied by the number of targets and the stimulus onset asynchrony (SOA). We report here the results from the 300- to 800-millisecond SOA and four-target condition. The data were statistically evaluated by a general 3 (age groups: 5–7, 19–32, 59–79) × 3 (visual field: right, left, both) ANOVA.

The young adults performed best and the children most poorly in the visual spatial selective attention task (see figure 14.5a). The young adults' performance was the most alike, regardless of the stimulus condition. The old participants' group had the most correct responses to the right-side targets, and the fewest to



**Figure 14.5**

Visual selective attention task (stimulus onset asynchrony = 300–800 milliseconds, four targets). (a) Percentage of correct reports to the left visual field (LVF), the right visual field (RVF), and the bilateral visual field (BVF) stimuli by the different age groups. (b) Bilateral stimulus condition. Percentage of errors made in the bilateral stimulus condition (i.e., responses only with right or left button) by the different age groups. The vertical bars represent the standard error of the mean.

the bilateral targets ( $p < .05$ ). The children made fewer correct reactions to the bilateral targets than to the unilateral targets ( $p < .001$ ), but there was no difference between the number of correct responses to the right and left visual field unilateral targets.

The error analysis (see figure 14.5b) in the bilateral stimulus condition revealed that all age groups more often preferred to press the right button only. There was a significant difference among all the age groups; the children had the most and the young adults the fewest unilateral reactions to the bilateral visual stimuli ( $p < .001$ ). As shown in figure 14.5b, there was no difference between children and seniors in right-side reactions ( $p = n.s.$ ). Thus, all age groups tended to show signs of extinction, that is, biased detection of the right-side stimuli when stimuli are presented bilaterally, but the bias was again strongest in the old participants.

### **Visual Spatial Divided Attention**

In the visual spatial divided attention test, dots of light were presented with a data projector to the LVF and/or RVF in white on a dark background. A single dot of light was projected at a horizontal visual angle of 30° to the right and/or left of the fixation point. The visual spatial divided attention test consisted of two tasks which differed in the difficulty level according to the SOA. We report here the results from the 750-millisecond SOA condition. The data were statistically evaluated by a general 3 (age groups: 5–7, 19–32, 59–79)  $\times$  3 (visual field: right, left, both) ANOVA.

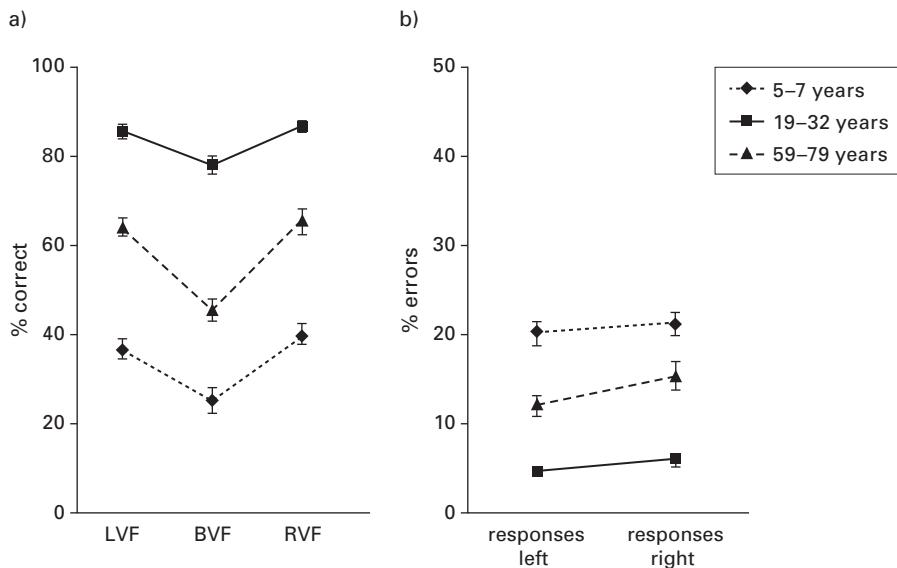
In this visual spatial divided attention task (see figure 14.6a), the similar type of pattern of responses was seen again: The three groups' performances were just as in previous tasks, the young adults obtaining the best score, and the children the poorest ( $p < .001$ ). There were no apparent side preferences in the correctly detected stimuli in any of these age groups, and the bilateral visual stimuli were the most poorly detected in all of them.

The error analysis (see figure 14.6b) in the bilateral stimulus condition showed a significant group difference ( $p < .001$ ); the children made the most and the young adults the fewest errors. All age groups tended to show biased detection of and responding to the right-side stimuli when stimuli were presented bilaterally ( $p < .005$ ).

## **Conclusions**

### **Spatial Right-Side Advantage**

The first finding in our studies was that the DL performance in the FL condition, the ability to voluntarily resist the REA and monitor the left-ear syllables, was only successful among the young adults. In contrast, both the 5- to 7-year-old children and the 59- to 79-year-old senior participants were unable to master this task. This inabil-



**Figure 14.6**

Visual divided attention task (stimulus onset asynchrony = 750 milliseconds). (a) Percentage of correct reports to the left visual field (LVF), the right visual field (RVF), and the bilateral visual field (BVF) stimuli by the different age groups. (b) Percentage of errors made in bilateral stimulus condition (i.e., responses only with right or left button) by the different age groups. The vertical bars represent the standard error of the mean.

ity was accompanied by a more general spatial RSA in the erroneous responses to binaural stimuli both in the auditory linguistic selective attention task and in the auditory nonlinguistic divided attention task, mainly by the old persons and the children. Finally, we demonstrated that the same type of RSA could also be noticed in the visual selective attention (linguistic) task, while this side preference was still present in the visual spatial divided attention (nonlinguistic) task.

### Right-Side Advantage and Extinction

In all these tasks covering the two modalities and linguistic as well as nonlinguistic stimuli, the RSA did not emerge as just preference of the right ear or visual field and/or neglect of the left ear or visual field. Instead, it emerged most distinctively in bilateral stimulus conditions as occasional erroneous responses with just the right-hand key press. This phenomenon mimics the neglect-related extinction typical of patients suffering from right-hemisphere lesions and occurring in auditory, visual, and tactile modalities (see above). It has been strongly linked with P1 and N1 components in corresponding modality-specific ERPs in neglect and extinction patients (Hämäläinen

et al., 1999; Marzi, Girelli, Miniussi, Smania, & Maravita, 2000; Eimer, Maravita, Van Velzen, Husain, & Driver, 2002). Interestingly, these same ERP components have been shown to be essential for stimulus awareness in normal healthy participants (Koivisto, Revonsuo, & Lehtonen, 2006; Schubert, Blankenburg, Lemm, Villringer, & Curio, 2006).

Thus, we may conclude that there is a predominantly extinction type of perceptual–attentional bias in the 5- to 7-year-old children, and even more in 59- to 79-year-old seniors, a bias that is multimodal and independent of the possible linguistic nature of the stimuli. It should be remembered that the DL task is a binaural dichotic task, and the REA noticed there may also be interpreted as extinction. Young adults, in contrast, do not show these features in their performance to the same degree as the two extreme age groups, although in some of the tasks a slight RSA could also be observed among the young adults.

### Executive Functions

The asymmetry of DL performance is one of the earliest cognitive functions to lateralize (Boles, 1996, 1998) and thus is well developed by the age of 5–7. Presumably, not many further changes in this basic asymmetry take place later in life, although this cannot be absolutely ruled out. Then why are the young adults able to resist REA in contrast to children and seniors?

The recent studies by Thomsen et al. (2004), Andersson, Reinvang, Wehling, Hugdahl, and Lundervold (2008), and Takio et al. (2009) demonstrate that the older (50–79 years of age) participants fail to monitor the left-ear stimuli in the FL condition of the DL test, and thus to resist the REA seen in NF and FR conditions. As a matter of fact, Takio et al. (2009) have shown that the performance level of the old participants drops back to that shown by 10- to 11-year-old children. The disruption of ear advantage in general has been demonstrated in left, but not in right, frontal lobe patients (Hugdahl, Bodner, Weiss, & Benke, 2003). In particular, the decline in REA resistance in the FL condition has been shown to correlate with left prefrontal structural and functional changes in the old participants (Thomsen et al., 2004) and has been interpreted as reflecting the failure of executive functions, that is, cognitive control (Hugdahl et al., 2009).

As reviewed by Boles et al. (2008), the asymmetry of visual processes develops early, the first signs of asymmetry being noticeable at the age of 5 years. However, asymmetry of spatial positional processes including spatial WM develop far later. Our results concerning the lateral bias, demonstrated by the 5- to 7-year-old children, are most unequivocal in the DL task, are also evident in other auditory spatial attention tasks, and even present in corresponding visual tasks. These findings fit nicely into the schedule for the development of asymmetry in different types of perceptual skills, reviewed by Boles et al. (2008). Based on their suggestions, we may hypothesize that

the DL asymmetry shown by our 5- to 7-year-old children coincides with the well-matured asymmetry in dichotic linguistic tasks evident already very early. Since the visual spatial positional processes, apparently loading the visual WM, require a more mature level to emerge, it is not surprising that the 5- to 7-year-old children in our study did not show much lateral bias in their performance on the visual spatial tasks. As far as we know, there are no corresponding data on the maturation of the spatial auditory skills. We may, however, hypothesize that the maturation and emergence of their asymmetry may emerge somewhere between the dichotic auditory–linguistic and visual spatial skills, thereby resulting in the stronger bias in auditory than in visual spatial skills seen in our results.

The last to mature are the executive functions (Luna et al., 2004; Luciana et al., 2005; Huizinga et al., 2006), which are thus not available to the 5- to 7-year-old children to balance the perceptual bias. As a matter of fact, the results by Takio et al. (2009) on the changes in DL performance at different ages suggest that the ability to resist REA in the FL condition in the DL task begins to emerge from the age of 10 to 11 years on. Thereafter, one should see the balancing of the lateral bias in auditory and visual perception, as evident in young adults. And, as shown in the figures above, the bias emerges again in the DL, as well as in auditory and visual spatial perceptual abilities, as a function of aging, and as a function of decline in executive functions (Thomsen et al., 2004; Hugdahl et al., 2009).

### **Right-Side Advantage and Hemispheric Asymmetry**

The most straightforward explanation—and the most often heard question or comment by the audience in symposia—for this RSA phenomenon is the right-handedness of our participants. This, however, is too vague an explanation, since the young adults do not show the RSA. Or perhaps the young adults can inhibit the handedness effect, unlike the seniors. In the latter case again, declining cognitive control, that is, executive functions (cf. Thomsen et al., 2004; Hugdahl et al., 2009) could be blamed for the inability to inhibit the response.

The explanation lies, however, not solely in hand preference and its inhibition. Instead, a hardwired right-hemisphere/right-side preference can be proposed as an explanation. Proverbio, Zani, Gazzaniga, and Mangun (1994) have demonstrated that a split-brain patient, in contrast to normal controls, shows a strong rightward attentional bias. This bias was seen as the shortest RTs and the largest P300 ERP potentials, reflecting processing speed and stimulus detection, respectively, to visual stimuli falling into the rightmost visual field. They further showed that the right hemisphere has bilateral control over the visual space, while the spatial orienting capability of the left hemisphere is biased toward the contralateral visual hemifield (Proverbio et al., 1994). These findings unequivocally demonstrated the visual spatial attentional-perceptual bias, based on hemispheric functional asymmetry. We propose that the

auditory and visual RSA in children and seniors originates from this mechanism. The role of the developing corpus callosum as a mediator of sensory information processing, and the later ability to voluntarily direct attention (Westerhausen & Hugdahl, 2008), appears very interesting in this context. The findings by Proverbio et al. (1994) fit well the models of spatial attention based on both experimental work and clinical studies on neglect and extinction (Oliveri et al., 1999; Driver & Vuilleumier, 2001; Corbetta & Shulman, 2002; Corbetta et al., 2008).

Thus, if the basic spatial attention mechanism is asymmetrical and biased to the right, then what explains the RSA in children and in seniors but not in young adults? In children, we propose the model of early maturation of spatial perceptual WM asymmetry, not yet balanced by the later development of frontal executive functions. Since the pioneering study by Thomsen et al. (2004), the candidate for the changes in the elderly in the DL REA (cf. Hugdahl, 2003; Hugdahl et al., 2009; Takio et al., 2009) and the more general multimodal RSA is the frontal executive mechanisms. Thomsen et al. (2004) demonstrated both structural and functional changes in the left middle frontal gyrus in the old. So far, this is the only evidence for specific, task-related changes, whereas the whole frontal hypothesis is dedicated to the explanation of cognitive decline as a function of aging. The frontal hypothesis itself is rather general and vague, and thus, there is a standing order for more specific task-related evidence of the frontal executive mechanisms and cognitive control. In addition to the DL, the more general multimodal (auditory, visual, and tactile) spatial RSA may offer a promising paradigm for such studies.

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## VI Asymmetry of Cognition



## 15 A Unified Structural-Attentional Framework for Dichotic Listening

**Stefan Pollmann**

In 1961, Doreen Kimura published her investigations of epilepsy patients who had undergone surgical treatment (Kimura, 1961a). She wanted to know how temporal lobe lesions would affect the recognition of auditory stimuli. Kimura borrowed a technique from Broadbent (1956), who had presented auditory digits either simultaneously or successively to both ears. The subjects' task was, after each series of six figures, to name as many digits as possible. She noted that the left temporal patient group was impaired at reporting digits presented to the contralateral ear, whereas no such effect was observed in a frontal lobectomy control group. The contralateral deficit in the temporal group, Kimura noted further, occurred only when digits were presented simultaneously to both ears. She compared this to earlier findings, where temporal patients were impaired when contralaterally presented words were distorted by low-pass filtering (Bocca et al., 1955) or by adding white noise (Sinha, 1959). Kimura also noted, almost in passing, that for all subject groups, right-ear scores were higher than left-ear scores, that is, her study revealed the right-ear advantage (REA) which has been reported time and again in subsequent studies.

The technique of simultaneously presenting similar, but not identical stimuli to both ears is called dichotic listening (dichotic from Greek δίχοι, 'split in two' and ὄτιον, 'ear') in contrast to diotic listening (from δύο, 'two') when the same stimulus is presented to both ears. Dichotic listening is today one of the most frequently used auditory tests. It is specifically used as a means for lateralized auditory input. However, it has not quite been clear whether the lateralization of auditory input achieved by dichotic presentation is due to structural anatomic factors, attentional factors, or a combination of both. This is the topic of the current chapter. The reader should not expect an exhaustive review of the dichotic listening literature. Excellent reviews have recently been published on several aspects of dichotic listening (Hugdahl, 2003b; Hugdahl et al., 2009; Westerhausen & Hugdahl, 2008; see also Bamiou et al., 2007). I will rather try to find a synthesis of the "structural" and "attentional" views of dichotic listening.

The chapter starts with Doreen Kimura's view on the mechanisms invoked by dichotic listening. I will then review more recent evidence on some of the central

topics of dichotic listening. These are the functional asymmetry of the auditory pathways, the callosal fibers involved in interhemispheric transfer, and, finally, the nature of the signal exchanged between the hemispheres, that is, whether it is primarily the auditory input or an attentional signal which is exchanged via the corpus callosum.

### **Kimura's View of Dichotic Listening**

Kimura (1961a), in her above-mentioned study, thought that her finding of reduced contralateral stimulus identification during simultaneous presentation was not necessarily due to the bilateral stimulation but may be a similar competitive situation as in the preceding studies by Bocca et al. (1955) and Sinha (1959), who had just added noise to the signal of interest. In all cases, a competition would exist in that a signal (the word or digit) would compete with a noise source (another digit, white noise, etc.). But then why would the contralesional ear be specifically affected? Here Kimura invoked physiological studies which had postulated stronger contralateral than ipsilateral auditory fibers (Rosenzweig, 1951; Tunturi, 1946).

In the case of a unilateral temporal lobe excision, ... the pathways ipsilateral to the intact cortex are less efficient than those contralateral to it.... Under some conditions presumably there will be no detectable difference in efficiency between the two remaining pathways, that is, between the two ears. If the stimuli are simple or highly familiar, even the activity of the weaker pathway will be enough to result in the firing of those central connections corresponding to correct recognition. If, however, the input is changed in some way such that recognition falls for both ears, the weaker input from the ipsilateral connection ... will cause it to suffer more, possibly through not lasting long enough to permit the recognition of stimuli (Kimura, 1961a, p. 163f).

In a follow-up paper, published in the same year, Kimura (1961b) investigated 120 epilepsy patients, many of whom had undergone sodium amytal testing (Wada & Rasmussen, 1960, 2007) to determine their speech-dominant hemisphere. It turned out that the usual REA was found in patients with a speech-dominant left hemisphere, but that a reverse left-ear advantage was found in subjects with a speech-dominant right hemisphere.

In a review of her work published in 1967, Kimura interprets the REA in a slightly different way. Again citing the paper by Rosenzweig (1951), she refers to an "occlusion" of ipsilateral signals at a point where the ipsi- and contralateral signals "overlap." In the terminology of a later model of attention (Desimone & Duncan, 1995), one could see this "occlusion" as a competition between signals, in which the stronger contralateral signal suppresses the weaker ipsilateral signal, when both reach this point of "overlap" simultaneously. Whereas this competition could presumably take place at an early stage of the auditory pathways, from the superior olivary complex on, Kimura also discussed a possible contribution of "central competition" (p. 171) between

ipsi- and contralateral auditory input to the REA. Only recently, it has been shown that Kimura's original procedure contained a significant working memory component. When subjects had to memorize three dichotic item pairs, as in Kimura's experiments, or even up to five pairs, an enhanced REA was observed with increasing working memory load, mainly due to a larger drop of correct left-ear recall (Penner, Schlafl, Opwis, & Hugdahl, 2009).

### **Contralateral Dominance in the Auditory Pathway**

Unlike visual cortex, in which a circumscribed lesion leads to a clearly delimited scotoma in the contralesional visual hemifield, there is no such localizable effect of an auditory cortex lesion. After unilateral lesions of auditory cortex, regardless of hemisphere, detection thresholds for stimuli on both ears are unimpaired (Cranford, 1984). Again in contrast to the visual (or the somatosensory) system with its contralateral organization, most thalamocortical auditory fibers carry binaural signals.

As mentioned, reports about stronger crossed auditory signal propagation existed even before Kimura's original studies (Rosenzweig, 1951; Tunturi, 1946). Later, Hall and Goldstein (1968) reported that in the left primary auditory cortex of the cat, the neurons responding to ipsilateral (left-ear) stimuli were a subset of the large number of neurons which responded to stimuli from the contralateral ear. They further reported that most neurons which represented both ears showed summation of inputs, but others also showed inhibition or even more complex interaction patterns.

In the human brain, contralateral dominance for auditory input has been documented in a number of magnetoencephalography (MEG) studies (Reite, Zimmerman, & Zimmerman, 1981; Hari & Mäkelä, 1988; Mäkelä et al., 1993; Pantev et al., 1998). Binaural stimulation often led to auditory responses which were much smaller than the sum of the responses of the monaural stimuli, sometimes even smaller than responses to the contralateral stimulus alone (Reite et al., 1981; Pantev et al., 1986; Tiihonen, Hari, Kaukoranta, & Kajola 1989). Lesions of the human auditory cortex, auditory thalamus, or acoustic radiation led to increased thresholds for signal frequency, intensity, and duration discrimination when masking band-pass noise was presented ipsilesionally and the signal contralesionally (Biedermann et al., 2008). In the reverse case, no impairment was observed. Thus, there is an asymmetry in the human auditory pathway in that signals from the contralateral ear are dominantly processed (see also converging evidence from commissurotomy studies, discussed below). Furthermore, the study showed that if only one auditory pathway is functional in the human brain, it can carry auditory signals from the nondominant ipsilateral ear, but this signal can easily be disrupted by a competitor on the dominant contralateral ear.

However, competition between auditory stimuli may, depending on the stimuli, not always be symmetrical in the cerebral hemispheres. In an MEG study, Fujiki,

Jousmaki, and Hari (2002) recorded neuromagnetic responses evoked by frequency-tagged sounds. During binaural attentive hearing, they observed a strong competition of the sounds. This competition was symmetrical for sounds from both ears in the right hemisphere. In contrast, in the left hemisphere, ipsilateral responses were significantly more suppressed, intensifying the REA of the left hemisphere.

While the reported studies used sound or noise stimuli, Della Penna et al. (2007) used consonant–vowel (CV) syllables in a variant of the typical dichotic listening setup. One stimulus of a dichotic pair was varied in intensity. The reasoning was that inhibition would lead to a stronger attenuation of the more intense stimulus. They observed that dichotic stimuli led to a stronger inhibition of the ipsilateral stimulus in left than right auditory cortex. Furthermore, this difference was only observed for dichotic stimuli with high spectral overlap (/da/, /ba/, in contrast to /da/, /ka/), whereas in right auditory cortex, left- and right-ear stimuli were comparably attenuated.

A task-dependent asymmetry in the effect of masking noise has been found in two functional magnetic resonance imaging (fMRI) studies by Behne et al. (2005, 2006). Their subjects had to categorize frequency shifts in one task and to make lexical decisions in the other. Right auditory cortex was dominantly activated by the frequency shift task, whereas left auditory cortex was dominantly activated by lexical decisions. When white noise was added on the ear contralateral to the signal (frequency modulation, respectively, words–pseudowords), it was found that the added noise influenced the activation in the dominant auditory cortex, whereas the activation of the non-dominant auditory cortex was largely unaffected. The change in the activation pattern in the dominant auditory cortex was due mainly to an upregulation of the ipsilateral activation. For instance, the activation elicited by words and pseudowords presented in the left ear was higher with simultaneous noise presented to the right ear, reaching the same level as elicited by pure right-ear words–pseudowords. A reverse increase of right auditory cortex activation by left-ear noise was not observed (Behne et al., 2006). Presentation of noise did not alter the generally high correct recognition of words.

Thus, there is converging evidence across species and investigation methods for a contralateral dominance of auditory input. However, this contralateral dominance appears to be strongest for task-relevant input in the hemisphere which dominantly processes a task.

Differences between methods still have to be clarified. Whereas addition of noise led to reduced MEG responses to the ipsilateral signal (Della Penna et al., 2007), an increase of the ipsilateral blood-oxygen-level-dependent (BOLD) signal was observed (Behne et al., 2005, 2006). The different paradigms used in these studies do not allow a direct comparison. However, a potential explanation for this apparent discrepancy may be that the blockwise BOLD increase observed by Behne and colleagues was caused by sustained increased neuronal activity in response to the deteriorated signal.

A sustained increase of neuronal activity (e.g., a baseline shift) would not be mirrored by the event-related MEG signal in the study by Della Penna et al.

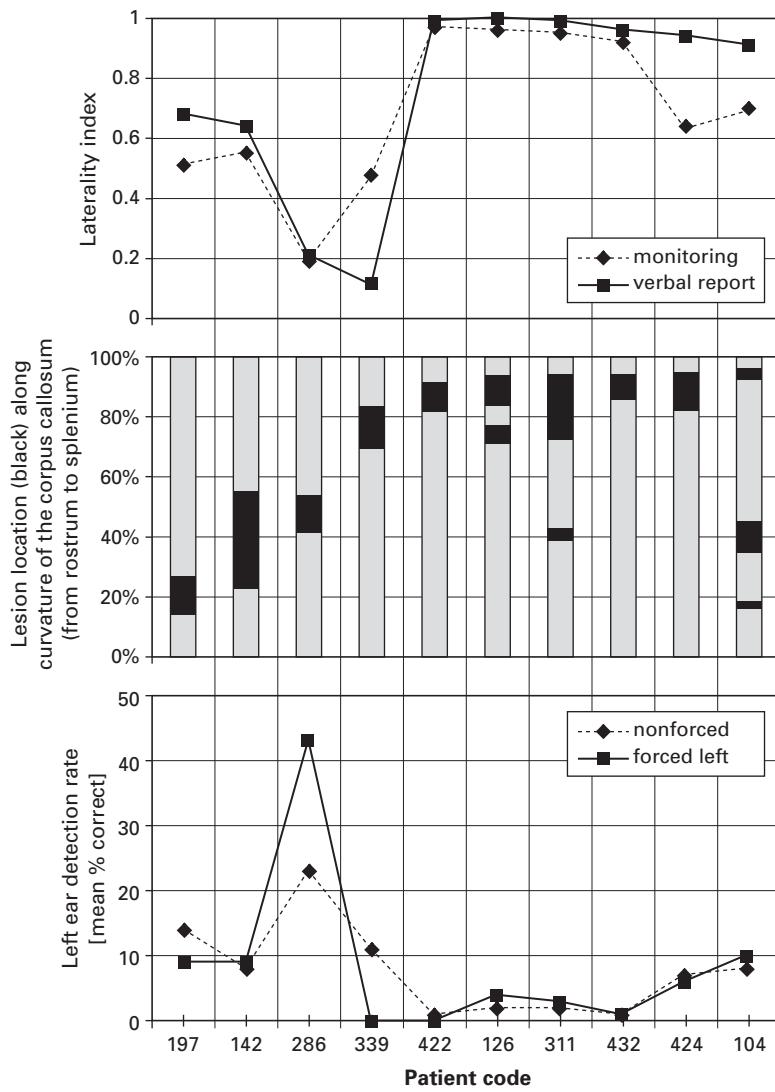
The generally observed contralateral dominance implies that signals from the ipsilateral ear may benefit from an indirect route, the transfer from the contralateral hemisphere via cortical commissures when the direct ipsilateral auditory pathways are too weak to compete with the dominant contralateral input. This is the topic of the next section.

### Dichotic Listening after Commissural Lesions

Sparks and Geschwind (1968) were among the first to note the importance of callosal transfer to dichotic listening. They tested a patient (W.J.) who had undergone complete commissurotomy for treatment of otherwise intractable epilepsy. W.J. showed a 100% extinction of dichotic left-ear stimuli. This extinction occurred only when different but very similar stimuli were presented to both ears. In control tasks, in which either white noise or babble noise was presented to the right ear, no left-ear suppression was observed. However, when familiar words were presented to the left ear, simultaneously with unfamiliar words to the right ear, there was still left-ear extinction. The role of the similarity of left- and right-ear input was further tested by adding various levels of distorting filters to the left- or right-ear inputs. The less distorted the right-ear speech sound was, the more suppressed was the left-ear score. Sparks and Geschwind interpreted these findings as evidence for a callosal transfer of left-ear verbal signals via callosal auditory fibers to the left-hemisphere speech areas.

In the same year as Sparks and Geschwind, Milner, Taylor, and Sperry (1968) published a report of dichotic listening in a group of seven complete commissurotomy patients. They, too, found complete or near complete suppression of left-ear digits in these patients. Report of unilateral left-ear digits was unimpaired, demonstrating that ipsilateral auditory connections are sufficient to relay left-ear input in the absence of competing stimuli. Interestingly, report of left-ear digits in dichotic listening was also near normal in left as well as right temporal lobectomy patients said to include Heschl's gyrus. Near normal dichotic left-ear report in patients lacking right Heschl's gyrus does not fit well with the view that left-ear dichotic stimuli are relayed in the normal brain via commissural fibers originating in the right auditory cortex.

These initial studies of complete commissurotomy patients were followed by investigations of partial callosotomy patients. Springer and Gazzaniga (1975) did not observe left-ear suppression in a patient with a section of the anterior commissure and the anterior third of the corpus callosum. Conversely, they reported left-ear suppression in another callosotomy patient in which "visual tests ... suggest that parts of the splenium were left intact" (p. 342). They concluded that "sections anterior to the splenium and posterior to the first one third of the corpus callosum" (p. 341) may



lead to left-ear suppression. About a decade later, a case with a discrete lesion in the most posterior part of the callosal trunk was reported (Alexander & Warren, 1988), who showed complete left-ear suppression for dichotic consonant–vowel–consonant syllables. The first study reporting midsagittal magnetic resonance images (MRI) to document the location and extent of callosal lesions was published in 1995 by Sugishita et al. They found that lesions of the posterior 20% to 25% of the callosal curvature were associated with left-ear suppression. In a study from my lab, this finding was by and large confirmed. In a group of ten partial callosotomy patients, documented by midsagittal MRI and quantitatively analyzed, we observed left-ear suppression with lesions affecting the caudal 20% of the callosal circumference (Pollmann et al., 2002; see figure 15.1). In fact, the normal left-ear performance of one patient whose lesion reached as far back as leaving only 17% of the caudal end of the corpus callosum intact suggested that lesions of the splenium proper, and not lesions of the posterior trunk, led to left-ear suppression (see also Gadea et al., 2002, for possible sex differences in the exact location of the fibers contributing to the REA).

When we began the Pollmann et al. (2002) study, we expected lesions anterior to the splenium, in the posterior part of the callosal trunk, to disrupt auditory transfer and lead to left-ear extinction. This hypothesis was derived from the anatomy of the rhesus monkey, in which the posterior trunk was found to contain auditory commissures (Cipolloni & Pandya, 1985). Left-ear suppression after splenial lesions in human subjects thus presented a puzzle. Either the auditory commissures were located more posteriorly in the human corpus callosum than in the monkey, or left-ear suppression was not due to disruption of auditory transfer. The question was, if it is not the auditory signal that is transferred via the corpus callosum in dichotic listening, what else is it? Before we return to this issue, let us consider the potential role of attentional processes in dichotic listening.

### Attentional Effects on Dichotic Listening

So far, this review has emphasized investigations into structural effects of brain asymmetry on dichotic listening. However, there is also a long tradition which attributes at least part of the REA in verbal dichotic listening to attentional factors.

#### Figure 15.1

Left-ear suppression in patients with partial callosal lesions. Individual patient performance in relation to lesion location. (Top graph) Laterality scores in the nonforced dichotic monitoring and verbal report tasks. (Middle graph) Lesion location in percentage of the curvature of the corpus callosum from the tip of the rostrum (0%) to the end of the splenium (100%). (Bottom graph) Left-ear detection rate in the nonforced and forced left dichotic monitoring tasks.  
(Reprinted with permission from Pollmann et al., 2002.)

### Kinsbourne's Hemispheric Preactivation Model

Kinsbourne (e.g., 1970) proposed that the REA in dichotic listening of verbal stimuli is not due to structural factors but to a greater preactivation of the language-dominant left hemisphere in tasks which afford verbal processing. He argued that the hemispheres are antagonistic with regard to spatial attention, each one with a stronger tendency toward contralateral attending. (Differences in the hemispheric strength of this contralateral tendency [Heilman, Bowers, Valenstein, & Watson, 1987; Pollmann & Zaidel, 1998] will not be discussed here.) While these tendencies can already be observed in nonhuman species, in the human brain, the situation is complicated by the lateralization of cognitive functions, especially language. In Kinsbourne's model, when a subject engages in linguistic processing, be it overt or covert, the left hemisphere is activated (in the majority of subjects with left-hemisphere dominance for language). This activation, in turn, leads to an activation of the left-hemisphere spatial attention system. The left hemisphere thus becomes a stronger competitor of the right-hemisphere spatial attention system, which results in a rightward attending bias of the subject. As an example, Kinsbourne (1970) presented evidence for such a bias in a visual experiment, in which silent verbal rehearsal led to better right-visual-hemifield processing, which was not observed in a control condition without verbal task demands. In dichotic listening, he claimed, the same bias leads to the REA for verbal material.

Kinsbourne's activation account found only limited support in subsequent studies. According to early reviews (Beaumont, Young, & McManus, 1984; Ehrlichman & Weinberger, 1978), only about half of the reviewed studies confirmed Kinsbourne's hypothesis. More recently, lateral biases induced by verbal and nonverbal tasks were observed by Galluscio and Paradzinski (1995), whereas Previc and Murphy (1997) could not replicate lateral biases in tasks similar to those used by Kinsbourne (1972).

### Attentional Biases to One Ear

Kinsbourne's task-dependent hemispheric preactivation account was a very specific attentional explanation of the REA in verbal dichotic listening. However, the typical dichotic listening paradigm, which simply asked for naming of the heard syllables or words, was open to all kinds of attentional biases to the left or right. Bryden (1978) wanted to separate true structural effects from such attentional or strategic effects which may bias processing to one ear without a structural basis. Subjects may have a tendency to attend more to one ear or the other, and these tendencies may even change from trial to trial. His reasoning was that such uncontrolled biases could be minimized if subjects were directed to pay attention to one ear and to report only the stimulus presented on this ear (Bryden, 1978). Then, performance with attention focused on the left ear should be compared with focused right-ear attention. In this

way, attentional bias should be optimal in both cases and should cancel each other when both conditions are compared.

Mondor and Bryden (1991) used a trial-by-trial auditory cueing paradigm, in which a tone cue on the left or right ear preceded presentation of a dichotic stimulus pair by a variable stimulus onset asynchrony (SOA). In parallel to visual cueing studies of attention, where peripheral and central cues may elicit exogenous and endogenous shifts of attention, effects of randomly changing peripheral auditory cues may elicit auditory attention changes more in the sense of attentional capture by salient cues than in the top-down controlled way elicited by task instructions which remain unchanged over a whole block of trials. Mondor and Bryden (1991, 1992) observed that the REA declined substantially when the SOA increased from 150 to 450 milliseconds. In a subsequent experiment (Mondor & Bryden, 1992), subjects were instructed to report only the word presented to the cued ear. Again they observed decreasing REA for word identification from SOA 150 to 450 milliseconds, which remained constant at 750 milliseconds. They further observed that intrusion errors (reporting the stimulus on the uncued ear) also declined from 150 to 450 milliseconds. This was regarded as evidence for the intended working of the cue, in that processing was more selectively focused on the attended ear with increasing SOA. Mondor and Bryden thus argued that REAs are typically inflated by uncontrolled biases. They further concluded that, after these biases are controlled, the remaining small perceptual asymmetries provided "little direct information about functional hemispheric asymmetries" (Mondor & Bryden, 1992).

Attentional biases to one ear can also be induced across trials by instruction to attend to the left or right ear. Studies which compared free report versus forced attention to one-ear instructions have yielded different results concerning the size and stability of the REA (reviewed in Hiscock, Inch, & Ewing, 2005). While some studies have found forced attention instructions to lead to more robust REA, as predicted when uncontrolled lateral biases are minimized, this was not observed in all studies. Hiscock and colleagues showed that these differences may have been due to the nature of the task employed. They compared target detection scores, irrespective of the ear of presentation, to target localization, where the target needs to be detected and localized to the correct ear (Hiscock, Inch, & Kinsbourne, 1999; Hiscock, Inch, & Ewing, 2005). They found that the localization depended strongly on the direction of attention, whereas no such dependence was observed for detection.

While Bryden and colleagues used focused attention to one ear as a means to control for otherwise uncontrolled attentional biases, already Asbjørnsen and Hugdahl (1995) noted that attentional biases could be facilitatory for the stimulus on the attended ear or inhibitory, suppressing the stimulus on the unattended ear. Hugdahl et al. (2009) pooled data from 1,507 participants of the Bergen dichotic listening database. All participants had been tested with an attentionally neutral ("unforced")

instruction, as well as a “forced left” and “forced right” instruction, in which they were asked to attend to the left or right ear, respectively (Hugdahl & Andersson, 1986). The data clearly show a shift of correct identifications on the attended ear. From the graphs (figure 2 in Hugdahl et al., 2009), it appears as if the effect of directed attention is particularly strong in the forced left condition.

These mechanisms may be differentially involved in the forced left and right conditions. Interestingly, schizophrenic patients tend to profit from the forced right but not the forced left instruction (Hugdahl, Rund, et al., 2003; Løberg, Hugdahl, & Green, 1999). This has been attributed to increased attentional control demands in the forced left condition, in which attention is directed at the nondominant stimulus (Hugdahl et al., 2009). Similarly, when intensity differences between left- and right-ear stimuli were introduced, neurologically normal participants were better at identifying a right-ear stimulus in the presence of a louder left-ear stimulus than vice versa (Tallus et al., 2007).

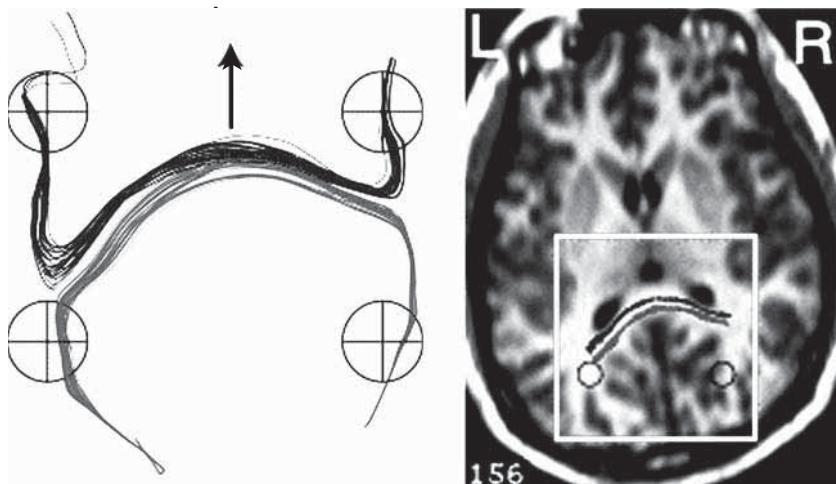
In our study with partial callosotomy patients (Pollmann et al., 2002), no improvement of the left-ear score was observed in nine out of ten patients when they were instructed to attend to the left ear. This lack of an effect was observed for splenial and presplenial lesions alike, in contrast to the left-ear extinction, which was only observed in the splenial lesion group. It is unclear whether this lack of an effect of the forced left condition can be attributed to the callosal lesions, which were very variable from patient to patient or whether it was a consequence of a generally lower capacity of sustained attention to one ear in the patients. In any case, the data showed that effects of sustained (blockwise) attention to one ear can dissociate from left-ear extinction.

### **Disengagement from the Dominant Ear**

We have ended the section on partial commissurotomies with the puzzle of what kind of signals are transferred in the splenium in dichotic listening. At the time of our study, the available anatomical evidence did not allow pinpointing of the location of auditory commissures in the human corpus callosum. De Lacoste et al. (1985) had observed degeneration of fibers in the posterior third of the callosal trunk as well as the splenium following lesions of the posterior half of the temporal lobe. This was not sufficient to answer the question of whether the splenium contains auditory commissures.

An early diffusion tensor imaging study had investigated the course of splenial fibers (Conturo et al., 1999). It was found that the splenium contains not only visual fibers connecting homologous visual occipital areas but also a bundle connecting the temporoparietal junction areas (see figure 15.2).

The latter was a hint at a possible attentional explanation of the left-ear suppression following splenial lesions. Converging evidence from animal (Steinmetz & Constantinidis, 1995), patient (Friedrich et al., 1998), and imaging (Corbetta et al.,



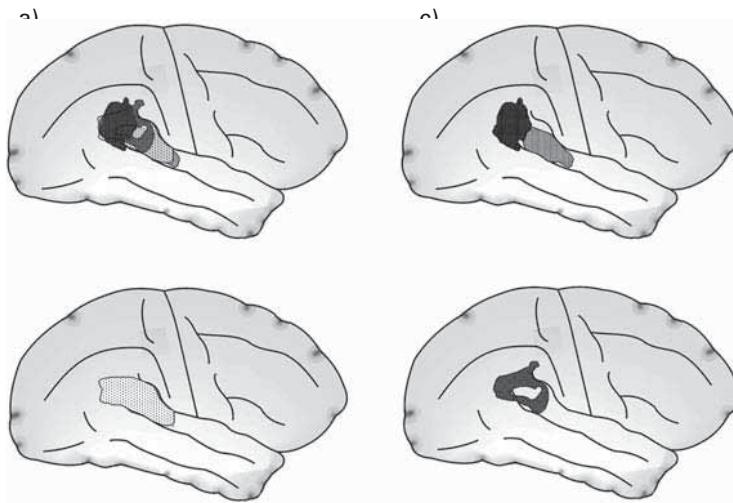
**Figure 15.2**

Diffusion tracking of commissural fibers. Tracks passing through the splenium (right) divide into two groups (left), projecting to the occipital and parietal lobes. L, left; R, right; Ant., anterior, 156, slice number.

(Adapted from Conturo et al., 1999. Reprinted with permission.)

2000) studies showed that neurons in the temporoparietal junction area respond to stimuli not currently attended and may serve to disengage attention from the currently attended aspects of the environment in the service of redirecting attention to new aspects. The majority of studies of the temporoparietal junction area come from the visual domain (Corbetta et al., 2008). However, temporoparietal junction lesions can lead to comparable effects on visual and auditory cueing (Farah et al., 1989). Attention changes within different sensory modalities are associated with different, but nearby and partly overlapping, activations within the temporoparietal junction. Intermodal attention changes activate the most posterior part of the superior temporal gyrus, with transitions between auditory stimuli activating the adjacent part of the posterior superior temporal gyrus, posterior to Heschl's gyrus (see figure 15.3; Downar et al., 2000).

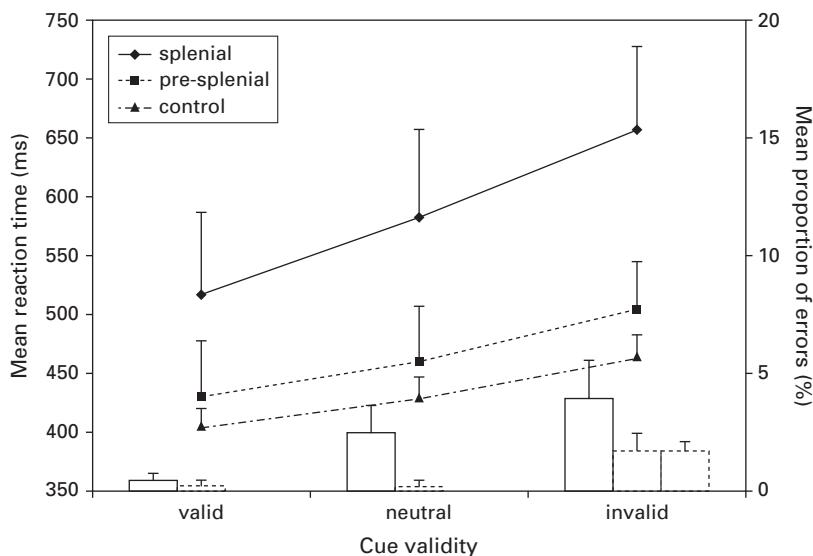
We reasoned that the right temporoparietal junction may serve an important function in dichotic listening in that it may be triggered by the left-ear input to disengage attention from the dominant right-ear input, thus strengthening the left-ear input in the competition with the right-ear input. Disruption of splenial fibers would interrupt signals from the right temporoparietal junction to the language-dominant left hemisphere, thus eliminating the left-ear support by the temporoparietal junction.



**Figure 15.3**

The posterior superior temporal cortex and the adjacent temporoparietal junction area support phonological processing as well as attentional functions. (a) Overlap of areas involved in phonological processing in dichotic listening, attentional reorienting, and extinction, as detailed in parts b–d. (b) The posterior superior temporal cortex supports phonological processing and is involved in interhemispheric transfer in dichotic listening (after Westerhausen et al., 2009 see also figure 15.5/plate 7). (c) Attentional reorienting between auditory stimuli (light gray) as well as between stimuli from different modalities (dark gray; after Downar et al., 2000). (d) Lesions in this area are frequently associated with extinction (after Karnath, Himmelbach, & Küker, 2003).

We investigated this hypothesis by testing our partial callosotomy patients again, this time with a visuospatial cueing task (Pollmann, Maertens, et al., 2004). Our reasoning was, if disruption of signals from the right temporoparietal junction to the left-hemispheric speech areas causes left-ear suppression in dichotic listening, then the same patients should show parallel deficits in visuospatial processing. If, on the other hand, left-ear suppression was caused by disruption of auditory transfer, no deficits of visuospatial cueing were expected. The results supported a supramodal, temporoparietal junction-dependent effect of callosal lesions. Overall, splenial lesions led to higher cueing effects in the splenial than the presplenial patients as well as neurologically normal controls (figure 15.4). The validity effect of the presplenial patients, in contrast, did not differ from that of the controls. In the splenial patients, both the benefits from valid cues and the costs induced by invalid cues were enhanced. This was expected when attention cannot be disengaged from the cued side.

**Figure 15.4**

Increased visuospatial validity effect in patients with splenial lesions. Mean reaction times (lines) and mean proportion of errors (%), bars) as a function of cue validity and group membership. Error bars represent standard errors.

(Reprinted with permission from Pollmann, Maertens, et al., 2004.)

Furthermore, within the four splenial patients who took part in both the dichotic listening and the visual cueing experiments, those two who showed the strongest left-ear suppression also showed the weakest effects of left-visual-hemifield cues, and vice versa for the two patients who showed the weakest left-ear suppression. Unlike verbal dichotic listening, there is no overall advantage for one side in visuospatial cueing. The interindividual variations in the strength of the REA and the accompanying visuospatial hemispace preference may indicate a stable individual bias to one side (as discussed earlier in this section).

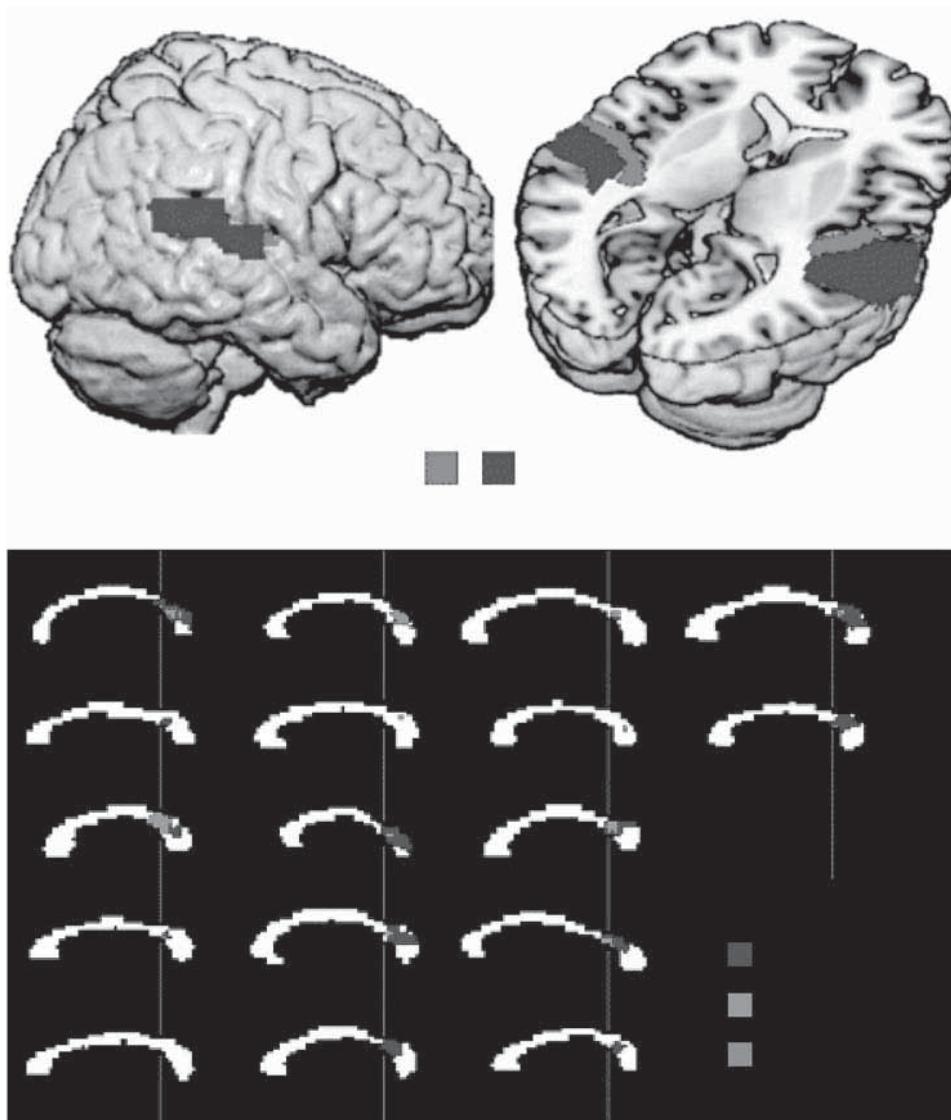
Activity in the temporoparietal junction can be suppressed during focused attention (Shulman et al., 2007). In dichotic listening, this may contribute to the forced attention effects, that is, the finding that top-down attention to one ear improves the identification of stimuli on the attended ear (Hugdahl et al., 2009), possibly by suppression of the temporoparietal junction support for the competing stimulus from the other ear.

As mentioned, the evidence on the location of auditory fibers within the human corpus callosum was too coarse when we conducted our studies with partial callosotomy patients to decide whether they transfer in the splenium. More recent diffusion

tensor tractography studies showed, with good agreement between studies, that the posterior 20% of the corpus callosum contains both temporal and parietal (and of course occipital) commissures (Huang et al., 2005; Hofer & Frahm, 2006; Zarei et al., 2006). A tractography study specifically carried out to trace commissures from temporal areas involved in dichotic listening reported fibers from Heschl's gyrus to cross in the isthmus region and the posterior superior temporal gyrus in the adjacent anterior splenial region of the corpus callosum (Westerhausen et al., 2009; figure 15.5/plate 7).

The localization of the fibers from Heschl's gyrus in the isthmus is generally in agreement with the monkey data, where auditory fibers were found in the posterior part of the callosal trunk (Cipolloni & Pandya, 1985). One could speculate that some of the patients who showed left-ear suppression in our study had caudal splenial lesions which should not affect auditory fibers (Pat. 432 and 104 from the Pollmann et al., 2002, sample), whereas others had lesions reaching into the isthmus area, which may well have disrupted auditory transfer. However, a cautionary note is needed, because these inferences rest on individual patient data on the one hand and tractography studies based on small samples on the other hand, which makes it difficult to estimate the variability of fiber tracts.

Westerhausen et al. (2009) went one step further in demonstrating a correlation between the size of the midsagittal area of commissures originating in the posterior superior temporal gyrus and left-ear performance in dichotic listening. The posterior superior temporal gyrus had been selected based on previous reports relating it to phonological processing (Boatman, 2004; Hickok & Poeppel, 2007). No significant correlation was reported for the size of the Heschl's gyrus fibers and left-ear performance. This would fit with the rather intact left-ear reports found after temporal lobe resection including Heschl's gyrus (Milner et al., 1968). In contrast, the correlation of the posterior superior temporal gyrus fiber area and left-ear performance appears to indicate that higher auditory transfer is involved in left-ear reports in dichotic listening. Recently, the posterior superior temporal gyrus has been found to respond to auditory-auditory and auditory-visual matches alike, with stronger responses to incongruent stimuli (Hocking & Price, 2008). However, things may be more complicated. The posterior superior temporal gyrus area overlaps with a posterior superior temporal gyrus/inferior parietal area which leads to extinction under double simultaneous presentation when lesioned (figure 15.3d; Karnath, Himmelbach, & Küker, 2003). These results show that it might be difficult to distinguish auditory processing from attentional processing on the basis of functional-anatomic data. However, maybe the question of whether stimulus information or auditory signals are transferred via commissures originating from the right posterior superior temporal gyrus to the left hemisphere is ill posed. Coding of the stimulus (e.g., whether a /da/ or /ba/ has been presented to the left ear) and increasing the competition of this left-ear stimulus



**Figure 15.5 (plate 7)**

Individual midsagittal fiber tracking (bottom) for Heschl's gyrus (HG, green) and posterior superior temporal gyrus (pSTG, blue; areas shown in top half of figure).

(Reprinted with permission from Westerhausen et al., 2009.)

with the right-ear stimulus directly delivered to the left hemisphere may go hand in hand.

Taken together, these studies indicate an important role of the posterior superior temporal gyrus in the processing of dichotic stimuli, in the sense that it may be involved in the discrimination of the competing dichotic stimuli and perhaps in raising the chances of the nondominant left-ear stimulus's being perceived in the presence of the dominant right-ear stimulus.

### Cortical Processing beyond Auditory Cortex

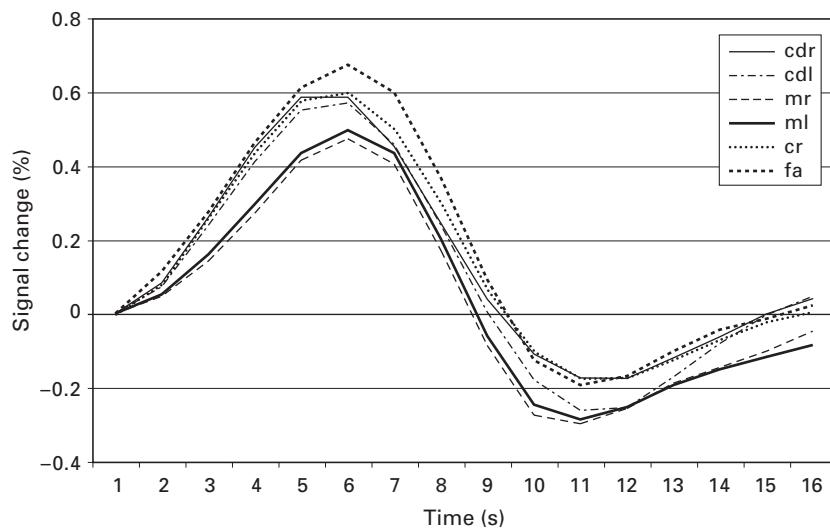
When discussing the role of the corpus callosum in dichotic listening, we have presented the "callosal relay" model (Zaidel, 1983), which assumes that auditory signals from the left ear, which reach the right auditory cortex first, are then relayed to the language-dominant left hemisphere. In principle, then, there may be a single transfer across the corpus callosum, from right to left hemisphere, which is sufficient for verbal left-ear stimuli to be processed (or not be processed in the case of callosotomy). This, however, may not capture the complexity of processing in dichotic listening. Instead, it is very likely that in the intact brain, there is a much more complex exchange of signals across the commissures. One piece of evidence supporting this view comes from studies of interhemispheric transfer time (IHTT) in the Poffenberger task, in which crossed and uncrossed responses to lateralized light flashes are compared. IHTT measures differ widely depending on stimuli and tasks (e.g., Clarke & Zaidel, 1989). More intriguingly, simultaneously measured response times and event-related (brain) potentials (ERPs) have been found to be uncorrelated (Saron & Davidson, 1989). This supports the view that there is a continuous exchange over the commissures, even in a task as simple as the Poffenberger task.

In dichotic listening, many more brain areas beyond auditory cortex are involved. They include prefrontal and anterior cingulate cortices (Jäncke & Shah, 2002; Thomsen et al., 2004). Likewise, in a trial-based ERP study, dichotic trials were accompanied by a pronounced shift from central to frontal electrodes (Bayazit et al., 2009). An absence of the REA was observed in nonaphasic patients with left frontal lesions, whereas patients with right frontal lesions showed a normal REA (Hugdahl, Bodner, et al., 2003).

These frontal activations may represent high-level control and decision processes involved in dichotic listening. The higher attentional control demands of forced left to forced right conditions go along with anterior cingulate activation (Thomsen et al., 2004). In an event-related fMRI study, we investigated decision processes in dichotic listening. Subjects had to decide whether a fixed target CV syllable was present in a dichotic pair or not. Trials were grouped as hits, false alarms, misses, and correct rejections of target presence. We found that bilateral orbitofrontal and pregenual paracing-

gulate cortices, as well as the amygdala and the hippocampal formation, showed stronger activation during target detection than during correct rejections (Pollmann, Lepsién, et al., 2004); for another report of frontal involvement in decision processes on auditory stimuli, see Binder et al. (2004). Within these areas, activation strength depended more on the subjective perception of target presence or absence than the actual physical presence of the target syllable. Thus, activation was often strongest for false alarms. As discussed above, lesions of the anterior parts of the corpus callosum, carrying the commissures between frontal cortices, appear not to lead to left-ear suppression. Nevertheless, given the involvement of frontal cortex in dichotic listening, the frontal commissures may influence target detection in dichotic listening in more subtle ways, such as changes in sensitivity and bias, which were typically not reported in previous studies.

In a reanalysis of the data, we found that subjective perception modulated activation strength not only in supramodal areas but also in Heschl's gyrus and planum temporale (Pollmann & Maertens, 2006; see figure 15.6). Here, too, activation was



**Figure 15.6**

Signal change in the auditory cortex as a function of perceptual decision and target presence. The figure shows the blood-oxygen-level-dependent response averaged over participants and regions of interest in Heschl's gyrus and the planum temporale. CDR, correct detection (hit) of right-ear targets; CDL, correct detection of left-ear targets; MR, missed right-ear targets; ML, missed left-ear targets; CR, correct rejection of target presence; FA, false alarm.

(Reprinted with permission from Pollmann and Maertens, 2006.)

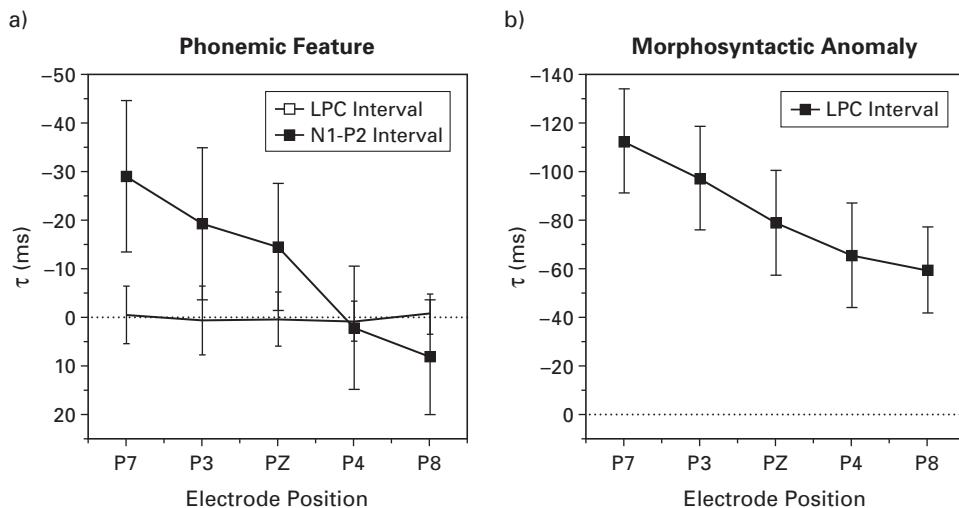
strongest for false alarms and weakest for misses, whereas hits and correct rejections did not differ in activation strength.

Subjective expectations can modulate activation even in subcortical structures of the auditory pathway. It was found that noise bursts elicited predominantly contralateral activation in the inferior colliculi, medial geniculate bodies, and auditory cortices (Schönwiesner et al., 2007). However, inclusion of a bilateral noise condition in a separate experiment led to the loss of contralaterally dominant activation in these structures in the right hemisphere. Instead, they now responded equally strongly to noise bursts from either ear. Unfortunately, the experiments differed also in attentional demands; a visual detection task was included in the experiment without bilateral noise bursts. Thus, it is not clear whether the mere presence of a bilateral noise condition led to the asymmetrical activation or whether this was due to increased attentional resources which could be devoted to the auditory task.

As in the case of the posterior superior temporal gyrus, discussed in the last section, these findings again show that no straightforward conclusions can be drawn from the anatomical location of a commissural bundle to the process it subserves. For instance, commissures originating in right Heschl's gyrus could not only transfer the left-ear input but also a subjective perceptual bias.

### Timing Issues

Jerger and Martin (2004) used cross-correlation analysis of ERP data to investigate lateralized timing differences in dichotic listening. They correlated ERP waveforms elicited by left-ear and right-ear targets within a preselected time window. By temporally shifting one waveform, the optimal correlation between the two waveforms was sought. The time shift at which this optimal correlation was obtained can be interpreted as delay with which the target on the shifted ear was processed relative to the target on the other ear at a given electrode. Two time windows were analyzed, an early one containing the N1-P2 complex and a later one, containing the late positive component (LPC). Furthermore, two tasks were applied. In both, continuous stories were read to the participants. The same story was presented to both ears but shifted in time by 60 seconds or 80 seconds. In the first task, participants had to detect a phonemic feature; in the second, morphosyntactic anomalous words had to be detected. Cross-correlations were calculated over five parietal leads. In the N1-P2 interval, the maximum of the cross-correlation function was close to zero at all leads (see figure 15.7). In contrast, there was a clear gradient in the LPC time window with a maximal lead time of the right-ear targets at the leftmost electrode (P7) and continuously smaller leads toward the rightmost electrode (P8), which in the phonemic task even changed into a left-target lead at P8. This remarkable left-right gradient across elec-



**Figure 15.7**

Shifts of cross-correlation maxima ( $\tau$ ) for N1-P2 and late positive component (LPC) intervals across the electrode array. Right-ear advantage (REA) (negative  $\tau$  shift) is plotted upward from zero.

(Reprinted with permission from Jerger and Martin, 2004.)

trodes was obtained in both tasks. However, the REA (or right-target lead time) at all electrodes was larger in the morphosyntactic task.

Two aspects of the data are remarkable. First, no time shift was found for early processing (N1-P2). This seems not to fit with the assumption that ipsilateral auditory signals reach the left hemisphere with a delay. The delay seen only in the later time window rather suggests that the (left-dominant) auditory input is first processed to some degree in the right hemisphere before it is transferred to the left hemisphere. Second, it is unclear why there is a temporal gradient with a monotonic decrease of the right-target lead time from the leftmost to the rightmost electrode. All concepts of hemispheric processing would predict rather a dichotomous difference between electrodes over the left and right hemispheres. It is unclear whether the gradient observed is due to a real neuronal processing gradient from left lateral over left and right medial to right lateral cortical areas or whether it represents rather different degrees of mixed left-hemisphere and right-hemisphere source contributions due to the rather unspecific localization of the EEG.

In a study using a more “traditional” dichotic listening paradigm with free report of CV syllables, Eichele et al. (2005) observed a latency difference for the N1 component measured over temporal leads, with an earlier N1 over the left hemisphere. Interestingly, the latency difference correlated with the behavioral laterality index

measured in the same experiment. Because there was no target to be detected, latencies could not be analyzed in relation to ear of target presentation.

### **Ear of Presentation versus Spatial Location**

Jerger and Martin used loudspeakers positioned to the left and right of the listener's head for stimulus presentation. In this way, there is no separation of the stimuli presented to the left and right ear, as in the commonly used headphone presentation of dichotic stimuli. Instead, the spatial position of the stimuli is coded by interaural time and amplitude differences. This method was introduced by Morais and Bertelson (1973) and refined by the same authors by using a stereophonic tape for presenting both stimuli of a pair to both ears, but with defined interaural time and amplitude differences resulting in spatial localization to the left and right (Morais & Bertelson, 1975). The results showed an REA, although somewhat weaker than that obtained with standard dichotic presentation (perhaps due to combined time and amplitude differences in natural hearing).

Morais and Bertelson (1975) regarded the REA obtained with time- and amplitude-manipulated presentation of both stimuli to both ears as a refutation of the structural theory of Kimura. After all, since both stimuli of a pair are presented to both ears, the REA cannot be due to the left-ear input's reaching the left-hemisphere language centers in a degraded fashion. However, on a closer look, it is readily apparent that this conclusion does not hold. If we take manipulation of interaural time differences as an example, we see that the right ear will receive a mixed presentation of the right stimulus and, delayed by the interaural transfer time, the left stimulus. If the left-ear input is suppressed or weakened, as assumed by Kimura (1967) and supported by the reviewed evidence, then the left hemisphere will receive a signal in which the right stimulus gets the head start and the left stimulus is delayed. Exactly this has been hypothesized to occur in the structural model, where the delay would be due to the relay of the left-ear input via the right hemisphere and the corpus callosum. The latter, callosal transfer, can also happen in the time-shifted diotic presentation, but the transferred left-ear input will be too late to compete with the direct presentation of the right-ear input. The same reasoning may also be applied to diotic presentation with amplitude modulations. In fact, dichotic presentation can be regarded as an extreme form of interaural amplitude differences.

Dissociations between ear extinction in dichotic listening and extinction of a hemispace in time-shifted diotic listening have, however, been reported after brain injury (Bellmann, Meuli, & Clarke, 2001; Spierer, Meuli, & Clarke, 2007). In most cases, the left ear or the stimulus in the left hemispace was extinguished. Left-ear extinction in dichotic listening occurred in the absence of spatial extinction in diotic listening and vice versa. This double dissociation supports the view that

left-ear extinction in dichotic listening cannot be reduced to disturbances of space representation.

### Conclusion

There is ample evidence for a contralateral dominance in the auditory pathways. This dominance becomes especially apparent in dichotic listening, that is, when two similar stimuli are presented simultaneously to both ears. In this situation, the competition between stimuli may lead to suppression of the ipsilateral stimulus. For tasks with a hemispheric dominance, the contralateral advantage may be apparent only in the dominant hemisphere as far as imaging data are concerned.

Disruption of splenial commissures bordering the isthmus leads to an exaggerated REA, often a complete left-ear suppression. This area contains commissures which originate in the posterior temporal and adjacent parietal cortex. Of these, the commissures from the posterior superior temporal gyrus are important for dichotic left-ear performance. The posterior superior temporal gyrus is involved in phonological processing, specifically matching of phonological stimuli. It is specifically active when incongruent stimuli are presented. This pattern, along with the extinction seen when the posterior superior temporal gyrus is lesioned, suggests that the posterior superior temporal gyrus is central to discriminating competing—auditory or multimodal—stimuli. It is unlikely that “raw” auditory signals are transferred via the corpus callosum: (1) Lesions of Heschl’s gyrus seem not to impair contralateral stimulus identification; (2) commissures from the posterior superior temporal gyrus, but not from Heschl’s gyrus, covary with individual left-ear performance; and (3) late, but not early, ERP components show a contralateral delay. Thus, patient, imaging, and ERP data indicate that interhemispheric transfer in dichotic listening occurs between high-level processes.

The ear advantage can be influenced by top-down attentional biases. However, in the absence of top-down biases, the REA appears to be due to the dominant input from the right ear to the language centers of the left hemisphere as proposed by Kimura. The exaggeration of this REA in patients with commissurotomy, often leading to complete left-ear extinction, may be due to disruption of right temporoparietal junction signals which strengthen the left-ear input in its competition with the dominant right-ear input, in this way reducing the bias in the competition of left and right stimuli.

Thus, splenial fibers may convey a highly processed auditory signal to the left hemisphere, which contains the information of what has been presented to the left ear, at the same time biasing the left-hemisphere language processing in favor of this left-ear input. Thus, in contrast to previous attentional explanations of dichotic listening, there may be no abstract attentional signal which is independent of the auditory

content. Instead, the left-ear input, preprocessed by the right auditory cortex, is relayed via the splenium to the left hemisphere to compete with the right-ear input for perception. In the normal brain, this bias counteracts the dominant right-ear input to create only a gradual REA. Following splenial lesions, this biasing signal does not reach the left hemisphere anymore, leading to extinction of the left-ear input.

### Open Questions

Many issues remain to be investigated concerning the nature of callosal transfer in dichotic listening. Some of the topics which deserve further investigation are whether auditory content and attentional signal are transferred in a single signal, as suggested in this paper, or whether they are transferred, perhaps within the same callosal section, by separate fast and slow commissural fibers, as has been suggested previously (Hugdahl, 2003a). Furthermore, is there a link between left-ear extinction in dichotic listening and extinction phenomena in other senses after lesions of the posterior superior temporal gyrus or its commissures? Are there subtle effects of frontal commissurotomy on dichotic listening, given that frontal cortex has been shown to be actively involved in this task? These questions show that half a century after Kimura's original studies, dichotic listening still leaves room for further research.

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## **16 Cognitive Control of Auditory Laterality**

**René Westerhausen and Kenneth Hugdahl**

The dichotic listening paradigm is perhaps the most frequently applied experimental paradigm to assess hemispheric laterality, described in numerous introductory textbooks on neuropsychological research, hemispheric asymmetry, and cognitive neuroscience (e.g., Gazzaniga, Ivry, & Mangun, 2002; Hellige, 1993; Hugdahl & Davidson, 2003; Springer & Deutsch, 1998). In the present chapter we advance a new view on dichotic listening, that it is also an ideal approach to study cognitive control or executive attention abilities in healthy subjects as well as in clinical settings. The terms “cognitive control” or “executive control” summarize a set of cognitive functions that enables an individual to cope with cognitive challenges present in everyday life, for example, to solve complex problems, to plan and monitor goal-directed behavior, to carry out tasks containing multiple parts, or to overcome habitual responses (e.g., Lezak, 1983). These listed behaviors might be supported by several underlying cognitive mechanisms, such as goal maintenance, rule generation and selection, and dynamic adjustments in control (Kerns, Nuechterlein, Braver, & Barch, 2008). However, there seems to be a general consensus that the ability to monitor and resolve cognitive conflicts that emerge during these processes is a key aspect of cognitive control (e.g., Botvinick, Braver, Barch, Carter, & Cohen, 2001; Braver, Cohen, & Barch, 2002; Fan, McCandliss, Sommer, Raz, & Posner, 2002; Miller & Cohen, 2001; Posner & Rothbart, 2007). Thus, cognitive control involves monitoring and overcoming processing conflicts between thoughts, feelings, responses, or sources of information. This is also expressed by the fact that most experimental paradigms that are used to study cognitive or executive control involve such conflict situations or conditions as the Flanker paradigm (e.g., Eriksen & Eriksen, 1974), versions of the Stroop task (e.g., Cohen, Barch, Carter, & Servan-Schreiber, 1999), or the attention network test (Fan et al., 2002). A cognitive conflict can thus be induced by conflicting stimulus properties with one or several properties being perceptually more salient than others, resulting in a preference for processing the more salient features, which, however, has to be suppressed in favor of a “weaker” alternative (Botvinick et al., 2001; Braver et al., 2002). In context of a dichotic listening situation, a strong processing preference exists which

is referred to as the right-ear advantage (REA), that is, the general tendency to report an auditory verbal stimulus presented to the right ear more often than a comparable stimulus presented simultaneously to the left ear (Bryden, 1988; Hugdahl, 1995). A cognitive conflict results when a top-down instruction is added that requires one to attend to and report the stimulus presented to the left ear (which would constitute the “weaker” stimulus compared to the “stronger” right ear stimulus). In this forced-attention situation (Hugdahl & Andersson, 1986), the top-down instruction is “pushing” for the left ear while the anatomy of the auditory and speech processing system would prefer the right-ear stimulus to be selected and reported. The solution is to inhibit processing, or to suppress responding of the right ear stimulus, which, due to the lateralized function of the left hemisphere, produces a strong cognitive conflict when the instruction is to attend to the left ear stimulus (cf. Hugdahl et al., 2009).

In the present chapter we present evidence that dichotic listening can not only be seen as an indicator of hemispheric asymmetry but can also be used to study functions of executive and cognitive control. For this purpose, we first would like to present the “classical” view on the use of dichotic listening, that is, to assess hemispheric laterality in the auditory domain. We then proceed by describing how a forced-attention dichotic listening paradigm creates a situation of cognitive conflict. Here we will present several applications of the dichotic listening cognitive control approach to various clinical groups, including schizophrenia, aging, and attention-deficit/hyperactivity disorder (ADHD), and other clinical studies, with the purpose of revealing a common cognitive impairment structure across different clinical etiologies and diagnoses. Finally, we will present a new approach to dichotic listening that allows the researcher or clinician to quantify the degree of cognitive control impairment in a given clinical group by combining bottom-up stimulus manipulations with top-down instructions.

### A Classic Measure of Hemispheric Laterality

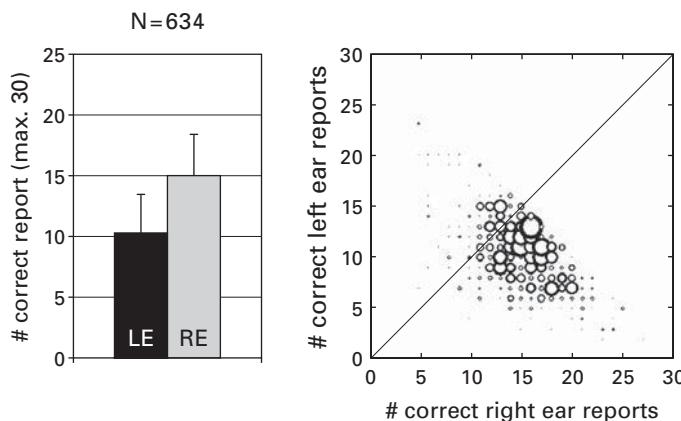
The term “dichotic listening” describes a group of paradigms in which two auditory stimuli are simultaneously presented, one to the left ear and the other one to the right ear, and where the subject is asked to report what he or she perceives in each trial (Bryden, 1988; Hugdahl, 1995, 2003). Donald Broadbent (1952, 1954) originally developed the dichotic listening paradigm in order to study vigilance and attention focus in flight controllers, probably related to research initiated during World War II. In 1961 Doreen Kimura (1961a, 1961b) applied a dichotic listening paradigm to address the issue of lateralization of function between the cerebral hemispheres, which had a tremendous impact on neuropsychology at the time. Examining a group of patients with temporal lobe epilepsy (Kimura, 1961b), for which the lateralization of language

was determined using the sodium-amytal procedure (also known as the Wada test), she was able to show that patients with a left-hemispheric language lateralization exhibit an REA in the report of dichotically presented digits. In contrast, patients with right-hemispheric language lateralization showed a left-ear advantage (LEA). Further, studying a group of healthy individuals and using the same paradigm, Kimura (1961b) also showed that the majority of healthy subjects showed an REA. These seminal studies and early replications (e.g., Bryden, 1963) led to the conclusion that the behavioral asymmetry detectable with dichotic listening might serve as a noninvasive indicator to assess the functional hemispheric lateralization for language processing. As a result, the focus of studies using dichotic listening shifted away from the study of attention to hemispheric lateralization, and dichotic listening with speech sound stimuli became one of the most frequently used paradigms in laterality research (Bryden, 1988; Hugdahl, 1995, 2003). It may, however, seem paradoxical that theories and models of asymmetry almost exclusively emphasized the perceptual aspects of asymmetry of speech and language processing, when in fact the original Kimura studies (1961a,b) were more studies of lateralization of working memory capacity than of perceptual salience. Kimura used dichotic presentations of digit pairs that were presented successively in series of three pairs before the subject had to report what he or she had perceived. Since the subjects had to "remember" the sequence of the digits in order to report the single items this would load on working capacity to bridge the time interval between the presentation of the first and last digit in the series (see also Penner, Schäfli, Opwis, & Hugdahl, *in press*, for a recent dichotic listening working memory study).

Although nonverbal stimulus material, such as tones, chords, or melodies, have also been used in dichotic listening research (e.g., Boucher & Bryden, 1997; Peretz & Morais, 1980; Spajdel, Jariabkova, & Rieckensky, 2007), the main focus of dichotic listening studies stayed on studying brain lateralization using verbal stimuli, such as digits, syllables, or words. The most frequently applied version of dichotic listening is based on the presentation of consonant-vowel (CV) syllables, which has yielded the most reliable and robust REA (e.g., Bloch & Hellige, 1989; Bryden, Munhall, & Allard, 1983; Foundas, Corey, Hurley, & Heilman, 2006; Hiscock, Inch, & Kinsbourne, 1999; Mondor & Bryden, 1991; Speaks, Carney, Niccum, & Johnson, 1981; Studdert-Kennedy & Shankweiler, 1970). One frequently used and standardized example for a CV-based paradigm is the Bergen Dichotic Listening test (for details, see Hugdahl, 1995, 2003; Hugdahl & Andersson, 1986). This version of the dichotic listening test employs six different stimuli that result from combining the six stop consonants /b/, /d/, /g/, /p/, /t/, and /k/ with the vowel /a/ to form syllable such as /ba/ or /pa/. The CV-syllables are paired with each other forming all possible combinations, thus yielding 36 dichotic pairs including the homonymic pairs (which are usually not included in the statistical analysis). In the standard version of the paradigm the complete list of 36 stimulus

pairs is presented to the participant with the instruction to orally report the syllable he or she perceives the best. Thus, the subject is explicitly instructed to report only one syllable in each trial irrespective of whether he or she perceived one or both items. This restriction to report only one item was originally suggested by Bryden (1988) in order to reduce working memory load as compared to a situation in which the subject has to provide two or even more responses.

During the last two decades, this standardized CV dichotic listening paradigm was used in several experiments from which data were collected to form a database. A summary of the results of 634 male and female right-handed participants can be found in figure 16.1. An overall REA is seen in the data, corresponding to an effect size of  $d' = 0.82$  (using Cohen's  $d$  for dependent measures). The degree of ear advantage is also commonly expressed using a laterality index (LI), which expresses the ear advantage as percentage difference between correct left-ear and right-ear report. The LI is



**Figure 16.1**

The right-ear advantage (REA) as obtained with the Bergen version of a consonant–vowel dichotic listening paradigm is illustrated. The figure summarizes the results of 634 right-handed male and female healthy subjects between 16 and 49 years of age. The left panel shows the mean and standard deviation for the number of correctly reported left-ear (LE) and right-ear (RE) stimuli. A significant REA is seen in the data ( $t_{633} = 20.54, p < .0001$ ), which is equivalent to an effect size of  $d' = 0.82$  and a laterality index of 18.8% (see text for details). The right panel shows the distribution of the individual scores by relating correct LE to RE reports in a scatter plot. The size of the circles in the scatter plot represents the number of subjects sharing the same coordinates in the scatter plot. Circles on the 45° symmetry diagonal represent subjects with identical LE and RE performance, i.e., no ear advantage. Circles above the diagonal line represent subjects with a left-ear advantage (LEA), while circles below the diagonal line represent subjects with an REA. As can be seen, the main cluster of participants is below the diagonal line, representing a significant REA.

calculated by dividing the difference between the correct right-ear and left-ear report by the sum of both scores, or, expressed in a formula,  $LI = 100 * (RE - LE)/(RE + LE)$ , adapted from Hugdahl and Andersson (1986). As a result, a negative LI reflects an LEA, and a positive LI reflects an REA. Expressed as an LI, the mean REA shown in figure 16.1 is 18.8%.

Based on the research presented by Kimura (1961a, 1961b), this REA is thought of as indicating the left-hemispheric processing of speech. Although other models have also been suggested (e.g., Kinsbourne, 1970a, 1970b), the so-called structural model of dichotic listening (Kimura, 1967) has until today received the most empirical support. The structural model explains the REA as an interaction of the anatomy of the ascending auditory projections with the hemispheric lateralization of speech processing. Auditory signals originating from the cochlear nuclei, located at each ear, pass relay stations in the superior olfactory complex, the inferior colliculus, and the medial geniculate thalamus before reaching the primary auditory cortex (Recanzone & Sutter, 2008). Although the auditory signals can reach both the contra- and the ipsilateral auditory cortex, the contralateral projections are stronger and more preponderant, resulting in a stronger representation in the hemisphere opposite to the originating ear. Furthermore, the model assumes that during dichotic stimulation the weaker ipsilateral pathways are blocked or inhibited (Brancucci et al., 2005; Della Penna et al., 2007; Fujiki, Jousmaki, & Hari, 2002), which leads to a selective contralateral representation of the auditory input. Assuming that speech processing can only take place in the left hemisphere, only the right auditory input is directly transferred to the relevant processing areas, while the left-ear input—initially projected to the right hemisphere—has to be transferred across the corpus callosum in order to get processed (e.g., Pollmann, Maertens, von Cramon, Lepsien, & Hugdahl, 2002; Sparks & Geschwind, 1968; Westerhausen, Grüner, Specht, & Hugdahl, 2009; for a review, see Westerhausen & Hugdahl, 2008). The REA thus results from a delay or attenuation of information during the additional transfer from the right to the left auditory cortex. Thus, according to the structural model, the basic REA is supposed to be a “hardwired” phenomenon, that is, it is determined by the anatomy of the auditory projections and the brain asymmetry. Further, the structural model can be interpreted as an instance of a “callosal relay” model (cf. Zaidel, 1983) in which the direction of the ear advantage (left or right) would indicate the hemispheric lateralization (in an absolute sense), whereas the magnitude of the ear advantage is directly associated with the interhemispheric transfer via the corpus callosum. However, as will be described below, although the REA for verbal stimulus material is a rather universal finding in verbal dichotic listening, it can be significantly modulated by manipulating the mode of stimulus presentation or stimulus characteristics (bottom-up) or through specific instructions to the subject to focus attention on either the right or the left ear stimulus (top-down). Examples of this manipulation and consequences for the

interpretation of the dichotic listening paradigm will be discussed in the subsequent sections.

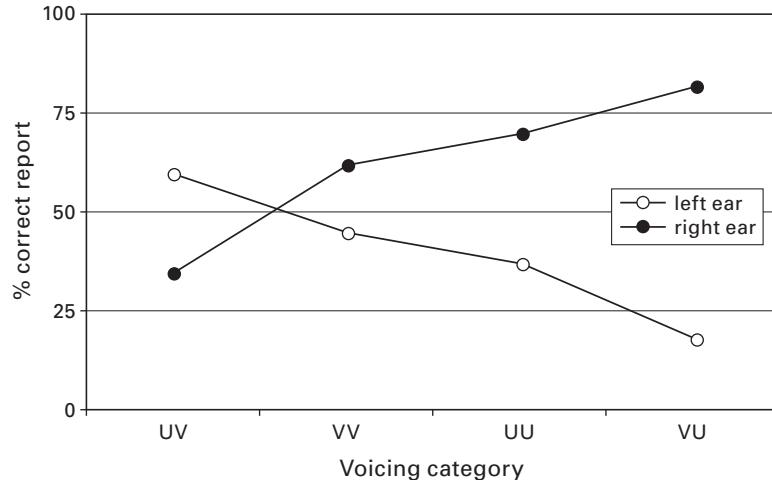
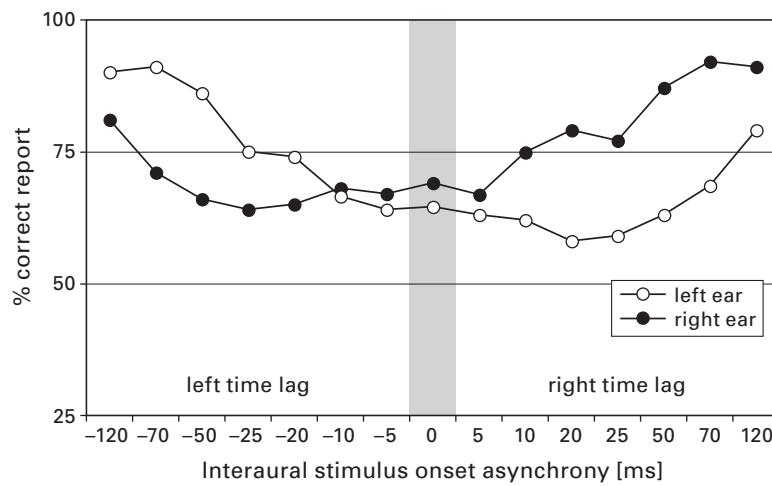
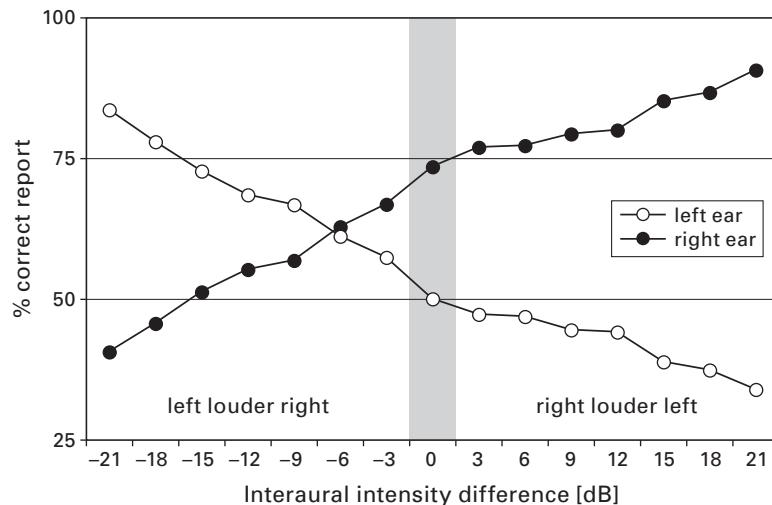
### **Bottom-up Manipulation of Auditory Laterality: Systematically Varying the Strength of the REA**

#### **Effects of Stimulus Presentation**

With the term bottom-up, or stimulus-driven, manipulation we like to refer to variations in stimulus characteristics or in the way stimuli are presented and their effects on the REA in a dichotic listening paradigm. A straightforward way of manipulating the stimulus characteristics is varying the stimulus intensity of either the right or left ear stimulus. It has been frequently shown that introducing relative intensity differences between the left- and right-ear stimulus systematically changes the degree of ear advantage toward the louder ear (Berlin, Lowe-Bell, Cullen, Thompson, & Stafford, 1972; Bloch & Hellige, 1989; Graves, Morley, & Marcopoulos, 1987; Hugdahl, Westerhausen, Alho, Medvedev, & Härmäläinen, 2008; Tallus, Hugdahl, Alho, Medvedev, & Härmäläinen, 2007; Westerhausen, Moosmann, et al., 2009). For example, Hugdahl et al. (2008) showed that varying the interaural intensity difference in steps of 3 dB changes the ear advantage in a linear fashion. As can be seen in figure 16.2 (top), by gradually increasing the intensity difference in favor of the right ear, the REA is correspondingly increased. Similarly, increasing the interaural intensity difference in favor of the left ear reduces the REA and eventually produces an LEA. The data also revealed a “transition interval” in which the right-ear stimulus is still reported more often despite increasing the left ear intensity. Depending on the study, this transition interval covers an interaural difference of up to 12 dB in favor of the left ear

#### **Figure 16.2**

Illustration of different forms of bottom-up manipulation of performance in dichotic listening. The top panel shows the effect of interaural intensity difference on the left- and right-ear report (data taken from Hugdahl et al., 2008), while the middle panel shows the effect of interaural stimulus onset asynchrony (SOA) on the ear advantage (data extracted from Studdert-Kennedy et al., 1970, figure 4, p. 601). Note that in the study by Studdert-Kennedy et al. (1970) subjects were allowed to report more than one syllable per trial, which can be seen in an increase of the correct report of the subdominant ear for larger SOAs. This was interpreted by the authors as an indication of a sequential processing of left- and right-ear stimuli in long SOA ranges. The bottom panel illustrates the effect of voicing by showing the left- and right-ear report for the four possible voicing conditions: unvoiced syllable presented to the left ear and voiced syllable presented to the right ear (UV), either voiced (VV) or unvoiced syllables (UU) presented to both ears, and voiced syllable presented to the left and unvoiced presented to the right ear (VU). Data taken from Rimol et al. (2006).



(Berlin et al., 1972; Hugdahl, Westerhausen, Alho, Medvedev, & Hämaläinen, 2008; Westerhausen, Moosmann, et al., 2009). Referring to the structural model of dichotic listening, an intensity difference effect can be explained by assuming that increasing the stimulus intensity in one ear also increases the activation of the (contralateral) auditory cortex (Jäncke, Shah, Posse, Grosse-Ryuken, & Muller-Gartner, 1998). When the right-ear stimulus is presented more loudly than the left, the right stimulus is more strongly represented in the left hemisphere than the left-ear stimulus is in the right hemisphere. This initial difference is then further increased by a degradation of the signal due to the attenuation caused by the transfer across the corpus callosum, which together results in an increased REA. However, when the left stimulus is louder than the right, the left-ear input to the right hemisphere is initially stronger, so that the callosal transfer loss gets partly or completely compensated for, resulting in a reduction of the REA or a switch to an LEA. We now suggest that using an interaural intensity difference manipulation makes it possible to express the strength of a cognitive (perceptual) effect, the REA, in terms of physical quantities (dB), i.e. allowing for a psychophysical approach to the quantification of a laterality difference that ranges between 6 and 12 dB.

Another phenomenon related to changing stimulus presentation characteristics is the so-called lag effect, which was first reported by Studdert-Kennedy, Shankweiler, and Schulman (1970). It describes the effect of introducing a stimulus onset asynchrony (SOA) between the left- and right-ear stimuli. This manipulation reliably shows that the lagging stimulus is reported more often than the leading one for a wide range of SOAs (cf. figure 16.2, middle; and see also Berlin, Lowe-Bell, Cullen, & Thompson, 1973; Wood, Hiscock, & Widrig, 2000). However, comparable to what is found in the intensity manipulation paradigm, there is a transition interval indicating that for a short left-ear lag (up to 10–20 milliseconds) the “built-in” right-ear preference withstands the lag-induced left-ear preference (Berlin et al. 1973; Studdert-Kennedy et al., 1970). The lag effect can be explained by assuming an interruption of the processing of the leading stimulus caused by the lagging stimulus, resembling a “backward masking” effect. Since for larger SOAs (greater than 90 milliseconds) subjects tend to report both stimuli (Berlin et al., 1973), a critical time period for the interruption can be assumed, that is, the lagging stimulus only has an interfering effect when the processing of the leading stimulus is not completed. Otherwise both stimuli are processed sequentially, which results in an increase of the correct report also of the subdominant ear for larger SOAs (see figure 16.2, middle).

Taken together, varying the interaural intensity and SOA difference can be used to increase, decrease, or even reverse the ear advantage in a dichotic listening situation. In other words, the built-in right ear preference for verbal stimulus material can be overcome by the bottom-up manipulation of the stimulus presentation parameters. This allows for a systematic manipulation of the relative saliency of the left- and right-

ear stimulus in the dichotic listening paradigm, allowing for a gradual and quantitative analysis of the strength of the ear advantage, that is, quantifying the relative strength of a lateralized effect in a psychophysical approach.

### Effects of Stimulus Characteristics

While both intensity and lag effect are evoked by changes in the way the stimuli are presented, phonological features of the stimuli themselves can also substantially modulate the degree and direction of the ear advantage. Depending on their phonological features, certain stimuli are reported more frequently in a dichotic situation regardless of the ear they are presented to, an effect generally referred to as a "stimulus dominance effect" (see, e.g., Speaks et al., 1981). Using CV-syllables as stimuli, one such a feature is the voicing of the syllables, a phonological concept that describes the vocal cord vibration during the articulatory process. Voiced syllables, like /ba/, /da/, or /ga/, are characterized by a short time interval (ca. 25 milliseconds) between the release of the consonant sound and the beginning of the rhythmic vocal cord vibrations of the vowel (also called voice-onset time). Voiceless or unvoiced syllables, like /pa/, /ta/, or /ka/, have a long voice-onset time (ca. 70 milliseconds). While the voice-onset time represents a physical measure that can vary along a continuum (measured in milliseconds), voicing represents an articulatory property of the stimulus that is directly linked to a categorical perception (e.g., /ga/ or /ka/). Systematically combining voiced and unvoiced syllables in dichotic pairs, Rimol et al. (2006) found that the unvoiced syllables dominate over the voiced syllables, having a systematic effect on the dichotic listening ear advantage (cf. figure 16.2, bottom; see also Berlin et al., 1973; Gerber & Goldman, 1971; Speaks et al., 1981). Rimol et al. (2006) found that while pairings of voiced with voiced and of unvoiced with unvoiced syllables showed an REA, a relatively stronger REA was observed when a voiced syllable was presented to the left ear and an unvoiced to the right ear. However, when presenting a voiced syllable to the right in combination with an unvoiced syllable to the left, a significant LEA was found (for a replication, see Sandmann et al., 2007). Thus, the general right-ear preference for verbal material was canceled out by a strong stimulus dominance of the unvoiced syllables. The dominance of the unvoiced syllable has been explained on the basis of the lag effect, by claiming that later voice onset in unvoiced as compared to voiced syllables acts comparably to presenting two syllables with a time lag (Berlin et al., 1973). Moreover, Brancucci et al. (2008) demonstrated in a magnetoencephalography (MEG) study that the presentation of stimulus pairs of unequal (e.g., /ga/-/ka/) as compared to equal voicing (e.g., /ga/-/ba/) results in a higher alpha coherence between the hemispheres, which can be interpreted as stronger involvement of interhemispheric interaction.

In addition to the voicing, CV syllables can also be categorized by the place of articulation, that is, the location of the blockage of air while articulating the conso-

nant. Three forms can be distinguished: bilabial articulation (blockage at both lips) like for the consonant /b/ or /p/, alveolar articulation (blockage at the alveolar ridge of the palate) like for /t/ or /d/, and velar articulation (blockage at the velum) like for /k/ and /g/. Also less frequently studied than the effect of voicing, place of articulation also appears to have a systematic effect on the ear advantage (Gerber & Goldman, 1971). Speaks et al. (1981) reported that velar articulated syllables dominate over both bilabial and alveolar forms of articulation.

As reviewed above, phonological stimulus features can substantially change the perception or processing of dichotically presented syllables. The existence of a stimulus dominance effects underline the necessity to carefully control for these factors in order to obtain reliable data. For example, regarding the voicing effect, this can be achieved either by realizing all possible combinations of voiced and unvoiced stimuli, so that the dominance effects would be cancelled out within an experiment, or by applying only those stimulus combinations that are least influenced by these effects (e.g., using only combinations with comparably voiced syllables).

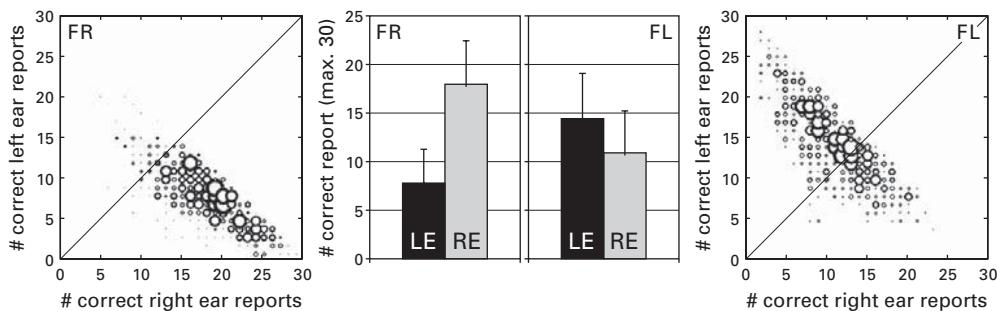
### **Top-Down Manipulation of the Ear Advantage: A Matter of Cognitive Control?**

The effects of focused attention on the REA has a long history in dichotic listening and auditory laterality research (e.g., Bryden et al., 1983; Hugdahl & Andersson, 1986; Kirstein & Shankweiler, 1969), and Kinsbourne suggested in 1970 that perceptual laterality differences in fact could be due to attentional bias favoring one hemisphere over the other (Kinsbourne, 1970a, 1970b, 2003). Kinsbourne suggested that limited attentional resources are allocated to the hemisphere that is specialized for processing of different kinds of sensory stimuli. In dichotic listening, such a view would mean that the REA would be due to the verbal nature of the stimuli typically used in such studies, which would predominantly activate the left hemisphere, which, in turn, would bias attention to the right side of auditory space. O'Leary (2003) goes even further and suggests that even the expectation that stimuli will be verbal can elicit an REA through the same attentional bias mechanisms. In the same vein, the expectation that stimuli will be nonverbal may elicit an LEA (e.g., Spellacy & Blumstein, 1970).

Kinsbourne's model was labeled "attentional" since it explains the REA by referring to an attentional bias toward the right side of space whenever verbal material is used, which is supposed to be an automatic, or bottom-up process. This needs to be contrasted with an instruction-driven attentional component which can be seen as a top-down volitional process of focusing attention on one ear. An example of such a top-down process is the so-called forced attention paradigm, (so labeled by Hugdahl & Andersson, 1986), in which the participants are verbally instructed to direct their attention to, and report from, only one ear. Attention-instruction approaches have been frequently used by different research groups and with different paradigms (Bryden et al., 1983; Foundas et al., 2006; Hiscock & Beckie, 1993; Hiscock et al., 1999; Mondor

& Bryden, 1991), and they typically produce the following pattern of results: Relative to the free report (labeled nonforced, NF, by Hugdahl & Andersson, 1986) condition (as shown in figure 16.1), directing attention to the right ear (forced-right attention; FR) significantly increases the REA. For the example data taken from the Bergen dichotic listening database and presented in figure 16.3, the REA increases from an LI of 18.8% in the NF condition to an LI of 38.3% in the FR condition (equivalent to an effect size of  $d' = 1.36$ ). However, instructing the subjects to attend to the left ear (forced-left attention; FL) decreases or even reverses the ear advantage to yield an LEA. For the data presented in figure 16.3 the corresponding LI = -13.4%, equivalent to an effect size of  $d' = 0.40$  (see figure 16.3; for an overview, see also Hugdahl, 1995, 2003 for further details).

Originally, the attention instruction was introduced to control for the confounding effects of attention that might result from the effect that subjects, without being explicitly instructed to focus their attention, might themselves develop an attention strategy (Bryden et al., 1983). At first glance, the FR and the FL conditions might be predicted to have similar effects on the ear advantage, but in opposite directions, i.e. the focusing attention on the right-ear stimulus would promote an REA as much as focusing attention on the left ear would promote an LEA. In both conditions the same stimulus material is used and the same instructions (to attend to, and to report from, the indicated ear) are given. Consequently, it was assumed that focusing of attention



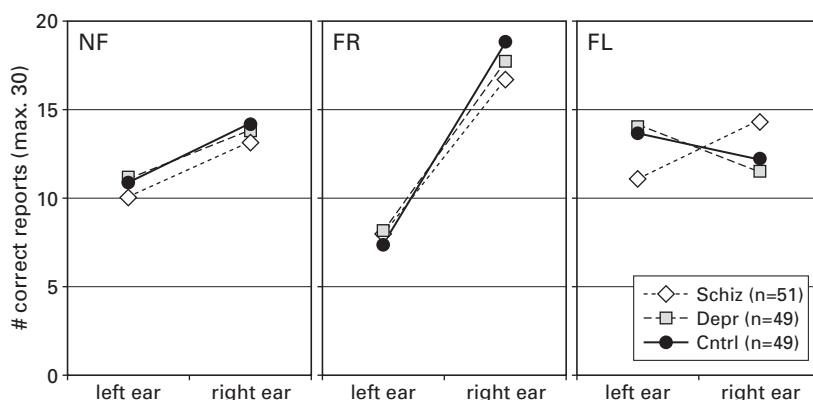
**Figure 16.3**

Top-down effect of directing attention to either the right (FR) or the left ear (FL) in the forced attention dichotic listening paradigm. The middle panel shows the mean left-ear (LE) and right-ear (RE) report for a group of 634 right-handed male and female healthy subjects between 16 and 49 years of age (data taken from the Bergen dichotic listening database). A significant right-ear advantage (REA) can be found in the FR condition ( $t_{633} = 34.37, p < .0001$ ) with an effect size of  $d' = 1.36$  (laterality index, LI = 38.3%), stronger than the REA in a nonforced condition (cf. figure 16.1). In the FL condition, a left-ear advantage (LEA;  $t_{633} = -10.26, p < .0001$ ) can be found, which equals an effect size of  $d' = 0.40$  (LI = -13.4%). The left and right panels give an overview of the distribution of the individual scores for the FR and FL condition, respectively. See figure 16.1 for further explanations.

to the left- or the right-ear stimulus would reflect the same underlying attentional processes (e.g., Bryden et al., 1983; Foundas et al., 2006; Hiscock et al., 1999; Mondor & Bryden, 1991; Voyer & Ingram, 2005; Wood et al., 2000). However, as suggested by Hugdahl et al. (2003), the FL condition may actually tap cognitive control functions related to executive processes, not seen in the FR condition. In this chapter we further advance this view by suggesting that asking the subject to focus attention on the right- or left-ear stimulus produces two different experimental set-ups which in turn rely on two fundamentally different cognitive functions. In the FR condition, the subject is required to report the syllable that is preferred anyway because of a left hemisphere advantage for verbal stimuli, that is, the attention instruction and laterality of speech processing would both favor the processing of the right-ear stimulus. In contrast, in the FL condition, the top-down instruction has to overcome the built-in right-ear preference. Thus, while the FR condition only requires the selection of the already more salient stimulus input, the FL condition specifically requires the ability to resolve a cognitive conflict between the stronger tendency to report the right-ear stimulus and the instruction to report the weaker left-ear stimulus. The ability to resolve such a conflict is one of the most fundamental aspects of what is usually referred to as executive attention or cognitive control (e.g., Baddeley, 1986; Botvinick et al., 2001; Braver et al., 2002; Fan, McCandliss, Fossella, Flombaum, & Posner, 2005; Fan et al., 2002; Miller & Cohen, 2001; Posner & Rothbart, 2007), that is, “the ability to select a weaker, task-relevant response (or source of information) in the face of competition from an otherwise stronger, but task irrelevant one” (Miller & Cohen, 2001, p. 170). Thus, comparing the task requirements of the FL and the FR conditions, it can be argued that both conditions require the subject to select a sensory input from a source of information, a function that was referred to as “orienting” (Fan et al., 2005; Posner & Rothbart, 2007), defined as “aligning attention with a source of sensory signals” (Posner & Rothbart, 2007, p. 7). However, the FL condition additionally requires the ability to resolve a cognitive conflict resulting from the requirement to select the weaker over the stronger source of information. This claim is supported by unpublished data from our laboratory obtained in a group of adult subjects ( $N = 27$ ) showing under FL instruction a significant positive correlation of right-ear correct scores ( $r = .50$ ) and a negative correlation of left-ear correct scores ( $r = -.55$ ), each with correct scores in the Wisconsin Card Sorting test (which is considered a gold standard to assess executive functions), but no significant correlation for the FR instruction condition. Thus, we now suggest that the FL and the FR conditions test different aspects of cognitive functioning. Further support for this notion would be provided by studies that can show that under certain circumstances subjects show a normal FR performance while the FL performance is altered. In the following sections, we would like to present clinical and experimental data that provide evidence for such a dissociation between the FR and FL conditions.

### Dissociation between FR and FL Attention Instruction

A first indication that different cognitive functions might be involved in the two attention conditions came from studies on psychiatric patients. Hugdahl et al. (2003) compared a group of healthy control subjects with two clinical groups, a group of patients with major depression and a group with schizophrenia. Interestingly, all three groups performed more or less comparably in the NF and the FR condition by showing the expected REA advantage in the NF condition, which was further increased in the FR condition. However, significant group differences were evident in the FL condition: While healthy controls and depressed patients showed the expected LEA, the schizophrenia group was not able to shift attention focus on the left ear and to report the left ear stimulus (see figure 16.4). Considering that the CV-syllables task is easy to perform, and that it should not be more difficult for the patients to understand and perform the task of reporting the left-ear stimulus than to report the right-ear stimulus, the selective impairment in the FL condition supports the notion that the FL and FR conditions test different aspects of cognitive functioning. Thus, while the FL condition is tapping a control process to resolve the cognitive conflict induced by the opposing bottom-up and top-down processing demands, no such conflict is present in the FR condition, which was the reason the control subjects, but not the schizophrenia patients, could handle the FL task. Furthermore, the selective deficits in the



**Figure 16.4**

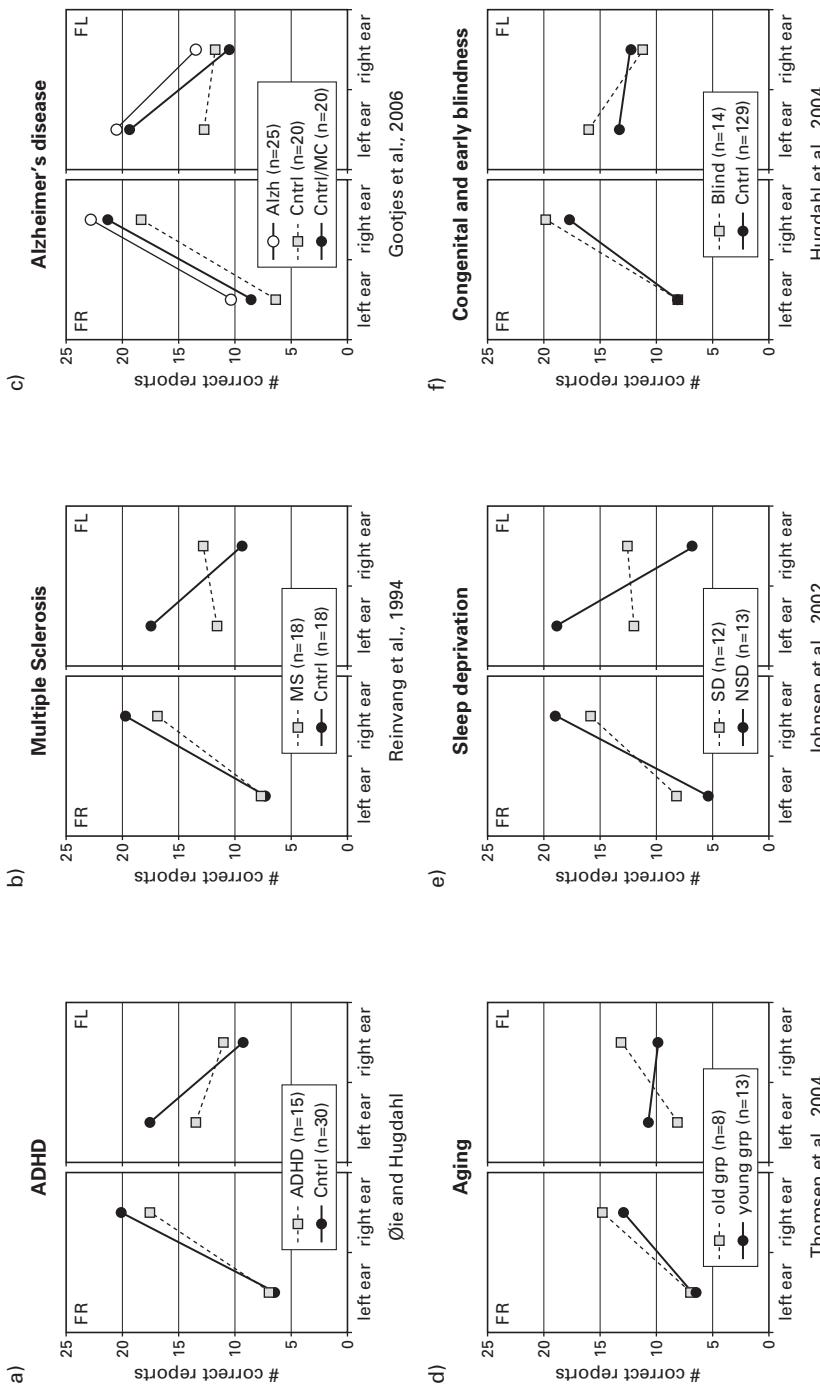
Results from a forced attention instruction paradigm comparing three groups of subjects: schizophrenia patients (Schiz), patients with major depression (Depr), and a healthy control group (Cntrl). For the nonforced (NF) and forced-right (FR) attention instruction conditions, all three groups showed comparable results. However, while patients with major depression also performed like the control group in the forced-left (FL) condition, the patients with schizophrenia were not able to successfully modulate the ear advantage. Data taken from Hugdahl et al. (2003).

FL condition in schizophrenia patients are in line with the assumption that focusing on the left ear requires cognitive control, since this patient group has been frequently shown to exhibit impaired performance in executive tasks like the Stroop task or the Wisconsin Card Sorting Test, which represent the gold standards for the assessment of cognitive control and executive function (e.g., Braver, Barch, & Cohen, 1999; Cohen et al., 1999; Green, 1998; Luck & Gold, 2008).

Similar results regarding a reduced ability to focus on the left ear stimulus in schizophrenia have also been shown in other studies (Green, Hugdahl, & Mitchell, 1994; Løberg, Hugdahl, & Green, 1999; Løberg, Jørgensen, & Hugdahl, 2004). One important factor appears, however, to be the duration of illness, with increasing failure to report the left ear stimulus in the FL condition with increasing illness duration. This was further substantiated by the findings by Øie et al. (1998), who did not find any differences between a group of recently admitted adolescent schizophrenia patients (duration of illness was 6 to 12 months) and healthy control subjects. However, in a follow-up examination after 10–13 years, the same schizophrenia patients could no longer perform the FL condition, although the healthy control subjects did not show a comparable failure of responding (Øie & Hugdahl, 2008). This implies that the FL condition could provide a neurocognitive marker of disease progression. At later stages of the illness (i.e., in chronic patients), the ability to orient to the stronger source of information, as implemented in the FR condition, might also break down.

A dissociation between FR and FL performance can not only be found in schizophrenia. Comparing a group of adult ADHD subjects with a matched healthy control group, Øie and Hugdahl (2008) reported a selective impairment in the FL condition also in this clinical condition. While both controls and ADHD patients showed a comparable REA in the FR condition, only the control subjects showed a substantial LEA in the FL condition (cf. figure 16.5a). The data for the ADHD and control subjects are from the same follow-up study as the schizophrenia data reviewed above with a 10- to 13-year follow-up period. While there were no differences between the ADHD and control subjects when they were adolescents, the results 10–13 years later showed significant differences (see Øie & Hugdahl, 2008). Thus, the data presented in the 2008 study could be seen as an indication of cognitive decline as the ADHD patients become older, selectively affecting the FL condition which mimics the clinical picture of increasing executive and cognitive control problems.

A study by Reinvang et al. (1994) on multiple sclerosis patients also confirms the suggested dissociation between the FR and FL conditions in a CV dichotic listening test. As compared to a group of matched healthy controls, there was a slightly reduced but still significant REA in the FR condition (see figure 16.5b); however, only the control subjects but not the patients showed a significant LEA in the FL condition. Later replicated in a study by Gadea et al. (2002), the selective FL impairment parallels studies showing a substantial impairment of cognitive control or executive abilities in

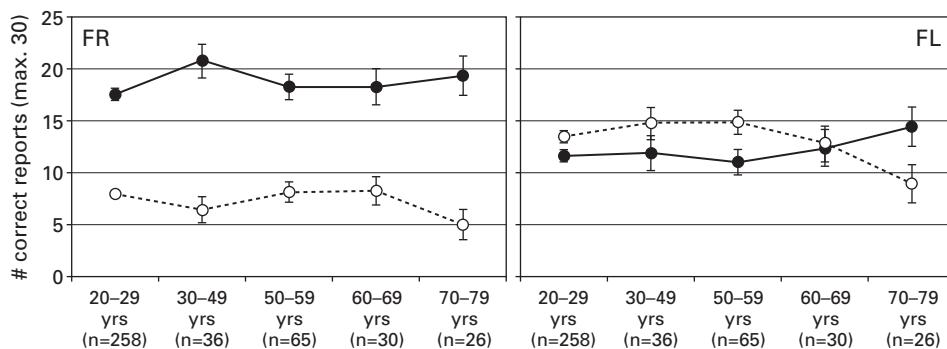
**Figure 16.5**

The forced right (FR) and forced left (FL) performance measured for different groups of participants in six different studies: (a) attention-deficit/hyperactivity disorder (ADHD); (b) multiple sclerosis (MS); (c) Alzheimer's disease (Alzh), compared with two age-matched control groups, one with (Cntr/MC) and one without (Cntrl) self-reported memory deficits; (d) healthy aging, comparing a younger with an older group (grp) of individuals; (e) sleep deprivation, comparing a sleep-deprived group (SD) with a non-sleep-deprived group (NSD); and (f) congenital and early blindness. Throughout all of the studies a dissociation between FR and FL performance can be seen: While the performance in the FR condition was, in all of the examined groups of interest, more or less comparable to the respective control groups, these groups deviated from the normal performance in the FL condition.

multiple sclerosis patients (e.g., Macniven et al., 2008; Rao, Leo, Bernardin, & Unverzagt, 1991; for a review, see Rao, 1995).

A fourth example stems from a dichotic listening study on patients with Alzheimer's disease (Gootjes et al., 2006). Using monosyllabic digits as dichotic stimuli (presented in chunks of three pairs), Gootjes et al. (2006) compared a group of 25 patients with probable Alzheimer's disease with two healthy control groups of comparable age: one group without and one group with subjective memory complaints. As can be seen in figure 16.5c, all three groups were able to follow the instruction to report the right-ear stimulus in the FR condition, producing a comparable REA. However, asked to report the left ear in the FL condition, the two healthy groups produced an LEA while the Alzheimer patients were not able to follow the instruction to the same extent. Using a series of three dichotic digit pairs per trial, the paradigm employed by Gootje et al. (2006) certainly had a higher working memory load than respective one-pair trial dichotic paradigms. Nevertheless, Alzheimer's patients showed the deficits only in the FL condition, excluding the possibility that impaired working memory performance might have substantially biased the results. The fact that they could perform the FR condition also rules out the possibility that the failure to report the left ear stimulus in the FL condition was because they did not understand the instruction to selectively attend only to one side in auditory space.

However, not only pathological aging but also normal aging is found to be accompanied by a decline in cognitive abilities. Executive functions and cognitive control as measured with the Stroop test or the Wisconsin Card Sorting Test are frequently shown to be impaired in individuals age 60 and above (e.g., Andrés, Guerrini, Phillips, & Perfect, 2008; Rodríguez-Aranda & Sundet, 2006; Rush, Barch, & Braver, 2006; Traykov et al., 2007). Thus, it can be predicted that if the FL condition tests cognitive control abilities, elderly individuals should be selectively impaired when performing in the FL condition. Initial evidence for such a selective impairment comes from a study by Thomsen, Specht, et al. (2004) in which a group of young subjects (age range: 19 to 34 years) was compared with a group of older subjects (age range: 53 to 63 years). While both groups performed equally in the NF and FR conditions, the group of older subjects was not able to successfully follow the FL instruction and no LEA was found (see figure 16.5d; see also Andersson, Reinvang, Wehling, Hugdahl, & Lundervold, 2008; Hällgren, Larsby, Lyxell, & Arlinger, 2001). To follow up on the reported aging effects in the literature, we reanalyzed the data from the Bergen dichotic listening database, focusing on the interaction of age with FL and FR instruction. The available sample was clustered into age groups by considering the decade of life the subjects were in when tested. As can be seen in figure 16.6, all groups showed a comparably strong REA in the FR condition, and age groups containing subjects between 20 and 59 years of age also showed an LEA in the FL condition. However, at the age of 60 and onwards, the ability to focus attention on the left ear is reduced, resulting in no



**Figure 16.6**

Mean number ( $\pm$  95% confidence limits) of correct left- and right-ear reports in the forced-right (FR) and forced-left (FL) attention instruction conditions as a function of age. In the FR attention condition (left panel) all age groups showed a significant right-ear advantage. However, in the FL condition the 60-69 and the 70-79 age groups did not show the left-ear advantage seen in the younger groups. Data taken from the Bergen dichotic listening database (Hugdahl, 2003).

significant ear advantage in the 60- to 69-year group and an REA in the 70- to 79-year group, despite the instruction to focus attention on the left-ear stimulus. Thus, in accordance with our predictions, older subjects (greater than 60 years of age) revealed a selective impairment in the FL condition, comparable what we have seen in clinical groups reviewed above.

The studies discussed so far have shown a disease- and age-related decline in the ability to successfully perform in the FL condition. However, there are also circumstances in which healthy subjects can show a relatively normal FR performance while at the same time the FL performance is impaired. Johnsen et al. (2002) studied two groups of navy cadets, one after 74 to 80 hours of sleep deprivation and one well-rested group. While both groups showed normal NF performance and were able to modulate the REA in the FR condition, only the non-sleep-deprived group showed an LEA in the FL condition. The sleep-deprived group yielded comparable left- and right-ear reports in the FL condition, that is, showed no ear advantage (see figure 16.5e). Extreme stress conditions like prolonged sleep deprivation has in other studies been shown to induce a breakdown of cognitive efficiency and vigilance, particularly in situations requiring higher cognitive functions like executive functioning and attention (see Orasanu & Backer, 1996 for review).

The examples discussed above showed groups or conditions in which the performance in the FL condition is impaired. However, the presented top-down model would also be strengthened if it could be shown that certain groups of individuals could actually perform better than controls in the FL condition. One such group where

it could be predicted that they would show enhanced performance relative to a normal control group is congenitally or early blind individuals. As pointed out by Noppeney (2007), early visual deprivation induces plastic functional and structural changes not only in the visual but also in intact auditory and sensorimotor systems that serve the purpose compensate for the loss of vision. However, these compensatory changes not only shape the abilities in the remaining sensory modalities, indicated by a superior perceptual sensibility for auditory stimuli than is the case for seeing individuals, but the compensatory changes are also associated with an improvement in attention and cognitive control functions (Collignon, Renier, Bruyer, Tranduy, & Veraart, 2006; Kujala, Alho, & Näätänen, 2000; Röder et al., 1999). Thus, a reasonable prediction is that congenitally or early blind individuals would perform better than seeing individuals in forced-attention dichotic listening and, in particular, in the FL condition. Comparing early blind individuals with seeing controls, Hugdahl et al. (2004) showed that the blind subjects had better overall performance as well as a stronger LEA than seeing subjects in the FL condition (cf. figure 16.5f). These findings therefore not only attest that blind individuals show enhanced perceptual accuracy in the auditory domain and possess a superior ability for cognitive control processes, the findings also validates the suggested top-down model as tapping different cognitive functions in the FR and FL instruction conditions.

Another group of subjects that might be predicted to show enhanced ability in the FL condition, based on their general enhanced executive and attention abilities, are individuals with a bilingual background. It has been previously shown that bilingual subjects outperform monolingual subjects in tasks relying on the ability to inhibit task-irrelevant cues and conflict solving (e.g., Bialystok, 2001; Costa, Hernández, & Sebastián-Gallés, 2008). The better performance of bilinguals is thought to result from their extensive experience in switching between languages and in the inhibition of the language not in use. Concerning the forced attention dichotic listening task, it can now be predicted that this experience also helps in the top-down modulation in the FL condition. Preliminary results from the Åbo University Academy in Finland (Matti Laine, personnel communication) have shown that Finnish-Swedish bilingual subjects performed better than Finnish monolinguals in the FL condition.

### Evidence from Functional Neuroimaging

The prefrontal cortex (PFC) and anterior cingulate cortex (ACC) have been shown to play a crucial role in cognitive control. From the existing literature, the ACC is either supposed to be the “center” of executive control (e.g., Fan et al., 2005; Posner & Rothbart, 2007) or thought to be especially responsible for the detection of cognitive conflict, while the PFC is more involved in the control function per se (e.g., Botvinick et al., 2001; Braver et al., 2002; Miller & Cohen, 2001). Thus, assuming that the FL

and FR conditions differ in the detection and resolution of a cognitive conflict, PFC and ACC involvement would be predicted to be stronger in the FL than in the FR condition. In a functional magnetic resonance imaging (fMRI) study, Thomsen, Rimol, et al. (2004) examined brain activation in the FL and FR conditions in a group of healthy subjects. Contrasting the FR and FL dichotic presentations with a binaural condition, both conditions showed blood-oxygen-level-dependent (BOLD) activation in left-lateralized (but bilateral) PFC and ACC areas (see also Jäncke & Shah, 2002). However, when contrasting images from the FL with images from the FR condition, a stronger ACC activation was seen in the FL condition, while the reversed contrast, FR images minus the FL images, did not result in any remaining significant activation. Thus, the fMRI data support stronger involvement of the ACC in the FL than in the FR condition. Together with the behavioral data reviewed above, the BOLD fMRI data thus fit well into the hypothesis that the FL instruction condition relies on conflict-solving abilities, requiring intact ACC and PFC brain regions and connections. It may be of interest to note in this context that patients with schizophrenia fail to activate the same brain regions in test situations tapping executive and cognitive control functions (Blakemore & Frith, 2000), as they fail in the dichotic listening FL instruction situation.

### A Reinterpretation of Dichotic Listening Performance

The above-discussed studies provide evidence for a dissociation between FL and FR performances in clinical and healthy subjects, supporting the idea that both conditions, although very similar in instruction with just the direction of the attention focus differing, indeed test different levels of cognitive functioning. As stated above, this opinion opposes the frequently stated assumption that both conditions represent the same attention process, and that using both an FR and an FL condition is just a control procedure (e.g., Bryden et al., 1983; Foundas et al., 2006; Hiscock et al., 1999; Mondor & Bryden, 1991; Voyer & Ingram, 2005; Wood et al., 2000). We suggest a reinterpretation, suggesting that the top-down modulated dichotic listening paradigm with instructions for attention focus to either the right or left side in auditory space is a paradigm for testing conflict solving and executive functioning (Hugdahl et al., 2009). In this context, we suggest that the FL condition can be seen as an auditory analogue to the interference and conflicting nature of the Stroop task (MacLeod, 1991; Stroop, 1935). In the Stroop task, the classic paradigm for studying cognitive control (see, e.g., Cohen et al., 1999), the strong tendency to report the semantic information is caused by a bottom-up effect, the overlearned focus on semantic information which automatically causes the subject to respond with the word and not the ink color. When the instruction is to report the ink color and not the word, this automatic response tendency has to be counteracted by the instruction-driven top-down effect to refocus on the ink color information. In a similar way, the right ear stimulus in the

dichotic listening situation automatically causes a response because of the left hemisphere lateralization for verbal stimuli, and the anatomy of the auditory system. This process requires ability for cognitive control and executive capacity. As in the Stroop situation, the right ear stimulus response tendency has to be overcome by refocusing attention to the less salient left ear stimulus in the FL condition, a process that requires cognitive control and executive capacity.

### **Combining Top-Down and Bottom-Up Manipulation—A Method to Quantify Cognitive Control?**

In the previous sections we have presented a model suggesting that the dichotic listening FR and FL conditions tap different aspects of cognitive functioning, that is, the FR condition only requires an orienting of attention toward a source of information, while the FL instruction additionally requires the ability to resolve a cognitive processing conflict. We have also seen that this difference is based on the stronger perceptual salience of the right ear, that is, the REA. In the FR condition, the attention instruction requires the subject to focus on the more salient right-ear stimulus, while the FL instruction requires overcoming the “hardwired” REA by refocusing of attention. Further, we have demonstrated that the ear advantage can also be systematically manipulated by gradually varying stimulus presentation or stimulation characteristics, such as introducing interaural intensity differences or SOAs. In other words, bottom-up stimulus manipulations can be used to gradually change the difference in the perceptual salience of the left- and right-ear stimuli. In turn, by combining bottom-up and top-down manipulations in one dichotic listening paradigm, it is now possible to gradually change the cognitive conflict between the attention instruction and the bottom-up stimulus preference. For example, regarding the FL condition, an increase in the interaural intensity difference in favor of the right ear would make it more and more difficult to report the weaker left-ear stimulus, while presenting the left-ear stimulus louder than the right would make it easier to follow the FL instruction. Moreover, the bottom-up manipulation also makes it possible to create stimulation conditions in which the left- and not the right-ear stimulus becomes the more salient one, allowing us to create a situation in which the FR condition is the more difficult task.

As a consequence, it should now be possible to use a CV-syllables dichotic listening situation to assess cognitive control parametrically, by gradually making it more and more difficult to use attention to overcome the bottom-up and stimulus intensity driven tendency to report the stronger, more salient stimulus. The advantage with such an approach is that it can be accomplished within a single experimental paradigm, with the *direction* of the instruction to focus attention as the only manipulation between experimental conditions. It can now be asked whether patient groups differ-

ing in degree of cognitive control impairment differ in their ability to, for example, overcome an interaural intensity or SOA difference by directing attention to the less salient input. For example, would patients with schizophrenia withstand only a 5 dB difference in favor of the left-ear signal, whereas patients with ADHD might withstand a difference of 10 dB? Would bilingual subjects be able to withstand a difference of twice that of the patients before they no longer report the left ear stimulus? To support this, it would be necessary to show that a decrease in, for instance, right ear stimulus salience through increasing the intensity of the left ear stimulus also makes it more effortful to report the weaker stimulus. One way to do so would be to show that bottom-up and top-down manipulation interact in explaining the performance in a dichotic listening paradigm. Initial evidence comes from two studies that report such an interaction (Tallus et al., 2007; Westerhausen, Moosmann, et al., 2009). More specifically, Westerhausen, Moosmann, et al. (2009) showed that the percentage overall correct report in the FL and the FR conditions decreases gradually with the bottom-up intensity manipulation more and more supporting the not-to-be attended ear. This observation contrasts with other studies that failed to show a comparable interaction relating top-down attention instruction to both intensity (Bloch & Hellige, 1989) and SOA bottom-up manipulation (Wood et al., 2000).

Another way of supporting an interactive model would be to use functional neuroimaging, like fMRI, and look for gradual changes in activation in the critical PFC and ACC regions reviewed above, as the right and left ear stimuli are gradually made more or less salient through manipulation of the interaural intensity in the three attention instruction conditions, NF, FR, and FL. It could be predicted that with task difficulty also the degree of cognitive control should vary, which would be detectable in a parametric modulation of, e.g., ACC activation.

A gradual approach to cognitive conflict and cognitive control is not possible in the Stroop task, since the conflict is either absent (focus on the semantic information) or present (focus on the color information) in an all-or-none way. In this respect, the current approach would be ideal for revealing an underlying common structure of cognitive control impairment in different clinical groups (and also in groups believed to have superior executive functions) that otherwise would not be considered as having a common denominator because of non-overlapping phenotypes when it comes to diagnostic categories. A common cognitive impairment across diagnostic categories would have theoretical implications for, e.g., psychiatric disorders where cognitive symptoms have been in focus in recent years (see, e.g., Elliott, 1998; Green, 1998; Rund et al., 2006). If a cognitive deficit, like dysfunctional cognitive control, is common across diagnostic categories, this may provide a new way of looking at psychiatric disorders as dimensional rather than categorical, which in turn could have consequences for development of new treatment strategies, both pharmacological and behavioral.

### A Clinical Perspective

In the present chapter we have aimed to demonstrate that the dichotic listening paradigm, beyond being a behavioral technique to test hemispheric specialization, can also be used to assess and quantify cognitive control abilities in both healthy subjects and clinical groups of individuals. Moreover, the current approach looks at commonalities in cognitive impairment across diagnosis, using a single experimental task applied to different clinical groups (see figure 16.5). In this respect, the current approach differs from the traditional neuropsychological test approach, which typically applies a multitude of tasks and tests to a single clinical diagnostic group to reveal the range of impairment across cognitive domains. A disadvantage with the latter approach is that the tests applied also differ in difficulty and requirement of general understanding of the test situation. For example, while both the Wisconsin Card Sorting and Stroop tests tap aspects of executive and cognitive control functions, the Wisconsin Card Sorting test in addition requires that the patient understand the overall structure of the test situation, not required in the Stroop test. Thus, a difference in test profiles between patients with schizophrenia and subjects with dementia could be due, at least in part, to the fact that one of the groups may have problems understanding the very nature of the test situation, which will affect test scores. The current approach will circumvent this problem by utilizing a task that, in the first place, is quite simple to perform and does not require the kind of intellectual reasoning necessary to solve, for example, the Wisconsin Card Sorting test. This makes it easier to compare different clinical groups for a common impairment structure, targeting a unique cognitive domain that is not confounded by differences in requirements for overall understanding of the situation. Second, the overall structure of the dichotic listening forced-attention paradigm is the same across instruction conditions, with the sole exception of the direction of the instruction, that is, attending to the right-ear stimulus in the FR condition and attending to the left-ear stimulus in the FL condition. This provides a classic example of an experimental approach where only one aspect of the task differs between conditions, to which any difference in performance between conditions must be ascribed. We hope that the present chapter will be helpful in advancing a new view on the use of dichotic listening in experimental and clinical neuropsychology research.

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## 17 Hemispheric Asymmetry of Memory

Grégoria Kalpouzos and Lars Nyberg

A fundamental neuroscientific question concerns the functional organization of the brain. Over the years, many different mapping rules have been considered and various functional brain maps have been proposed. At the heart of many functional charts is the notion of asymmetry of functions. That is, are specific brain functions lateralized to one of the cerebral hemispheres? As is evident from the current volume, much progress has been made in addressing this issue, and functional asymmetries have been described for several functions. The best known example is language functions, but many additional functions have been considered in this context as well. The present chapter is concerned with the possibility of functional asymmetries in the organization of memory functions.

It is generally agreed that human memory can be decomposed into a variety of systems and processes. A well-known division is that between short-term versus long-term memory. In turn, long-term memory can be subdivided further into specialized functions. A basic distinction, proposed by Larry Squire (2004), is between declarative and nondeclarative memory systems. The declarative branch includes separate memory systems for events (episodic memory) and factual knowledge (semantic memory), a distinction originally proposed by Endel Tulving (1972).

In this chapter, we will focus on episodic memory, since a large majority of functional asymmetries have been suggested within this system. Its content is extremely rich and complex, as it “renders possible conscious recollection of personal happenings and events from one’s personal past and mental projection of anticipated events into one’s subjective future” (Wheeler et al., 1997, p. 332). In other words, remembering a personal past event implies the recovery of specific details surrounding this event, like the spatiotemporal and emotional context in which this event happened.

In terms of its functional organization, episodic memory has been linked to an extensive set of brain regions. Foremost among these regions is the medial-temporal-lobe (MTL) system (Squire et al., 2004; Tulving & Markowitsch, 1998). In addition, interactions between MTL regions and prefrontal cortical regions have been suggested

to be critical for episodic memory functioning (e.g., Simons & Spiers, 2003). More recently, a lot of attention has been directed to parietal brain regions (Wagner et al., 2005). The MTL, frontal, and parietal lobes are also relevant from the point of view of functional asymmetries, and the discussion below will revolve around these regions.

The classical approach to studying functional asymmetries is the lesion method, where the cognitive consequences of lesions to homotopic regions are compared (e.g., left and right hippocampi). Lesion studies are valuable but also problematic because lesions do not respect anatomical boundaries, patients could engage in different strategies, and patients could also cope with their lesion by using compensatory neurocognitive mechanisms. One way to overcome these limits is to use functional neuroimaging in healthy subjects, controlling the cognitive mechanisms engaged in the tasks. Three main techniques have been used so far: positron emission tomography, functional magnetic resonance imaging (fMRI), and electroencephalography (EEG). A limit of functional neuroimaging is the difficulty in determining whether the activated regions are truly necessary to complete the task. Repetitive transcranial magnetic stimulation (rTMS) has been used to address this issue. This technique allows one to produce a brief and reversible decline of the performance *in vivo* in order to determine if the stimulated area is crucial to the task. In the present chapter we consider evidence from a variety of methodologies, with special focus on data from fMRI studies.

### **The Medial Temporal Lobe**

The first consistent finding provided by lesion studies was the material-specific lateralization of the MTL, where the left hippocampus is crucial for verbal memory while the right hippocampus is specialized for nonverbal memory (Milner, 1998). Many subsequent investigations have attempted to validate this dissociation using functional neuroimaging. In addition to this functional asymmetry, investigations also attempted to discover differential functions of the MTL within each hemisphere. These attempts generally failed in the sense that even in the presence of unique results describing functional MTL asymmetries, no general theory or model has emerged yet. Indeed, meta-analyses and reviews of the literature could not reveal any consistent process-specific MTL asymmetry (Henson, 2005). Below, we will consider the consistency of the material-specific MTL lateralization and then discuss attempts to find other MTL functional asymmetries.

#### **Material-Driven Mnemonic Asymmetry**

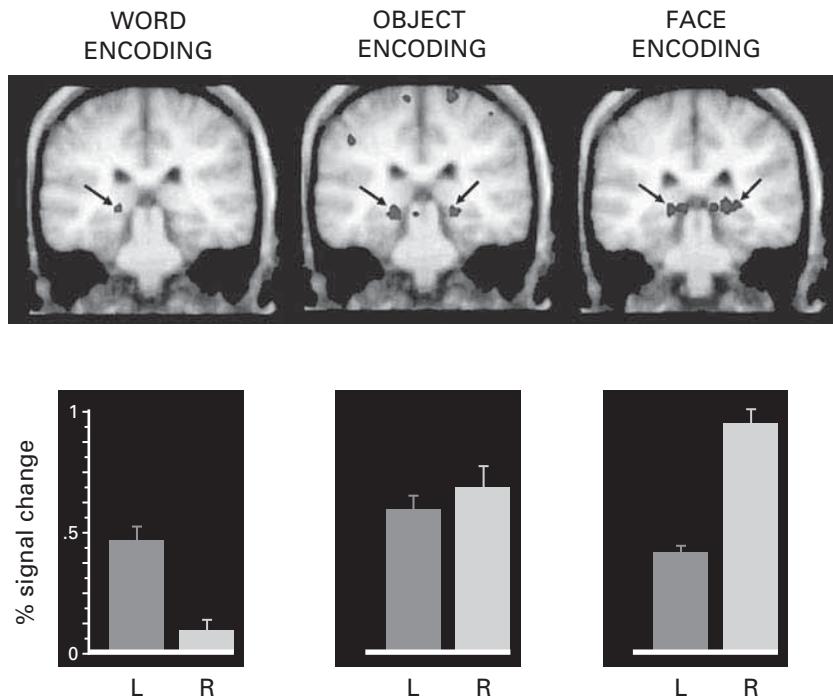
One of the first relationships between memory and the brain was established after resection of the medial temporal lobe bilaterally (mainly the hippocampal complex)

in epileptic patients and schizophrenic individuals (Scoville & Milner, 1957). In turn, the medical profession and researchers were faced with an unexpected syndrome: amnesia. The very first idea on asymmetry related to memory processes was that the MTL resection of the dominant hemisphere (usually the left, supporting language) would lead to more severe memory impairment than MTL resection of the nondominant hemisphere. In their data set, Scoville and Milner highlighted that bilateral resection was a prerequisite for inducing amnesia. However, some unilateral lesions were shown to induce amnesia as well. Brenda Milner pointed out one such observation in her thesis in 1952: Using a pictorial visual discrimination learning task, she found that deficits were seen more reliably after right- than left-temporal-lobe lesions (see Milner, 1998). She also had some assumptions regarding the memory complaints of left-temporal-lobe lesions patients, particularly focused on verbal memory. A few years later, Brenda Milner's group showed a clear impairment in recognition memory for abstract visual patterns and new faces after right temporal lobectomy (see Milner, 1998). Overall, these first observations indicated that the left MTL is crucial for verbal memory tasks, while the right MTL is more likely specialized for nonverbal memory tasks. Thus, the predominant factor that distinguishes between the left and right MTL would be the nature of the to-be-remembered material.

Spiers, Maguire, and Burgess (2001) presented an exhaustive list of published hippocampal amnesia cases. Examining the unilateral MTL lesion cases, the results are not so obvious, since amnesia can arise from either left- or right-sided lesions, regardless of stimuli (words, objects, face). However, items containing visuospatial features do involve verbal processes, as the items can be verbalized—for instance, a common object of everyday life can be categorized as a visual item with a certain shape, color, and texture but also as a verbal item, as this object refers to several words that define it, such as its name, its function, and further words characterizing it or being related to it. Thus, stimuli typically cannot be categorized as exclusively verbal or nonverbal. In order to accurately investigate whether the nature of the material is differentially processed by the left or the right MTL, a distinction between visuospatial and visuoverbal items has been used instead (for a review, see Spiers, Burgess, et al., 2001). The findings are in agreement with the material-driven MTL hypothesis, showing that the right MTL is activated for items containing visuospatial features while the left MTL is recruited for verbalizable items.

Using functional neuroimaging in healthy subjects, the following patterns of activations within the MTL emerge. Most previous studies have investigated episodic memory encoding and have shown that words strongly activate the left MTL rather than the right (Binder et al., 1996; Branco et al., 2006; Dolan & Fletcher, 1997; Golby et al., 2001; Kelley et al., 1998; Kirchhoff et al., 2000; Martin et al., 1997; Richardson et al., 2003). Encoding visual patterns results in preferentially right-MTL-lateralized asymmetry (Branco et al., 2006; Golby et al., 2001). MTL lateralization of encoding of faces,

scenes, and objects is less clear, but it seems that both left and right MTL are similarly activated (objects: Kelley et al., 1998; scenes: Branco et al., 2006; Gabrieli et al., 1997; Golby et al., 2001; Kirchhoff et al., 2000; faces: Golby et al., 2001). An important point emphasized by Golby et al. (2001) is that encoding activations are better characterized as "asymmetrical" rather than unilateral. Although the authors found global bilateral MTL activation for faces, objects, and scenes, it seemed that both kinds of stimuli showed a right-sided trend toward asymmetry (Grady et al., 1995; Haxby et al., 1996; Martin et al., 1997). Another important point was provided by Kelley et al. (1998). In addition to the classical MTL asymmetry for words, objects, and faces, the authors demonstrated that the left MTL was activated for all three kinds of materials. Thus, contrary to the left MTL, which does not appear to be highly specialized for any particular material, the right MTL clearly shows a specialization for material containing visuospatial features, as words only weakly activated this area (see figure 17.1).



**Figure 17.1**

Material-driven memory asymmetry in the medial temporal lobe. The hippocampus activity during episodic encoding depends on the nature of the material. Word encoding is underpinned by the left hippocampus (left) while object (middle) and face (right) encoding activates the hippocampus bilaterally. L, left; R, right.

(Reprinted with permission from Kelley et al., 1998.)

This pattern of asymmetrical MTL activity during encoding is also of relevance in predicting successful retrieval: Items that are later retrieved elicit greater left and/or right MTL activation during their encoding compared to items subsequently forgotten depending on material-specific properties (Bernard et al., 2001; Brewer et al., 1998; Otten et al., 2001; Powell et al., 2005; Wagner, Schacter, et al., 1998).

Taken together, the right MTL is consistently implicated in nonverbal memory tasks, supporting its specialization for the processing of visuospatial features. The left MTL seems to be involved in memory processes for most kinds of materials. A possible interpretation is that left MTL is engaged whenever meaningful information has to be processed.

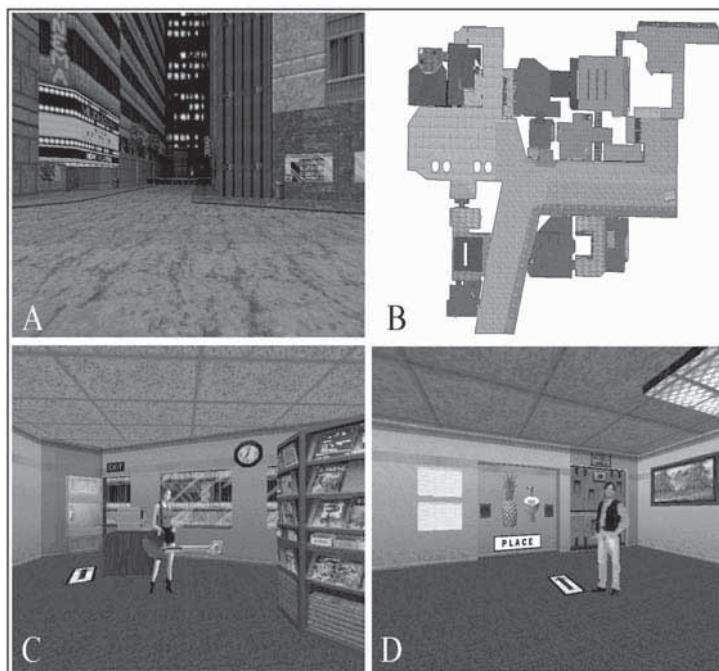
### **Contextual Processing**

Contextual memory refers to memory for the elements surrounding an item during encoding. It can refer to the spatial environment at the time of acquisition, temporal characteristics, a specific emotional state, as well as details related to the item. To induce a rich episodic memory, the recovery of an event requires a successful association of the item *and* its context. An interesting paradigm has been used to investigate memory for stimuli and their context. Spiers, Burgess, et al. (2001) used a virtual reality task depicting a town in which unilateral temporal lobectomy patients had to navigate and perform specific actions at given places (see figure 17.2). The right-temporal-lobectomy patients performed worse on topography memory tasks, whereas the left-temporal-lobectomy patients performed worse on context-dependent episodic memory tasks. The finding regarding the right-temporal-lobectomy group is in line with the importance of the integrity of the right MTL for spatial memory. Moreover, a new left-MTL specialization was highlighted in this study: This region may be crucial for context memory in the framework of the episodic memory system. Two important details must be stressed. First, the context-dependant tasks did not involve any verbal feature, excluding the possibility of interpreting the results in light of the material-type brain asymmetry, and second, the greater difference in performance between the two patient groups concerned temporal context performance (the patients had to remember which of two scenes occurred first in the virtual reality town). Thus, the left MTL, rather than the right MTL, could participate in temporal order discrimination. Further studies have corroborated this interpretation, using different materials and modality. Lancelot et al. (2005) used an auditory episodic memory task in which patients who underwent left- or right-MTL resection had to bind bird songs with spatial locations. A specific left-lateralized MTL bias for spatial context information was demonstrated, such that patients with left, but not right, MTL lesion were impaired.

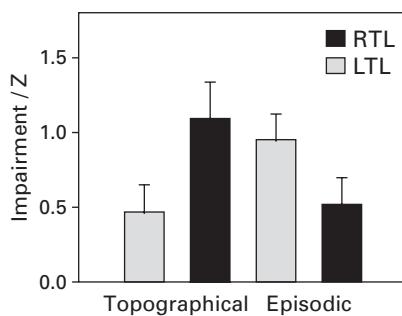
The findings regarding the requirement of the integrity of the left MTL for spatial contextual information is surprising, since, as discussed above, other studies pointed

out the importance of the right MTL structures for spatial learning and spatial recall (see also Petrides, 1985; Smith & Milner, 1989). However, memory for spatial locations and memory for spatial locations as a context of an event must be distinguished. This distinction was emphasized in an fMRI study in which Burgess et al. (2001) used the virtual reality task described above (Spiers, Burgess, et al., 2001). The authors confirmed right hippocampus involvement during spatial navigation, while the left hippocampus was activated in the processing of spatial contexts of episodic memories. In their review, Burgess et al. (2002) evaluated the contribution of the left and the right hippocampi in spatial memory and provided hypotheses regarding the relationships between the “spatial right hippocampus” and the “episodic left hippocampus” (see figure 17.2). According to the authors, the strongest hypothesis was that the left hippocampus is specialized in allocentric rather than egocentric spatial memory. In accordance with the place cells in the rat, the hippocampus establishes a map of the environment which is independent of the position of the individual (O’Keefe, 2007). Consequently, even if the individual is oriented differently in space at retrieval compared to encoding, the left hippocampus would have the possibility to reinsert an independent location into an episode. Thus, the left hippocampus would have an associative function in episodic memory, so that it can bind the spatial context to a given event.

The hippocampus has a general associative function during encoding processes. Staresina and Davachi (2008) investigated this general function by assessing binding of different features, (1) between an item and a color (a blue shirt—the item is written while the color is displayed in the background) and (2) between an item and a context by assessing the plausibility of an association (Is a red elephant plausible?). The results showed that both associations elicited left-hippocampus activation. Although a greater number of studies on the associative function of the hippocampus have shown more activation in the left than right hippocampus, this is not consistent across studies, since a material effect seems to confound the results of associative encoding tasks. For example, Achim et al. (2007) found right hippocampal activity in picture association encoding, and Sperling et al. (2003) found bilateral-hippocampal activation during the encoding of novel face-name associations (see also Zeineh et al., 2003). In order to clarify this issue, Prince et al. (2005) assessed the neural correlates of semantic and perceptual associative memory during successful encoding and retrieval. Their results showed that, in contradiction with the material-type effect, left anterior hippocampal activity was greater for perceptual encoding than for semantic encoding, whereas left posterior hippocampal activity was equivalent for both perceptual and semantic retrieval. Noteworthy is that the right parahippocampal cortex was activated during perceptual encoding and retrieval in contrast with the semantic conditions, showing a right-sided preference for nonverbal material but in an adjacent structure of the hippocampus.



**Functional lateralization**



**Figure 17.2**

Asymmetry of spatial memory versus episodic memory in the medial temporal lobe. At the top is the virtual reality town task used to examine spatial memory and episodic memory. (A) View of the town, (B) map of the town (corresponding to the topographical testing), (C) example of a situation where the subject receives an object in a room (event to be recalled later by the subject—which object, when, and where—corresponding to the episodic memory testing), and (D) example of a situation where the subject has to answer a place question. At the bottom is a graph showing stronger impairment of the right temporal lobectomy (RTL) patients in comparison to the left (LTL) patients in topographical memory and the reverse pattern regarding episodic memory (including memory for the object, temporal order, and place). (Reprinted with permission from Burgess et al., 2002.)

Context retrieval can be evaluated by asking participants to provide the response R (remember) in the case where he or she remembers contextual aspects of the encoded item and the response K (know) in the case where he or she remembers having encountered the item during the encoding phase without being able to give any detail regarding the context of acquisition. Thus, information can be retrieved via two different processes: recollection or familiarity. Generally, it has been observed that patients with right-MTL damage consistently make more R than K judgments, or in other words they show a deficit in familiarity. This is in contrast to left-MTL-damage patients, who make more K than R judgments, exhibiting a deficit in recollection (Blaxton & Theodore, 1997). This suggests that the left and right MTL may be differentially involved in recollection and familiarity. Yonelinas (2002) interpreted these findings in the light of the material-specific model. According to him, right-MTL patients have to rely on the left hemisphere, which would be specialized for verbal encoding strategies, which in turn increase recollective judgments. In contrast, left-MTL patients have to rely on the right hemisphere, which would be specialized in perceptual processes, which in turn increase familiarity judgments. A similar R-K lateralization effect has been demonstrated in the parahippocampal gyrus (Eldridge et al., 2000; Henson et al., 1999).

Recollection and familiarity retrieval processes are strongly affected by the depth of processing at encoding. Items which have been deeply (semantically) processed at encoding are more likely retrieved via recollection processes because contextual information has been previously processed. In contrast, items which have been shallowly processed at encoding (e.g., via a perceptual task) are more likely retrieved via familiarity processes, because few contextual features have been generated during encoding. Thus, it is not surprising to find more left hippocampal activity for deep than shallow processing of items during encoding tasks (Otten et al., 2001; Rugg et al., 1997). This effect is even more pronounced when taking into consideration subsequent performance to isolate successful encoding (Henson et al., 2005).

These findings converge on the hypothesis of an integrative role of the left hippocampus, allowing the association of an item with its context.

### **Encoding versus Retrieval**

A majority of studies have failed to find any consistent MTL asymmetry as a function of encoding and retrieval processes. Some early proposals were that the left MTL was recruited during encoding while retrieval would engage the right MTL (Schacter et al., 1995), but this pattern is not consistent throughout the literature. Most studies have focused on the segregation within substructures of the MTL according to the processes engaged, and two recent studies (Eldridge et al., 2005; Kennepohl et al., 2007) have found interaction effects between the rostrocaudal axis, the different substructures of the MTL, the material type, and laterality in episodic memory (see Wais, 2008, for a

meta-analysis). Importantly, though, regardless of the subfields of the MTL, both studies converged toward greater left MTL activity for successful encoding of both verbal and nonverbal items. The results were inconclusive regarding retrieval.

### Detection of Novelty

Early observations of an automatic activation of the hippocampus at encoding spurred the idea that this structure would be able to detect, and then automatically encode, novel items (Knight, 1996). Tasks investigating the novelty effect usually involve presentation of a list of items, which is followed by a second presentation of old and new items. The novelty effect is measured by subtracting the *old* condition from the *new* condition. Tulving and colleagues (Tulving, Markowitsch, et al., 1994; Tulving et al., 1996) have reported a specific activation of the hippocampus during novelty detection. Across several data sets (Tulving et al., 1996), it appeared that the laterality of the hippocampal activations was generally material dependent (pictures of people, scenes, landscapes, and faces elicited right hippocampus, whereas words engaged left hippocampus). Moreover, left or right hippocampal activity seemed to be located in the anterior part of the structure (see also Dolan & Fletcher, 1997; Saykin et al., 1999). However, another set of studies postulated a generic role of the left anterior hippocampus in novelty detection, regardless of the material. For example, Strange et al. (1999, 2005) conducted two studies in which both perceptual and semantic novelty detection engaged this specific area. According to these authors, the left anterior hippocampus would be engaged to process “unexpectedness of stimuli.”

Thus, two different hypotheses have been highlighted for novelty detection in the hippocampus: the material-driven hypothesis and the specialization of the left anterior hippocampus regardless of material. If the second hypothesis is confirmed in future studies, the two hypotheses are not in contradiction, since supplementary right hippocampal activation during nonverbal encoding of novel items could still emerge.

### Time Scale and Phenomenological Aspects in Autobiographical Memory

In autobiographical memory, the multitrace theory (MTT; Nadel & Moscovitch, 1997) claims a time-invariant involvement of the hippocampus, while the consolidation theory (Squire, 1992) states that the role of the hippocampus would be reduced as the remoteness of the memories increases. Some data have shown asymmetrical activations of the hippocampus as a function of remoteness and the phenomenological aspects of the memories. Maguire and Frith (2003) found that only the right hippocampus showed a temporal gradient, with its activity increasing with recency. By this view, the left hippocampus would be activated independently of the remoteness, which fits well with the MTT theory, while the right hippocampus pattern would preferentially fit the consolidation theory. The authors suggested a link between the

age of memories and their visuospatial salience (recent memories being more salient), but no difference was found in visuospatial details as a function of the age of memories. In another study (Addis et al., 2004), the right hippocampus activity was found to be modulated by remoteness of *specific* memories (events that happened just once) but also by phenomenological aspects of *general* memories (level of detail, emotion, personal significance of events that have been repeated at least ten times). In contrast, the phenomenological parameters modulated the activity of the left hippocampus only for *specific* memories. The authors hypothesized that the right hippocampal modulation could be related to the retrieval of spatial content for *general* memories (as the retrieval of *general* memories might be based on a stronger place remembering than remembering of other details), whereas the retrieval of *specific* memories might be based on more contextual details (including memory for place, but related to the specific context of the event), thus relying on the left hippocampus.

MTL laterality in autobiographical memory is a matter of debate, since some authors have argued for a dominant left-MTL involvement (Maguire, 2001; see Svoboda et al., 2006 for a meta-analysis), while an increasing number of studies tend to show a stronger activation of the right hippocampus in relation to phenomenological qualities, such as reactivation of perceptual details during the reexperiencing of the events (see Piolino et al., 2009, for a review). The latter suggestion would be in contradiction with the conclusion we provided above concerning the preferential involvement of the left MTL in recollection. However, a majority of studies have shown bilateral activation of the MTL. Thus, a hypothesis could be that the right hippocampus would be activated while retrieving distinct perceptual details of an episode, and the left hippocampus could be involved in the binding process of the retrieved contextual details to the specific event.

To sum up this first section on MTL, three major characteristics seem to drive MTL asymmetry. The first one is the *nature of the material*, such that the right MTL is specialized for processing nonverbal stimuli while the left MTL would be engaged for verbalizable stimuli. The second characteristic is that the left MTL would be involved in *contextual processing and recollection* of events. The third feature, which has to be further investigated, would be the systematic engagement of the (anterior) left MTL in detection of *novelty*, whatever the nature of the stimuli, and thus its role in the automatic encoding of novel information.

### Frontal Lobes

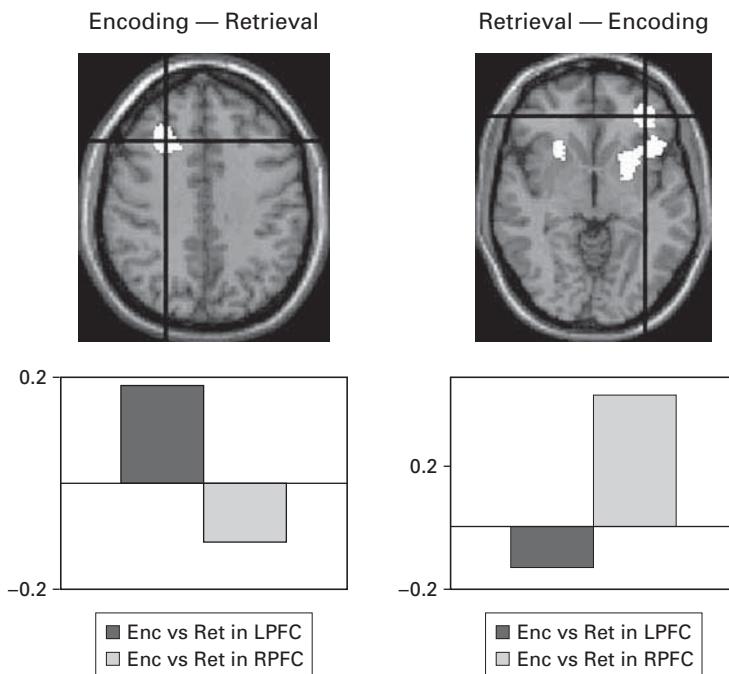
In contrast to MTL lesions, frontal-lobe damage produces more subtle memory impairments related to process-based deficiencies, suggesting that the frontal cortex is preferentially involved in controlled or strategic cognitive mechanisms. Early neuroimaging studies of episodic memory showed strong activation of the frontal cortex,

and a striking laterality effect was noted. A model emerged in 1994 postulating that encoding processes in episodic memory preferentially engage the left frontal cortex, whereas retrieval more strongly activates the right frontal cortex (Tulving, Kapur, Craik, et al., 1994). This was the hemispheric encoding–retrieval asymmetry (HERA) model, and it dominated the scene for several years until some studies claimed that this model could not account for all types of material, that is, nonverbal stimuli. A reevaluation of the model established its generalization for different materials and offered a sharper formulation of the model as well (Habib et al., 2003). The HERA model is still the most well-established model regarding the functional asymmetry of the brain in terms of encoding and retrieval in episodic memory, but other interesting laterality-based models also exist, and both HERA and newer models will be discussed below.

### Encoding versus Retrieval

An important characteristic of episodic memory is the distinction between encoding and retrieval processes. Tulving, Kapur, Craik, et al. (1994) reviewed the results of episodic memory investigations using functional neuroimaging, and they related the observed pattern to their own findings regarding the frontal asymmetry observed in encoding (Kapur et al., 1994) and retrieval (Tulving, Kapur, Markowitsch, et al., 1994). Based on eight studies reporting encoding data and six others reporting retrieval data, the hypothesis of a hemispheric encoding–retrieval asymmetry was then formulated as the HERA model (see figure 17.3). As postulated in this model, the left frontal cortex is involved both in episodic memory encoding and retrieval from semantic memory. Indeed, encoding into episodic memory requires that the subject retrieve the presented item—a word, for example—from his or her semantic memory. Also, in semantic memory tasks, such as when the participants are asked to generate verbs for a given noun, the left frontal cortex is systematically activated. In turn, retrieving information from semantic memory constitutes encoding into episodic memory, as one can assume that the subject will be able to later remember this event and associated information.

After the publication of the HERA model, many studies confirmed the robustness of the model (see Nyberg et al., 1996). Two observations can be made concerning these early studies: (1) The activations for encoding and retrieval in episodic memory were the result of subtraction between the task of interest and a reference task (rest, fixation, learning vs. reading), and (2) the majority of the reported studies used verbal material. Relatedly, one criticism of the HERA model was raised on the basis of the material-driven asymmetry hypothesis. That is, some authors argued that the HERA model was valid for verbal materials only (Owen, 2003). Subsequently, HERA has been tested with nonverbal materials in several studies (Kelley et al., 1998; Owen et al., 1996; Wagner, Poldrack, et al., 1998). For example, Kelley et al. (1998) assessed the neural correlates of episodic memory encoding, using different types of material



**Figure 17.3**

Hemispheric encoding-retrieval asymmetry in the frontal lobe. On the left is a brain map showing left prefrontal cortex (LPFC) activity during episodic memory encoding. The graph below indicates that the difference between encoding (Enc) and retrieval (Ret) is greater in the left than the right prefrontal cortex (RPFC). On the right is a brain map showing right prefrontal activity during episodic memory retrieval. The graph below indicates that the difference between retrieval and encoding is greater in the right than the left prefrontal cortex. Based on Nyberg and Habib (2008).

(words, nameable drawings of objects, and faces). Word encoding elicited left frontal regions, object encoding activated frontal areas bilaterally, and right-sided frontal cortex was highlighted for face encoding. The authors concluded that the HERA model was valid for verbal material, at least for encoding, and that lateralization in the frontal cortex would depend on the material type.

Habib et al. (2003) presented a more specific formulation of the model and suggested that HERA must be true if, for encoding,

$$(Encoding\ Left - Retrieval\ Left) > (Encoding\ Right - Retrieval\ Right)$$

and, for retrieval,

$$(Retrieval\ Right - Encoding\ Right) > (Retrieval\ Left - Encoding\ Left)$$

The main point is that a test of HERA is valid, whatever the material type, when the two memory processes of interest are directly compared, and not relatively to a baseline task. Importantly, HERA does not challenge the reality of other asymmetries, such as the one regarding the material type, and they can indeed coexist (Nyberg et al., 2000). Habib et al. (2003) showed that word encoding and retrieval activated the left frontal cortex more than did the encoding and retrieval of faces, whereas face encoding and retrieval activated the right frontal cortex more than did the same processes for words, fitting with the material-type hypothesis. Adopting the HERA logic by assessing direct comparison between encoding and retrieval, it appeared that word as well as face encoding activated more left than right frontal cortex for the (encoding–retrieval) contrast, and both word and face retrieval activated more right than left frontal cortex for the (retrieval–encoding) contrast.

One issue that cannot be easily addressed using fMRI is whether the activated left or right frontal areas are crucial to successfully perform encoding and retrieval. rTMS allows a more direct test, by transiently disrupting the function of a given region. Rossi et al. (2001) showed, using complex images as items, that when the left frontal cortex was disrupted during encoding, the subjects later retrieved fewer items than when the right frontal cortex was stimulated, providing evidence that the left frontal cortex is partly responsible for successful encoding mechanisms. The reverse pattern was found regarding laterality and retrieval (fewer hits—as well as more false alarms—when the right frontal cortex was disrupted at retrieval in comparison with left frontal disruption). Thus, both functional neuroimaging and rTMS have provided evidence for a functional encoding–retrieval asymmetry in the left and right frontal cortex.

A weak characteristic of the HERA model is its lack of a precise description of left or right frontal regions involved in episodic memory processes. Lepage et al. (2000) specifically focused on the frontal regions involved during recognition in episodic memory. The idea was that some frontal areas would be systematically activated during a certain state of retrieval in which the individual voluntary treats online information as retrieval cues and actively searches for the specific event to be remembered. This state would be a necessary condition for remembering. Gathering the data from four experiments (Düzel et al., 1999; Kapur et al., 1995; Nyberg et al., 1995, 2000), the authors highlighted a set of regions involved in this RETrieval MOde (REMO). The retrieval tasks of the meta-analyzed studies consisted of old–new recognition judgments about previously presented items (words, sentences, or landscapes). Six clusters were found to correspond to REMO sites, four in the anterior right hemisphere and two in the left frontal hemisphere. The two left frontal clusters were homologous regions of two of the four right clusters, but the left clusters were of smaller size and less strongly active than their right-sided counterparts. The bilateral activations were in the frontal pole (Brodmann's area [BA] 10) and the frontal

operculum (BA 45/47). The two additional right anterior clusters were located in the dorsal prefrontal cortex (BA 8/9) and the anterior cingulate gyrus (BA 32).

According to the REMO theory, these six regions would be activated during this specific mental state of retrieval in episodic memory. At first, the assumption was that this specific mental state would be maintained during the entire retrieval phase, so that these right frontal regions would be activated in a sustained fashion (Donaldson et al., 2001). However, in a recent study, Marklund et al. (2007) found sustained activity in the right frontopolar cortex (BA 10) and medial anterior areas including the anterior cingulate (BA 32), not only for retrieval in episodic memory but for other tasks as well, suggesting a *general* role of these areas in the maintenance of a neurocognitive set. The right inferior frontal BA 47, another REMO site, showed a specific *transient* activity for episodic retrieval. Thus, contrary to the earlier proposal that the retrieval mode would be a sustained mental state, here the authors suggested that a REMO state would be initiated only when the retrieval cues are presented and not in between cues when no episodic mnemonic activity is required (at least not under conditions of relatively long interstimulus intervals).

The REMO sites, mainly located in the right frontal lobe, were expected to be activated during episodic retrieval, but left frontal activations often found in retrieval experiments remained largely unexplained. Hypotheses have subsequently been tested to find out during which conditions the left frontal cortex is activated during retrieval, and these efforts have contributed to two other models discussed below.

### **Contextual Processing**

Several studies attempted to highlight the conditions in which left frontal regions were activated in addition to the right-sided ones during episodic retrieval. Based on a meta-analysis, the cortical asymmetry of reflective activity (CARA) model was proposed by Nolde et al. (1998). The authors considered a general cognitive model, the multiple-entry, modular memory system model (Johnson, 1992), which distinguishes between perceptual and reflective processes. Reflective mechanisms, mediated by the frontal cortex, are executive-like and allow maintenance, manipulation, and evaluation of the output generated by the perceptual processes. Nolde et al.'s hypothesis was that some reflective processes subtended by the right frontal cortex would be sufficient to perform simple episodic retrieval tasks, whereas more complex tasks would require additional processes underpinned by the left frontal cortex. Processes supporting simple tasks would be those implicated in deciding whether a presented item has been previously presented (yes-no recognition), or, in other words, whether this item matches a representation already activated during encoding. These mechanisms—refreshing activated information, shifting between representations, and noting relations—have been labeled as *heuristics*. Processes involved in more complex retrieval tasks, in which information is inactive, have been labeled as *systematic*. They would

be more effortful cognitive operations such as rehearsing, initiating strategies, and generating cues in order to retrieve information (e.g., the context of an event).

Nolde et al. (1998) selected studies in which simple or complex old-new episodic recognition tasks were assessed, and they reported the results of eight simple and fifteen complex tasks. All eight simple tasks elicited strictly right-sided frontal activation, and nine complex tasks induced bilateral frontal activation. A direct comparison of simple versus complex tasks supported the hypothesis that activation of the left frontal regions is supplementary in the latter (Buckner et al., 1998). A similar profile of right versus bilateral frontal activity was obtained when comparing simple cued-recall and complex cued- and free-recall tasks. To sum up, Nolde et al. (1998) confirmed the involvement of right frontal areas during retrieval, supporting the retrieval part of the HERA model, and provided further insights regarding the conditions under which left frontal areas also are engaged during retrieval. Specifically, right frontal areas would be engaged whatever the conditions of retrieval, as these areas would mediate heuristic mechanisms (such as REMO), and supplementary left frontal regions would complement the pattern of frontal activations when the task is more demanding, engaging systematic mechanisms. This is in agreement with lesion studies showing that patients with left-frontal-lobe damage had impaired performance in free recall tasks, which are more demanding than recognition tasks (McDonald et al., 2006; Wheeler et al., 1995).

Cabeza, Locantore, et al. (2003) also aimed at identifying the respective contributions of the left and right frontal cortex during verbal episodic retrieval, and they proposed the production-monitoring hypothesis. They presented a review of the literature providing evidence for generation processes (production) controlled by the left frontal cortex and for verification and checking operations (monitoring) handled by the right frontal cortex. This hypothesis predicts that recall would preferentially engage production processes, as no cues are available, these processes being underpinned by left frontal areas. By contrast, cues (and distractors) are provided in recognition tasks; consequently, monitoring processes would be preferentially engaged to check the validity of information, and these processes would depend on right frontal regions. Frontal asymmetry can also be modulated within both recall and recognition according to the amount of required production and monitoring mechanisms. The difference between this model and the CARA model lies in the production versus monitoring processes involved in given tasks and how these tasks were classified according to the systematic versus heuristic mechanisms. Testing both the production-monitoring hypothesis and the CARA model, it appeared that the former predicts the side of the activations more accurately than the latter. In addition, the results provided information regarding subregions of the frontal cortex. The tasks thought to induce production processes engaged, in the left frontal lobe, a ventrolateral area (BA 45) involved in semantic processing, an opercular area (BA 44) involved in

orthographic–phonemic processes, and a dorsolateral area (BA 9) involved in strategic retrieval of semantic associations established during encoding. The tasks requiring monitoring mechanisms elicited right-sided frontal areas, but their respective roles were not detailed.

The recovery of contextual information implies recollection processes rather than familiarity-based mechanisms. Thus, generation of cues, systematic processes, related to semantic information may induce greater left frontal activation than familiarity-based responses, for which retrieval is based on simple evidence that an item has been seen before. Frontal asymmetries appeared in studies which investigated activations during recognition using the R–K paradigm: Recollection elicited left anterior prefrontal regions, while the right dorsolateral frontal cortex was more active during familiarity-based recognition (Dobbins & Wagner, 2005; Eldridge et al., 2000; Henson et al., 1999; Kahn et al., 2004; Lundstrom et al., 2003; Rugg et al., 1999; Slotnick et al., 2003; Takahashi et al., 2002; Yonelinas, 2002).

As suggested by the CARA model, context recollection would require more effortful cognitive mechanisms than simple item recognition, and production processes as stated by the production-monitoring hypothesis. Since many studies involved verbalizable material (see, for instance, Dobbins et al., 2002; Raye et al., 2000), the *systematic* mechanisms underpinned by the additional left frontal regions activated during source or context retrieval would be of a verbal type. As asserted for the left MTL involvement in verbal and nonverbal context processing, the nature of the processes of the left frontal cortex could extend the verbal dimension as well. Slotnick et al. (2003) used abstract visual shapes (stimuli) displayed in different spatial locations (spatial context) to investigate the neural substrates of successful item and context memory retrieval. The results showed that item retrieval, in comparison with correct rejections, was associated with enhanced activity of the right middle frontal cortex (BA 9); activation of the medial superior frontal gyrus was seen when item memory was compared with spatial context memory, whereas the reverse contrast showed that spatial context memory retrieval elicited activation of the left frontal cortex (BA 9 and BA 47) but also the right hemisphere (BA 9). Thus, context memory for spatial locations of abstract shapes elicited bilateral frontal cortex with a strong left bias, and, thus, it seems reasonable to conclude that the left frontal cortex is consistently activated when a context memory judgment has to be made, regardless of its verbal or nonverbal dimension.

In conclusion, the strongest frontal asymmetry would be due to processes engaged during encoding and retrieval, such that the former process recruits left frontal areas and the latter right frontal areas. This general pattern is modulated by the nature of the material, as well as by the nature of the cognitive processes involved, notably during retrieval, where more effortful and/or additional mechanisms would engage left frontal areas.

## Parietal Lobe

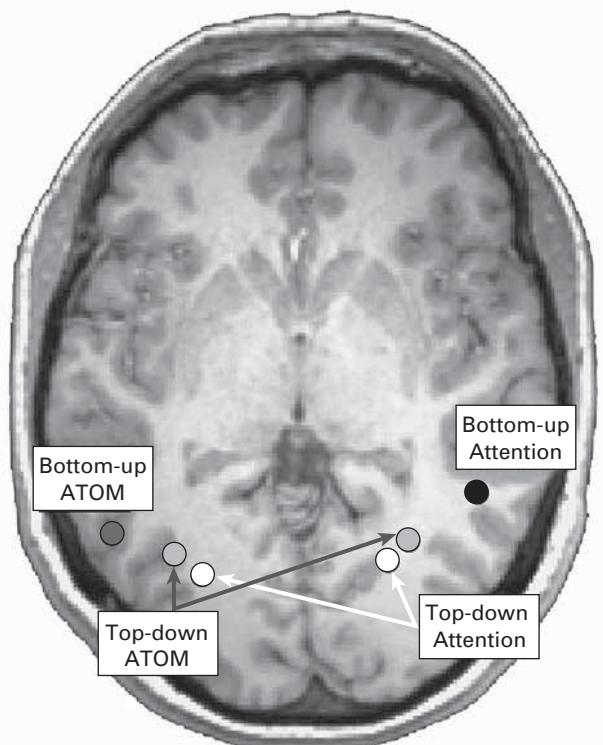
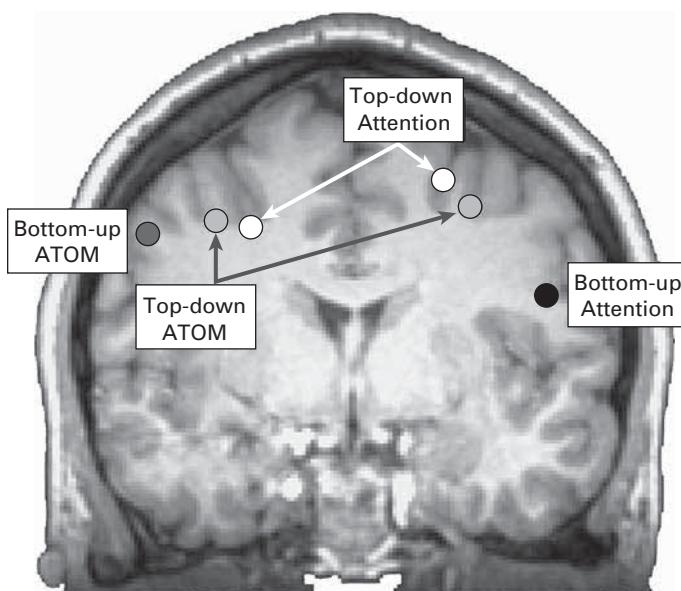
While a large majority of studies have focused on the MTL and the prefrontal cortex functions in memory, a growing interest has emerged during the last years regarding the roles of the parietal lobe in memory (Naghavi & Nyberg, 2005; Olson & Berryhill, 2009; Wagner et al., 2005). Medial parts of the parietal cortex are mainly involved in processes related to the content of the memories, as lesion studies as well as pathology have shown that its disruption induces amnesia (see Chételat et al., 2003, for an example concerning the early stages of Alzheimer's disease). Functional neuroimaging studies have shown activation of these parietal areas in autobiographical retrieval (Gilboa et al., 2004; Viard et al., 2007), in source memory (Lundstrom et al., 2005), and in context memory (Cavanna & Trimble, 2006). A review of the literature (Cavanna & Trimble, 2006) did not provide evidence for laterality effects of the medial parietal regions, contrasting with interesting recent findings regarding asymmetry of the lateral regions of the parietal lobe.

### Attention and Memory

Lateral regions of the parietal cortex are involved in attentional processes, with a right-sided bias with respect to specific attentional processes such as maintaining an alert state and vigilance (for a review, see Posner & Petersen, 1990). Associated with frontal areas, attention is involved in monitoring processes during episodic retrieval, constituting a general attentional frontoparietal network thought to be lateralized to the right hemisphere (Cabeza, Dolcos, et al., 2003; Nyberg et al., 2002).

Recently, the attention to memory (ATOM) model has been proposed to account for attentional processes specifically involved in the retrieval of episodic memory (Cabeza et al., 2008). Two attentional systems can be characterized: The top-down (or superior) attentional system includes the superior parietal lobe and the intraparietal sulcus (BA 7/19). This system is voluntarily engaged when the subject has representations in advance of the target he or she has to identify. The bottom-up (or inferior) attentional system includes the inferior parietal areas, such as the supramarginal gyrus, the angular gyrus, and the temporoparietal junction (BA 39/40). This system is automatically engaged when attention is captured by a relevant stimulus in the environment. Thus, the ATOM model postulates that the top-down attentional system would be engaged in strategic retrieval in episodic memory, while the bottom-up attentional system would be engaged in automatic retrieval. In attentional tasks, the top-down system is activated bilaterally, while there is a bias toward the right hemisphere for the bottom-up system.

Laterality effects can be explored by considering the results of a recent meta-analysis (Ciaramelli et al., 2008; see figure 17.4). The authors calculated for each region the percentage agreement across studies, after which they established a center of mass



for activity. The center of mass related to top-down attention in memory retrieval was located in the posterior intraparietal sulcus bilaterally, in keeping with top-down attentional findings. The center of mass related to bottom-up attention in memory retrieval was located in the left supramarginal gyrus, which is different from bottom-up attention since studies have consistently shown activations in the right hemisphere. Bottom-up ATOM is thought to occur when a representation is automatically reactivated and accessed into memory as attention is captured by the retrieved item. Indeed, the perception of the cue at retrieval would drive the recollection of further information that was integrated at encoding, constituting the whole event, such as in the case of high confidence at retrieval, for previously deeply encoded items, and recollection of details.

Even if verbal material was typically used in the reviewed studies, Ciaramelli et al. (2008) supported the idea that the left lateralization could not be due to a material bias, as this lateralization was also present for faces. However, according to the authors, the most plausible hypothesis to explain this left bias was based on autobiographical memory studies and recollection: The left hemisphere would be able to produce a descriptive framework about a specific event. This hypothesis fits with findings on recollection as discussed in the next subsection.

### Recollection

Recollection is strongly associated with increased activity in the parietal lobe. Specific assessment of source memory retrieval in patients with frontal-lobe damage failed to highlight any deficit in recollection processes (Simons et al., 2008), but in the same study, the authors used fMRI to assess the role of parietal regions in memory processes. The task involved deep encoding of words and famous faces. Source memory was tested by asking the participants to recollect how each stimulus was processed during the study phase (semantic or pleasantness judgment). In healthy participants, recollection of words activated the left lateral parietal cortex, whereas bilateral lateral parietal regions were recruited during recollection of faces. The left lateral parietal cortex was equally activated for words and faces, whereas the right lateral parietal cortex was significantly more activated for faces than words. Thus, it is possible that a laterality effect exists according to the material used (see also

### Figure 17.4

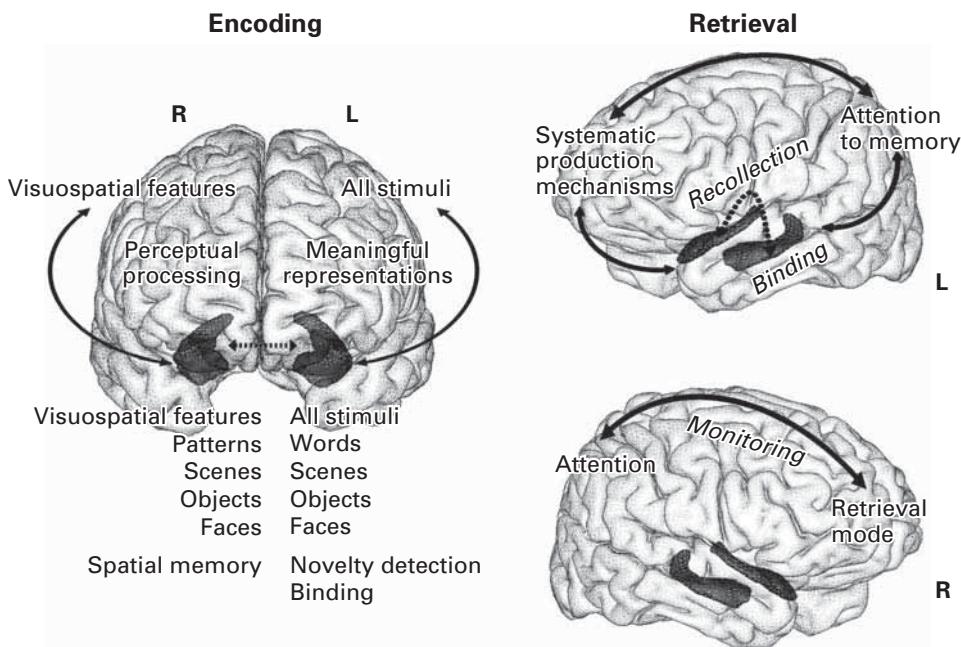
Asymmetry of attention to memory (ATOM) processes in the parietal lobe. Coronal (top) and axial (bottom) views of a standard brain showing the mean location of bottom-up *attention* (black) and *ATOM* processes (dark gray), and top-down *attention* (white) and *ATOM* processes (light gray) in the parietal lobe. Note that while top-down processes are bilateral, bottom-up processes are left-lateralized for *ATOM* and right-lateralized for *attention*.

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Davidson et al., 2008). Although patients' lesions overlapped the activated areas in healthy subjects, they all performed at a normal level when it came to recollection for words and faces. A hypothesis was that vividness of recollection had contributed to parietal involvement. "Vividness" refers to retrieval based on recollection, and, indeed, some studies using the R-K paradigm showed functional parietal asymmetry. Skinner and Fernandes (2007) conducted a meta-analysis in order to determine the regions involved in recollection and familiarity during recognition. The authors calculated the percentage agreement in activation for each region of the brain. Overall, they showed that more activity was found during recollection than familiarity in the left inferior parietal cortex (BA 39/40). Daselaar et al. (2006) suggested that this region might be involved in the retrieval of available details, but they also suggested that this region could be related to the strength of the memory trace. Indeed, some investigations found significant activation in this region during retrieval following deep versus shallow encoding (Eldridge et al., 2000; Henson et al., 1999, 2005; Nyberg et al., 1995; Shannon & Buckner, 2004; Wheeler & Buckner, 2004). Also, Iidaka et al. (2006) showed a functional asymmetry of the parietal lobe during retrieval as a function of the depth of processing at encoding: In agreement with the previous studies, they found increased left parietal activation (left intraparietal sulcus) during the retrieval of deeply encoded items, and they also highlighted a specific activation when they investigated the neural correlates of familiarity in the right parietal cortex.

Overall, a general pattern emerges regarding laterality effects in recognition memory in the lateral parietal cortex, indicating that left parietal regions are more involved during recollection than during familiarity-based retrieval.

Findings regarding the parietal cortex in memory should be considered cautiously. Few and nonspecific investigations have been done so far, especially regarding asymmetry. As to the hypothesis raised by some authors that parietal laterality effects are not due to the nature of the material, one cannot reject this possibility, as the majority of studies used verbal materials. This factor must be controlled in future investigations (Vilberg & Rugg, 2008). With these caveats, it can tentatively be concluded that the lateral parietal cortex is asymmetrically recruited in the sense that the right side, together with the right frontal cortex forming the general attentional network, would be activated in memory when the retrieval requires low-level processes such as checking whether a presented item has been previously shown during encoding. The left lateral parietal cortex would be specifically engaged in episodic memory, maybe together with the left frontal cortex, when more complex information has to be retrieved, such as in recollection and context remembering when a retrieval cue is provided, triggering bottom-up attentional processes (see figure 17.5).

**Figure 17.5**

Integration of memory asymmetries in the brain. During encoding (left), the left frontal cortex is activated for all kinds of material while the right frontal cortex is activated for materials containing visuospatial features. The left medial temporal lobe (MTL), and more particularly the hippocampus, is activated for all kinds of stimuli; it detects novel items and binds different features of an event in order to create, together with the left frontal cortex, meaningful representations. The right MTL is more specialized in perceptual-based encoding and is engaged in perceptual processing together with the right frontal cortex. During retrieval (right), the right frontoparietal network is engaged when monitoring processing is sufficient, and the left frontal, hippocampal, and parietal regions are activated when additional processes are required to recollect information. L, left; R, right.

(Brain maps courtesy of Nicolas Villain and Renaud Lajoie.)

## Conclusions and Prospects

In this chapter, we have discussed asymmetries that may exist in three main areas of the brain that often are engaged during episodic memory tasks: the MTL and the frontal and parietal cortices. The findings converge toward preferential involvement of the left hemisphere when meaningful information has to be processed (semantic information, context, and source of memories). The right hemisphere seems to be preferentially activated when nonverbal material has to be processed. However, each region (and subregion) shows specific asymmetry patterns. The MTL functional asymmetry is strongly modulated by the nature of the material (e.g., verbal material is mainly underpinned by the left MTL), frontal asymmetries have been highlighted when considering cognitive processes (e.g., encoding vs. retrieval, production vs. monitoring mechanisms), and parietal asymmetries would depend on attention and recollection processes.

An issue that we have not considered concerns the existence of lateralized networks connecting the frontal cortex, the parietal cortex, and regions of the MTL. At first glance, it seems as if all three regions share two conditions under which they are activated. First, the nature of the material is a candidate in activating left or right networks, at least regarding the lateralization of the fronto-MTL interactions, as suggested by Simons and Spiers (2003). Second, when contextual features of an episode have to be processed, the left frontal and parietal cortices and the left MTL are more active than the same regions in the right hemisphere, and one can suspect the involvement of a specific left neural network connecting these regions. In support of this hypothesis, Iidaka et al. (2006) highlighted, during a picture recognition task, a stronger frontoparietal functional connectivity pattern in the left hemisphere, with this connectivity being related to recollection. Therefore, it seems that the left hemisphere is able to contextualize an event or item, by associating elements together, and produce a meaningful outcome from memory. By contrast, the right frontoparietal network would be engaged in memory when general attention and heuristic-monitoring processes are sufficient to perform the task.

Another issue that has been largely neglected is the generalization of HERA outside the frontal cortex. Following the results of a study which showed activity changes in the left and the right parietal lobe during encoding and retrieval, respectively (Babiloni et al., 2004), Babiloni et al. (2006) used EEG to measure the functional coupling of frontal and parietal regions during the encoding and retrieval of visuospatial contents. During encoding, spectral coherence between the two regions was stronger in the left than right hemisphere, whereas it was stronger in the right than left hemisphere during retrieval. Thus, the frontal asymmetry predicted by the HERA model could be extended into the parietal cortex as well (cf., Nyberg et al., 1996).

Another issue that we have not raised in this chapter is that functional asymmetries may not be fixed. Differences in functional asymmetries in different populations are certainly related, to a great extent, to structural modifications, such as differential maturation of regions and therefore different networks during development (Prayer et al., 2006; Radoš et al., 2006; Toga et al., 2006, for structural data; Chugani, 1998, for metabolic findings), atrophy in neurodegenerative diseases, and also structural changes that occur in the course of normal aging. In contrast with the HERA model, which postulates that left frontal regions are more activated during episodic encoding and right frontal areas are more involved during episodic retrieval, Cabeza (2002) observed an age-related reduction in frontal episodic memory asymmetry, conceptualized within the hemispheric asymmetry reduction in older adults model. Dedifferentiation would explain such results: This neuronal process is the reverse of the differentiation that takes place during development, such that brain areas become more and more specialized for specific cognitive processes. In the course of normal aging, this specialization is lost, so that old individuals cannot recruit brain regions that are optimally used by younger subjects (Dolcos et al., 2002). Bilateral activations can also be viewed as compensatory attempts, which are sometimes successful (Cabeza et al., 2002) and sometimes insufficient (for a discussion, see Persson et al., 2006).

In figure 17.5 the discussed findings on episodic memory asymmetry in the brain are tentatively integrated in a functional model. Globally, it appears that regions of the right hemisphere would mainly be engaged in episodic retrieval when cognitive demands are low; in other words, when basic processes like general attentional mechanisms and monitoring processes are sufficient to respond to the task. Also, it is possible that the right hemisphere, and more particularly the right MTL, would be preferentially involved when perceptual information has to be processed. Regions of the left hemisphere would be engaged in more specific and effortful episodic memory processes. While encoding processes would elicit left frontal and MTL areas, left frontal, MTL and parietal areas seem to be engaged in order to proceed to the generation and manipulation of various elements to be bound together, the output being meaningful and elaborate memories. A lot of work remains to be done in the field of memory asymmetries in the brain. Also, besides the need to better understand the asymmetries of the brain regions we considered in this chapter, efforts will be needed in the future to examine asymmetries in other brain regions (e.g., cerebellum, subcortical nuclei) involved in memory.

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## **VII Asymmetry in Neurological and Pediatric Disorders**



## **18 Visuospatial Function and the Neglect Syndrome**

**Victoria Singh-Curry and Masud Husain**

One of the striking conclusions to emerge in neuroscience over the course of the last century is that the right hemisphere of humans—the so-called “nondominant” hemisphere—plays a crucial role in visuospatial function. Broca himself suggested in 1866 that the right posterior lobe might in some way complement the specialization of the left frontal regions for speech (Harrington, 1985). Hughlings Jackson (Jackson, 1864), with masterly prescience but very little evidence, went further by proposing that the posterior region of the right hemisphere is specialized for the interpretation of sensory inputs, particularly in the visual domain—the highest modality of sensation. Individuals who could no longer interpret sensory representations, he argued, would suffer from what he called “imperception,” a term subsequently replaced by Freud’s “agnosia.”

However, it was not until much later, well into the twentieth century, that the evidence for a special role of the right hemisphere in visuospatial functions began to develop (De Renzi, 1982; Young & Ratcliff, 1983). A series of investigations which started in the 1930s and 1940s demonstrated that while insults to the left hemisphere resulted in difficulties with verbal ability, damage to the right hemisphere consistently led to poor performance on tests involving the manipulation of geometrical figures, completion of missing parts of shapes and patterns, and other tasks incorporating the analysis of form, distance, and spatial relationships (Brain, 1941; Hecaen, Penfield, Bertrand, & Malmo, 1956; McFie, Piercy, & Zangwill, 1950; Newcombe & Russell, 1969; Paterson & Zangwill, 1944; Weisenberg & McBride, 1935). Particularly prominent in such considerations was the disorder of visuospatial agnosia, including the striking syndrome we now call visuospatial neglect or simply neglect, a disorder which is most evident and enduring following right-hemisphere damage, especially strokes affecting the right posterior parietal lobe (Heilman & Watson, 2001; Mort et al., 2003; Vallar & Perani, 1986).

Remarkably, such patients may have intact visual fields but nevertheless fail to register or respond to events toward their left or contralateral side—the side opposite the brain lesion. In other words, despite possessing a normal sensory apparatus,

individuals with neglect following right-hemisphere damage seem not to be consciously aware of objects—even people—to their left. Although right-sided neglect following left-hemisphere damage is well recognized, it tends to be less severe and less enduring than left-sided neglect after right-hemisphere damage (Stone et al., 1991). Inevitably, such a striking deficit in the visuospatial representation of the external world following right-hemisphere lesions has fueled the proposal of a special role of the right hemisphere in visuospatial and, more generally, spatial functions.

As we shall see, further evidence for right-hemisphere specialization for visuospatial processes came from examination of patients with surgical section of the cerebral commissures, or the “split-brain” operation; divided visual field studies; and functional brain imaging techniques in healthy people. In this chapter we review some of this evidence, but in addition we draw attention to other findings which show that neglect cannot simply be characterized as a visuospatial disorder. Rather, investigations demonstrate deficits in nonspatial functions that contribute to the syndrome (Husain & Nachev, 2007; Nachev & Husain, 2006).

Similarly, functional imaging studies in normal people suggest a special role of the right hemisphere in nonspatial aspects of attention, such as the ability to sustain attention on a task (Adler et al., 2001; Häger et al., 1998; Johannsen et al., 1997; Pardo, Fox, & Raichle, 1991; Sturm et al., 1999; Sturm et al., 2004; Vandenberghe, Gitelman, Parrish, & Mesulam, 2001), detection of salient task-relevant events (Clark, Fannon, Lai, Benson, & Bauer, 2000; Gur et al., 2007; Huang et al., 2005; Kiehl, Laurens, Duty, Forster, & Liddle, 2001; Kiehl et al., 2005; Lagopoulos, Gordon, & Ward, 2006; Linden et al., 1999; Marois, Leung, & Gore, 2000; Williams et al., 2007), and identification of novel—potentially behaviorally important—items in the world around us (Bunzeck & Duzel, 2006; Downar, Crawley, Mikulis, & Davis, 2002; Gur et al., 2007; Kiehl et al., 2001; Kiehl et al., 2005). Importantly, it is becoming increasingly apparent that such nonspatial attentional processes can also be impaired in neglect, perhaps exacerbating the severity of the syndrome (Husain & Rorden, 2003; Robertson, 2001). These findings call into doubt a simple caricature of right-hemisphere specialization for spatial processes and raise the possibility of a more complex account, particularly with respect to the functions of the right posterior parietal cortex (PPC).

### **Early Studies of Right Parietal Patients**

In 1941, Brain described a series of patients with lesions involving the right parietal lobe, who experienced difficulty with a number of activities which have a spatial component (Brain, 1941). These individuals had problems finding their way around even familiar environments (including their own homes) frequently turning right instead of left and bumping into objects on their left. Some were impaired at judging distances—particularly on the left—and had difficulty dressing—for example, trying

"to put his dressing-gown on upside down" and being "unable to knot his tie" (Brain, 1941, p. 258). Brain concluded that these deficits were not due to defects in visual acuity but to a deficient visual localization of objects in the affected half-field, which he attributed to an inattention or "neglect" of the left half of space resulting from right parietal damage.

A few years following Brain's descriptions, Paterson and Zangwill gave a particularly clear account of a patient with a very focal lesion affecting the right inferior parietal lobe (see figure 18.1), found at surgery to be localized to the supramarginal and angular gyri (Paterson & Zangwill, 1944). He demonstrated a tendency to neglect items to the left as well as demonstrating left-sided *extinction*: He could detect the presence of a single visual stimulus when presented on either side of space but failed to report a contralateral (left) stimulus when this was presented with a simultaneous one on the ipsilesional side (the same side as the brain lesion, i.e., the right side in this case).

This patient also revealed a more "complex disorder affecting perception, appreciation and reproduction of spatial relationships in the central field of vision" (Paterson & Zangwill, 1944, p. 337). He was documented to draw complex shapes or scenes in a "piecemeal" fashion: item by item or detail by detail, appearing to "lack any real

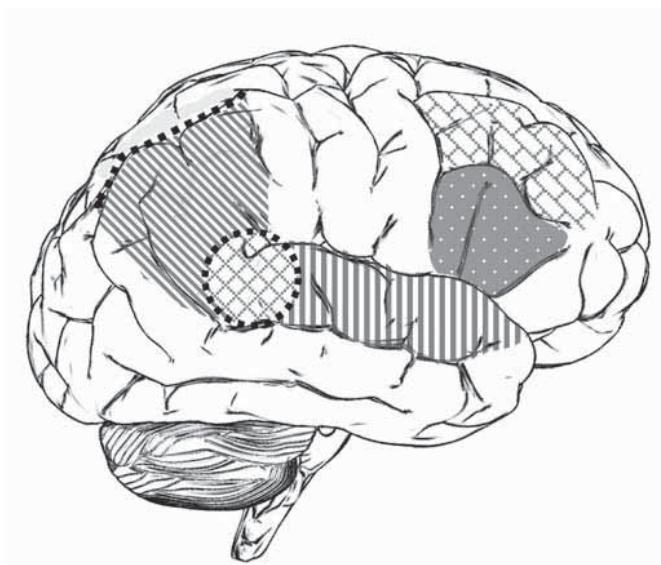


Figure 18.1

The anatomy of neglect. Damage to a number of brain regions can lead to neglect, including the inferior parietal lobe (IPL), the temporoparietal junction (TPJ), the inferior frontal gyrus (IFG), the middle frontal gyrus (MFG), and the superior temporal sulcus (STG). The area most frequently implicated is the IPL. The intraparietal sulcus (IPS) separates the superior and inferior parietal lobes.

grasp of the object as a whole" (p. 342). Paterson and Zangwill also noted a similar "piecemeal approach" in the context of mild left-sided neglect in a second case of parieto-occipital injury.

Subsequent reports by Zangwill, Hecaen, and others began to establish a special association between right-hemisphere lesions and visuospatial deficits (Hecaen et al., 1956; McFie et al., 1950). Neglect, loss of topographical memory, deficits in copying the spatial relationships of objects or object parts (constructional apraxia), dressing apraxia, impairments in stereopsis, judging of the identity of objects haptically (astereognosis), and spatial localization have all been associated with lesions of the right hemisphere, particularly the parietal lobe (De Renzi, 1982). Moreover, it has been recognized that many of these disorders have a tendency to occur together in the same individual (Hier, Mondlock, & Caplan, 1983).

### **"Split-Brain" Studies**

In concert with these developments, studies of split-brain patients began to support claims of a special role for the right hemisphere in spatial processes. The split-brain operation was first performed in 1961 by R. W. Sperry and colleagues in an attempt to control intractable epilepsy (Bogen, Fisher, & Vogel, 1965). One of the appeals of these studies has been the ability to study the functions of the individual hemispheres without the presence of focal lesions, which are often large and unrestricted to the brain region of interest. However, brains of patients with intractable epilepsy can hardly be considered healthy, and individual patients within this small sample have also had varying degrees of extracallosal damage (Beaumont, 1983). Furthermore, even in cases where the left and right cerebral cortices are completely disconnected, information can still be transferred from one hemisphere to the other via intact subcortical routes. This perhaps explains why split-brain patients seem generally unaffected in their everyday lives (Gazzaniga, 1995).

Nevertheless, studies presenting visual stimuli to one hemisphere at a time have revealed differences in how the left and right hemispheres of these patients process visuospatial information. Because of the organization of the optic pathways, information from each half of the visual field is initially projected solely to the contralateral hemisphere. Normally, each hemisphere receives information from the ipsilateral half-field via the corpus callosum. In patients in whom the corpus callosum has been transected, visual analysis in the ipsilateral visual field is severely reduced—with subcortical pathways transmitting only crude information. Hence, it is possible to stimulate one hemisphere at a time with visual stimuli presented in the contralateral hemifield—provided of course, the subject maintains fixation. This was previously achieved by flashing stimuli very briefly or tachistoscopically (with presentation times of around 150 milliseconds; Beaumont, 1983) to either side of fixation, so that there

is not time to move the eyes toward these events, and more recently by using eye-tracking devices (Gazzaniga, 1995).

Studies in which split-brain patients have been instructed to respond manually to visual stimuli have revealed that these individuals are slower to respond to left-sided stimuli compared to those on the right (Berlucchi, Aglioti, & Tassinari, 1997; Proverbio, Zani, Gazzaniga, & Mangun, 1994). In other words they demonstrate a right-sided bias reminiscent of patients with left hemispatial neglect due to right parietal lesions. Event-related potentials (ERPs) in response to visual stimuli, recorded during one of these investigations, revealed that the P3 wave (a brain electric potential elicited by task-relevant events) had an amplitude that was maximal over the left hemisphere for right-hemifield stimuli and intermediate over the right hemisphere for events occurring in *both* the left and right hemifield (Proverbio et al., 1994).

This finding is consistent with a notion proposed by Kinsbourne that in the normal brain, attentional shifts in either direction are controlled by the contralateral hemisphere, but that the rightward bias of the left hemisphere is stronger than the leftward bias of the right. Indeed, Kinsbourne argued that the right hemisphere is able to direct attention to both sides of space, that is, it is the dominant hemisphere for directing visuospatial attention (Kinsbourne, 1993). This proposal has had a major influence on understanding why the neglect syndrome appears to be so much more prominent after right-hemisphere lesions. According to this scheme, while left parietal injury might lead to some deficits in directing attention rightward, an intact right parietal cortex can compensate to some extent—hence producing mild or very transient neglect in most such patients (Stone et al., 1991). However, right parietal damage leads to severe problems in directing attention leftwards because the intact left hemisphere can compensate for deficits in directing attention rightward but not leftwards. This provides one account for the hemispheric asymmetry observed in neglect frequency.

### Divided Visual Field and Functional Imaging Studies in Healthy Individuals

Before the advent of functional imaging techniques, the most profitable technique used to study hemispheric asymmetries in normal subjects was *divided visual field presentation*: tachistoscopic presentation of stimuli in one or the other visual field just as in split-brain patients (Beaumont, 1983). Using this technique, it has been shown that the right hemisphere (left-visual-field presentation) demonstrates a *small* advantage in the detection of the position of dot stimuli (Bryden, 1976), in the estimation of the number of laterally presented dots (Kimura, 1966; McGlone & Davidson, 1973), and in the perception of line orientation (Atkinson & Egeth, 1973; Fontenot & Benton, 1972; Phippard, 1977; Sasanuma & Kobayashi, 1978; Umiltà et al., 1974). A problem with these studies—as already alluded to in the previous section—is that although brief stimulus presentation, or the monitoring of eye movements, can ensure that stimuli

are presented initially to one hemisphere or the other, there is nothing to prevent subsequent interhemispheric transfer of information. This, of course, will take an additional amount of time but perhaps accounts for the smaller than may have been expected, and at times inconsistent, right-hemisphere advantage (De Renzi, 1982).

Nevertheless, this small right-hemisphere advantage for the processing of visuospatial information has been supported by more recent studies using positron emission tomography (Corbetta, Miezin, Shulman, & Petersen, 1993; Nobre et al., 1997) and functional magnetic resonance imaging (Giesbrecht, Woldorff, Song, & Mangun, 2003; Molenberghs, Mesulam, Peeters, & Vandenbergh, 2007; Serences & Yantis, 2007; Stephan et al., 2003; Thiel, Zilles, & Fink, 2004; Vandenbergh et al., 2005; Woldorff et al., 2004). Such studies have demonstrated the relative importance of the right (over left) parietal lobe in the spatial reorienting of attention, particularly with respect to the superior parietal lobe (Corbetta et al., 1993; Molenberghs et al., 2007) and intraparietal sulcus (IPS; Molenberghs et al., 2007; Nobre et al., 1997; Vandenbergh et al., 2005; see figure 18.1). Of course, this is not to say that the left parietal lobe is not also activated to a certain extent by such events; in healthy individuals the presence of connections between the hemispheres makes it more difficult to find absolute differences between them. Moreover, the temporal resolution of imaging studies makes it difficult to separate out attentional from motor planning processes, which, some argue, may be a more specific function of left parietal regions.

It is therefore in this respect that lesion studies can add most value. Although, as with any other method, there are limitations, lesion studies can provide evidence of causality: that a brain region might be *essential* for a particular function, rather than simply being activated during it. Hence, it is for this reason that the clinical syndrome of neglect may help shed more light on the functional specialization of the right hemisphere, and in particular the right PPC.

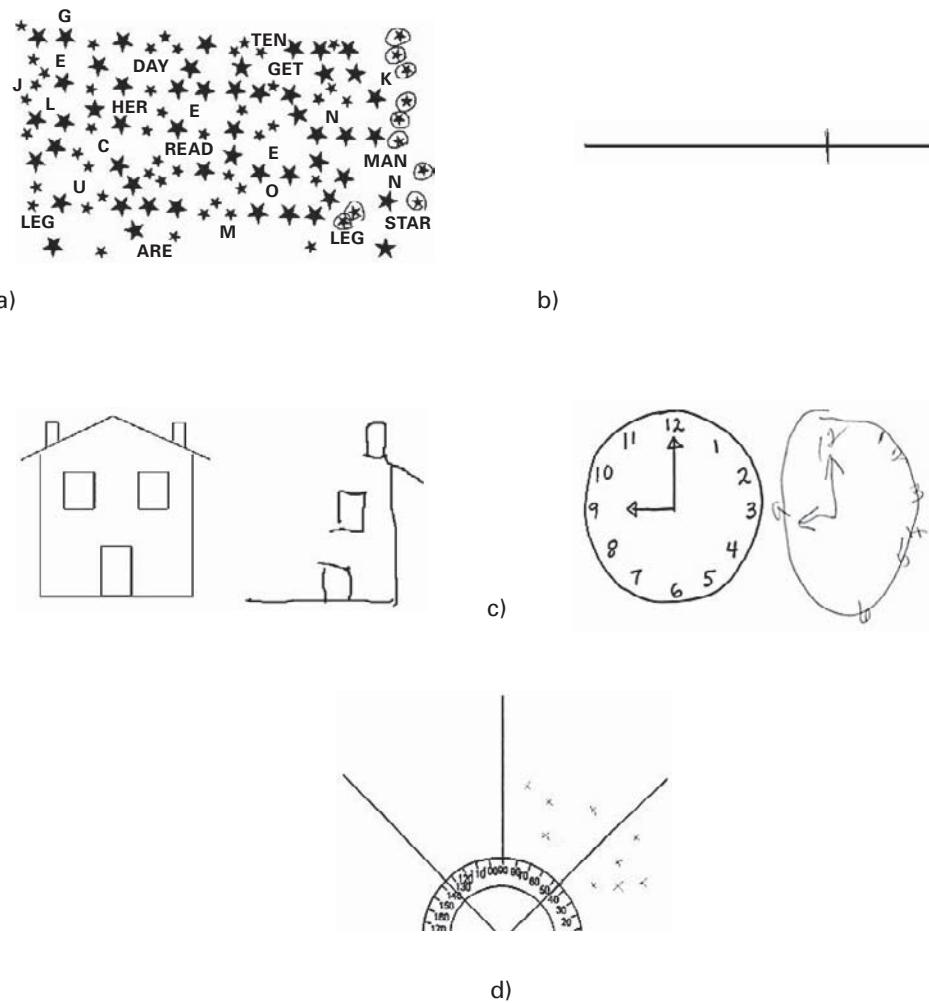
### The Neglect Syndrome

The most striking feature of neglect is the inability of patients to orient to stimuli on their contralateral (neglected) side (Mesulam, 1999; Parton, Malhotra, & Husain, 2004). Importantly, the syndrome is not confined to the visual modality; it can also be associated with neglect of contralateral sounds or tactile stimuli. Indeed, some patients show “personal neglect,” failing to attend to the contralateral side of their own bodies. However, at the bedside, the most striking deficits are often visual: Patients may fail to respond to the approach of a person from their neglected side or complain that they are still hungry after a meal despite food being present on the neglected half of the plate. In severe cases, their heads are turned almost continually to the ipsilateral area of space, and their gaze directed away from the neglected side of space.

If right-hemisphere patients with left neglect are presented with visual search tasks (often referred to as cancellation tasks by neuropsychologists and neurologists), they may find (cancel out or mark) only some targets to the right of the page, ignoring those to the left (see figure 18.2a). When asked to bisect a horizontal line, they may err to the right, as if unaware of the true leftward extent of the line (see figure 18.2b). Similarly, when asked to copy objects (see figure 18.2c,d) or draw them from memory, they may fail to complete the leftward parts. If asked to name objects around a room, they may point out some on the right, sometimes completely failing to report any to the left (see figure 18.2e).

What has become clear over the last few decades, however, is that neglect is not a unitary disorder. Rather, it is a syndrome composed of multiple and varying component deficits, only some of which are spatial (Husain & Rorden, 2003). These component deficits are not mutually exclusive; instead, their combination may serve to exacerbate the severity of the syndrome. Furthermore, the manifestation of neglect in individual patients may differ (Buxbaum et al., 2004), perhaps related to the variety of brain regions which, when damaged, can be associated with the syndrome. For it is now also evident that lesions to the right PPC are not the only ones which can give rise to the syndrome.

Although neglect is most frequently associated with right PPC lesions—specifically involving the inferior parietal lobe (IPL) and nearby temporoparietal junction (TPJ; Mort et al., 2003; Vallar & Perani, 1986)—damage to other regions has also been implicated, including the right inferior frontal gyrus (IFG; Husain & Kennard, 1996), a close homologue of Broca's area in the left hemisphere. Such a finding is consistent also with functional imaging studies which implicate a frontoparietal network in directing attention (Corbetta & Shulman, 2002). In addition, more recent work has implicated subregions within the lateral (Hillis et al., 2005; Karnath, Ferber, & Himmelbach, 2001) and medial (Bird et al., 2006; Mort et al., 2003) temporal lobes of the right hemisphere in the genesis of neglect. Focal lesions restricted to subcortical areas are also capable of causing neglect, probably due to hypoperfusion of overlying cortical regions or the disconnection of frontoparietal circuits (Doricchi & Tomaiuolo, 2003; Hillis et al., 2005; Karnath, Himmelbach, & Rorden, 2002; Thiebaut de Schotten et al., 2005). Even within the parietal and frontal areas implicated in neglect, the extent of damage can vary considerably among patients. Recent work also suggests that these areas may not serve unitary functions; instead they exhibit subspecialization with different parts of the PPC and IFG serving different functions (Corbetta & Shulman, 2002; Husain & Nachev, 2007; Culham & Valyear, 2006; Culham & Kanwisher, 2001; Husain & Rorden, 2003; Singh-Curry & Husain, 2009). Thus, the precise extent of damage is likely to influence the nature of the cognitive deficits observed in any particular patient. However, the situation is further complicated by the remote effects of the lesion (diaschisis) on other cortical areas, as well as direct disconnection

**Figure 18.2**

Examples of bedside pen-and-paper tests used to assess neglect. (a) *Star cancellation*: Subjects are asked to cancel all of the small stars, but this patient has only managed to circle those on the far right of the sheet. (b) *Line bisection*: Patients are asked to place a mark at the midpoint of the line. This example deviates to the right of the middle. (c) Examples of *copied drawings*: The left side of the house has been omitted, and most of the numbers on the left of the clock face have not been drawn. (d) *Neglect of far space*: People are asked to name objects they can see around the room. This patient has pointed out only those on their left-hand side.

due to the lesion interrupting connections between cortical regions (Thiebaut de Schotten et al., 2005; Bartolomeo, Thiebaut de Schotten, & Dericchi, 2007; Singh-Curry, Roberts & Husain, 2008).

This plethora of findings, and the complexities that arise from them, perhaps explain why neglect can be so frequent following stroke. It also might explain why the syndrome can be so diverse in terms of its constituent cognitive components. Thus, although most patients appear to be unaware of events to their neglected side, there may be many different factors contributing to such behavior. One way to view the cognitive deficits that might be involved in the syndrome is to consider them in terms of spatial and nonspatial processes.

### Spatial Deficits Contributing to Neglect

As we have seen, Kinsbourne proposed a highly influential directional model of neglect based on different capacities of the two hemispheres, with the left one able to shift attention rightward and the right hemisphere able to shift attention in both directions (Kinsbourne, 1993). He considered that a *bias in the gradient of spatial attention* may contribute to the manifestation of neglect. According to his model, if the left hemisphere is damaged, the right hemisphere can still direct attention rightwards, whereas with right-hemisphere lesions, the left is unable to fully compensate, and a rightward bias in the gradient of spatial attention results.

Posner, on the other hand, has suggested that a crucial difficulty right-hemisphere-neglect patients encounter is in *disengaging attention and shifting it leftward* (Posner, Walker, Friedrich, & Rafal, 1984). This is resonant with an alternative view advanced by investigators who have proposed a *biased competition model* of normal attention. These authors suggest that because the brain has limited capacity, it needs to select items for processing. In effect, this is the key role for "attention." Following right-hemisphere injury, they argue, events in the right visual field are automatically at an advantage to those on the left. They are treated effectively as being more salient or relevant so that they win in the competition for selective attention over left-sided stimuli (Duncan, Humphreys, & Ward, 1997).

In addition to these attentional accounts, other authors have considered the possibility of directional motor deficits contributing to the lack of exploration of the neglected side of space. In fact, there is evidence to suggest that patients with neglect demonstrate *directional hypokinesia*, that is, they are slower to initiate movements contralesionally or into contralesional space (Heilman, Bowers, Coslett, Whelan, & Watson, 1985; Mattingley, Husain, Rorden, Kennard, & Driver, 1998).

More recently, it has been proposed that some patients with neglect fail to keep track of spatial locations they have inspected, that is, they have a deficit in *spatial working memory* (SWM). When asked to perform visual search or cancellation tasks,

individuals with neglect typically only mark targets to the right (see figure 18.2a), missing those toward the left, although if the same stimuli are presented without right-sided distractors (nontargets), performance is much improved (Eglin, Robertson, & Knight, 1989). In fact, new evidence suggests that some neglect patients repeatedly search through rightward items. Using computerized search tasks, coupled with monitoring of eye movements, it has been shown that neglect patients often refixate targets they have previously identified and treat them as novel targets, failing to remember that they have inspected these before (Husain et al., 2001; Mannan et al., 2005). This failure in SWM was also found to correlate with the severity of neglect: The greater the problem in keeping track of rightward locations, the less the exploration of left space. Furthermore, the impairment in SWM is not caused by problems in encoding left-sided items; neglect patients have been shown to be poor at keeping track of spatial locations even when stimuli are presented only in the vertical meridian (Malhotra et al., 2005).

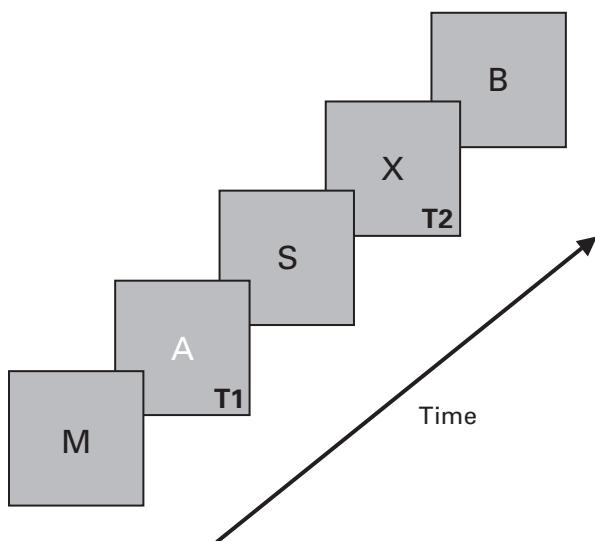
### Nonspatial Components of Neglect

Although the striking finding in neglect patients is their lack of response to items on one side of space, a growing body of evidence also demonstrates that impairments in nonspatial cognitive processes can contribute to and exacerbate the severity of neglect (Husain & Rorden, 2003; Nachev & Husain, 2006; Robertson, 2001; Heilman, Schwartz, & Watson, 1978). For example, it has been shown that deficits in *sustained attention*, or maintaining *vigilance*, correlate with the spatial severity of neglect (Robertson et al., 1997). This is true even when vigilance tasks demand attention to be maintained to stimuli that are presented centrally. Furthermore, studies have demonstrated that persistent neglect is often related to an impairment in sustained attention (Hjaltason, Tegner, Tham, Levander, & Ericson, 1996; Samuelsson, Hjelmquist, Jensen, Ekholm, & Blomstrand, 1998) and that improving vigilance can ameliorate the signs of neglect (Wilson & Manly, 2003). The use of computerized tasks designed to improve sustained attention has shown not only that there is an improvement in the signs of spatial neglect but that this benefit is associated with increased perfusion of the right hemisphere (Sturm, Thimm, Kust, Karbe, & Fink, 2006; Thimm, Fink, Kust, Karbe, & Sturm, 2006). The noradrenergic agonist guanfacine has also been associated with an amelioration of neglect in some patients, most likely as a result of improving the maintenance of attention (Malhotra, Parton, Greenwood, & Husain, 2006).

In addition to impaired sustained attention, patients with neglect have deficits in *nonspatial selective attention*, for example, when presented with a rapid serial visual presentation or attentional blink (AB) paradigm. In such tasks, subjects are asked to report the identity of a target letter (a different color to the other stimuli) and the presence or absence of a second probe letter, which occur in a stream of rapidly and

sequentially presented letters, usually at central fixation. The time between target and probe stimuli is manipulated by varying the number of interposed distractor letters in the stream (see figure 18.3). Healthy individuals require about 400 milliseconds between target and probe in order to be able to accurately report both (Broadbent & Broadbent, 1987; Duncan, Ward, & Shapiro, 1994; Shapiro, Raymond, & Arnett, 1994). This time period is the AB and is attributed to an inability to retain a usable representation of the probe during the period when the target is being processed. Neglect patients have been shown to have a pathologically long AB (of the order of three times longer than controls), even when stimuli are presented purely at a central location (Husain, Shapiro, Martin, & Kennard, 1997; Rizzo, Akutsu, & Dawson, 2001; Shapiro, Hillstrom, & Husain, 2002; Van Vleet & Robertson, 2006). Furthermore, this spatio-temporal deficit can be ameliorated by the presence of an alerting auditory tone after target presentation (Van Vleet & Robertson, 2006).

The results of functional imaging studies in healthy control subjects also support the contention of posterior parietal involvement in sustained and selective attention,



**Figure 18.3**

The attentional blink paradigm. In this paradigm, a sequence of stimuli (often letters) is presented in rapid succession at central fixation. Subjects are asked to report the identity of a target letter, usually displayed in a different color than the other stimuli (T1—shown here in white). They will then also have to report whether or not this T1 target is followed by a probe letter X (T2). The time between T1 and T2 can be systematically manipulated by varying the number of interposed distractor letters in the stream. The interval between T1 and T2 which is necessary in order to be able to accurately report both is termed the *attentional blink*.

a finding which is consistently biased toward the right hemisphere. For example, tasks involving sustained attention (to *single* central locations in space) strongly activate the right IPL and inferior frontal regions in normal people (Adler et al., 2001; Coull & Frith, 1998; Foucher, Otzenberger, & Gounot, 2004; Häger et al., 1998; Johannsen et al., 1997; Pardo et al., 1991; Paus et al., 1997; Sturm et al., 1999; Sturm et al., 2004; Vandenberghe et al., 2001). Similarly, right parietal regions in or close to the IPS, as well as frontal regions, are activated when healthy subjects perform selective attention tasks, such as the AB paradigm at central locations (Coull & Frith, 1998; Marois, Chun, & Gore, 2000; Wojciulik & Kanwisher, 1999). Taken together, these findings provide strong evidence for a role of the right IPL in intensity, as well as selective aspects of attention—even when there is no spatial component to a task.

### **Interaction and Specificity of Cognitive Deficits to Neglect**

Some studies have attempted to examine the possible interaction of spatial and non-spatial components of neglect. Thus, the prolonged AB in neglect has been found to interact with the pathological spatial gradient of attention, with longer durations between target and probe necessary when the probe is presented at a leftward compared to a rightward location (Hillstrom, Husain, Shapiro, & Rorden, 2004). More recently, the deficit in sustained attention has been shown to be particularly marked when neglect patients have to attend to spatial locations compared to nonspatial visual information (Malhotra, Coulthard, & Husain, 2009). The results of these types of study demonstrate that specific cognitive deficits within the neglect syndrome can articulate and interact with each other.

It is also clear that none of the cognitive component deficits identified in neglect need be specific to the syndrome. Studies assessing patients *without* neglect have, for example, implicated the right parietal lobe in SWM processes (Berryhill & Olson, 2008; Finke, Bublak, & Zihl, 2006; van Asselen et al., 2006). Similarly, deficits in sustained attention can be observed in patients with lesions of the right frontal or parietal lobe who also do not suffer from neglect (Rueckert & Grafman, 1996, 1998). Deficits such as these, when combined with an initial bias to direct attention to the right following right-hemisphere damage, probably lead to the syndrome we recognize as neglect (Kinsbourne, 1993). Initial biases to orient attention rightward probably are not sufficient in themselves to explain why patients should not eventually explore leftward items.

### **The Role of the Right PPC in the Processing of Stimulus Salience**

In this next section, we discuss some new considerations regarding the role of the right PPC and associated frontal regions in detecting and responding to different types

of salient information. One highly influential model of attentional orienting has proposed that a right-hemisphere system involving the TPJ and IFG plays a key role in reorienting attention to unexpected locations or novel, salient items (Corbetta & Shulman, 2002). Since these areas are often involved in neglect patients, the authors argue that deficits in these processes play an important role in the syndrome. Although we agree that deficits in processing salient information are a key aspect of neglect (Husain & Rorden, 2003), our perspective of salience processing in the right IPL is different. In our scheme, the right IPL plays a key role in *both* sustaining attention over time to task-relevant activities as well as switching to a more exploratory mode when salient information appears in the environment (Singh-Curry & Husain, 2009).

Salience refers to the properties of a stimulus which make it stand out from the surrounding environment. This may be because its physical properties are different from surrounding items, for example, a red poppy in green grass, or because it has particular behavioral significance or relevance to the task being performed (*behavioral* or *target-related salience*). Alternatively, it may represent something *novel* that we have not encountered recently or act as a warning that an event of behavioral significance is about to occur. The sounding of an alarm in a building signaling an evacuation would be one example of such a *phasic alerting* stimulus.

### Target-Related Salience

Target related salience refers to a process in which it is necessary to hold in mind the characteristics of the target, so that actions can be directed depending on what is perceived in the environment or during a task. As such, it involves both an endogenous, or "top-down," component, as well as a stimulus-driven, or "bottom-up," element. It is most frequently assessed using the oddball paradigm, which consists of infrequently occurring target stimuli (to which the subject is instructed to respond) embedded within a stream of identical, frequently occurring distractors, to which responses should be withheld. ERPs have been used to study the neurophysiological correlates of orienting to target stimuli within the oddball task. Detection of salient events normally elicits a characteristic positive potential, occurring 300 to 500 milliseconds after target presentation and centered over the parietal lobe (Vaughan & Ritter, 1970). This wave has been termed the P300 (Smith, Donchin, Cohen, & Starr, 1970) or P3 (Ritter, Vaughan, & Costa, 1968) response and is not elicited by the frequently occurring, familiar distractor stimuli. Lesions of the TPJ abolish the P3 (Knight, Scabini, Woods, & Clayworth, 1989), while prefrontal lesions lead to a reduction in the amplitude of the P3 over parietal regions (Barceló, Suwazono, & Knight, 2000). Furthermore, patients with neglect also show a reduction in P3 amplitude (Lhermitte, Turell, LeBrigand, & Chain, 1985).

Additional support for the importance of the right parietal lobe in salient target detection comes from functional imaging studies employing the oddball paradigm (at

single central locations), performed in healthy subjects. The areas most consistently activated are the right IPL, IPS, TPJ, and frontal regions (Bunzeck & Duzel, 2006; Clark et al., 2000; Foucher et al., 2004; Gur et al., 2007; Huang et al., 2005; Kiehl et al., 2001; Kiehl et al., 2005; Lagopoulos et al., 2006; Linden et al., 1999; Marois, Leung, & Gore, 2000; Williams et al., 2007).

### **Novelty**

Novel events, which have not been encountered in a particular behavioral context or environment recently, are highly salient. It is an essential attribute of the nervous system that attention should be easily attracted to a new stimulus, so that, if threatening, aversive action can be quickly taken, and, if beneficial, it can be exploited for maximum benefit. As with target-related salience, it may be argued that novelty detection is primarily a bottom-up process. However, in order to distinguish between something which is new and something familiar, it is necessary that memory for previous items be readily available for comparison, a process more top-down in nature.

Novelty detection too has been extensively studied using the oddball paradigm. In these circumstances, occasional novel stimuli also appear embedded within the stream of infrequent targets and frequently occurring distractors. The subject is not usually given any instructions regarding these new stimuli and hence should not respond to them. Despite this, like targets, the novel distractors also elicit a P3 potential centered over parietal cortex. However, the P3 to novel events occurs slightly earlier—and is termed the P3a—compared to that occurring in response to targets—termed the P3b (Courchesne, Hillyard, & Galambos, 1975; Squires, Squires, & Hillyard, 1975). Lesions of the TPJ eliminate both the P3a and the P3b (Knight et al., 1989). Again, further support for the role of right parietal regions in the processing of novelty comes from functional imaging studies, using oddball tasks (with centrally presented stimuli) in healthy controls. These studies demonstrate prominent involvement of the IPL, TPJ, and also ventral frontal areas (Bunzeck & Duzel, 2006; Downar et al., 2002; Gur et al., 2007; Kiehl et al., 2001; Kiehl et al., 2005).

### **Phasic Alerting**

One final aspect of salience, from our perspective, is phasic alerting. This refers to a readiness to detect or respond to environmental changes as a result of an exogenous warning stimulus (Posner & Boies, 1971). There may be predefined associations between an alerting cue and a target, such as a set interval, for example, reaction times to targets are least if they are preceded by an alerting cue occurring 500 to 1,000 milliseconds beforehand (Posner & Boies, 1971). On the other hand, there may be no such predetermined associations, in which case the phasic alerting stimulus becomes very similar to a novel one. In fact, it could be argued that all salient events are

to varying degrees phasically alerting. Nevertheless, even when we consider only situations in which an alerting cue warns of an impending target (at single central locations) and is of no other informational value, such events in themselves have been associated with prominent activation in the right IPL, TPJ, and frontal regions (Fan, McCandliss, Fossella, Flombaum, & Posner, 2005; Thiel & Fink, 2007).

Lesions in the right hemisphere are known to be associated with impaired arousal, measured by galvanic skin responses (Heilman et al., 1978) or heart rate changes to warning cues (Yokoyama, Jennings, Ackles, Hood, & Boller, 1987). On the other hand, patients with neglect can benefit from an alerting tone during tasks designed to assess their leftward inattention (Robertson, Mattingley, Rorden, & Driver, 1998). It has been argued that ascending noradrenergic pathways from the locus coeruleus (LC)—a nucleus in the midbrain—play an important role in the modulation of alertness through innervation of the parietal cortex (Posner & Petersen, 1990), which receives particularly dense projections (Foote & Morrison, 1987; see figure 18.4). For example, it has been shown that the activity of these LC neurons is reduced in states of low arousal (Aston-Jones, Gonzalez, & Doran, 2007).

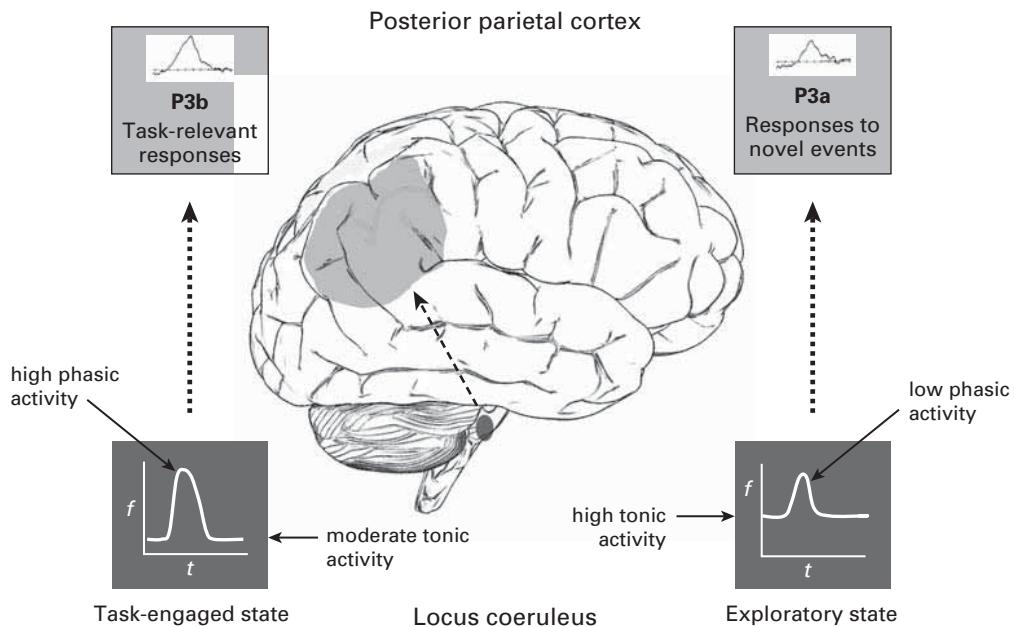
Aston-Jones and colleagues have specifically argued that the LC contributes to regulation of behavior between two opposing functional states:

- a focused, task-engaged state, facilitating detection of target events and the filtering out of distractors, and
- a more labile, exploratory mode, allowing flexible responding to novel events, that is, stimuli which are not current targets but which may nevertheless be behaviorally important (Aston-Jones & Cohen, 2005; Aston-Jones, Iba, Clayton, Rajkowski, & Cohen, 2007).

These authors argue that *phasic* bursts from the LC may be important in mediating a task-engaged state, while higher *tonic* levels of LC activity are associated with the exploratory state (see figure 18.4). But how does the brain switch between these states of exploiting current goals and exploring new ones? This is where we consider the right IPL to play a crucial role.

### **Reconfiguration of Behavior between Task-Engaged and Exploratory States**

Functional imaging studies assessing cerebral activation during the process of switching between tasks have often implicated frontal regions, but in addition the IPL is frequently activated in such studies, although not necessarily solely in the right hemisphere (Rushworth, Passingham, & Nobre, 2005; Travers & West, 2008). However, a recent conjunction meta-analysis of studies using a variety of paradigms in which switching of response sets was required (Wisconsin Card Sorting Task, go/no-go task, and more classical task-switching paradigms) reported the right—and not the left—IPL



**Figure 18.4**

Reconfiguration between task-engaged and exploratory states. In the *task-engaged state*, locus coeruleus (LC) tonic or baseline activity is moderate, with optimal phasic bursts occurring in response to task-related events ( $f$ : firing rate of LC neurons,  $t$ : time or latency). This leads to a *P3b* potential in the posterior parietal cortex (PPC), facilitating accurate task performance. *Novel* events (of no task relevance) can also produce phasic LC responses. These are associated with a *P3a* potential in PPC, which is generally smaller than the *P3b* potential. The *P3a* does not correlate with behavioral responses when performance is task-engaged but may be more likely to do so as behavior becomes more *exploratory*. Note that, in contrast to either target or infrequent novel stimuli, *frequently* occurring task-irrelevant stimuli do not evoke *P3* responses.

to be significantly activated across such tasks (Buchsbaum, Greer, Chang, & Berman, 2005). Thus, the right IPL may play a key role in switching between conflicting responses when a prepotent response must be overcome to make the appropriate action.

Intriguingly, neurophysiological evidence suggests that task switching—like detection of salient targets and novel stimuli—is accompanied by a *P3* potential overlying the parietal cortex (Rushworth et al., 2005; Travers & West, 2008), supporting the contention for an important parietal role in this process (Singh-Curry & Husain, 2009). Converging evidence from neurophysiological, pharmacological, and lesion studies suggests that the *P3* over parietal cortex might reflect phasic activity

of the LC noradrenergic system (for a review, see Nieuwenhuis, Aston-Jones, & Cohen, 2005).

A key factor affecting the amplitude of LC phasic responses appears to be the *motivational salience* (or associated reward) of the stimulus (Aston-Jones et al., 1994; Rajkowski, Majczynski, Clayton, & Aston-Jones, 2004). Recent computational modeling has raised the possibility that such *phasic* noradrenergic activity might function as a “neural interrupt signal,” acting to *reconfigure* ongoing attentional processes and shifting behavior toward a more task-engaged state or signaling the occurrence of events within a task (Dayan & Yu, 2006).

Importantly, the level of phasic LC activity is affected by the *tonic* level of LC neuronal discharge. Low tonic levels are found in drowsy animals, and in this state there is also very little phasic activity. Similarly, at very high tonic levels there is also very little phasic activity. However, between these two extremes—at moderate tonic noradrenergic levels—phasic LC bursts are most effective and are strongly correlated with accurate target detection and, by inference, the P3b potential recorded over parietal cortex in response to salient task-related stimuli (see figure 18.4; Dayan & Yu, 2006; Yu & Dayan, 2005; Aston-Jones, Rajkowski, Kubiak, & Alexinsky, 1994; Singh-Curry & Husain, 2009). It is in this state that behavior seems to be most easily maintained on task, corresponding to our view of the state of sustained attention in human observers.

These considerations suggest that the parietal cortex, most prominently in the human right hemisphere, might receive crucial motivational salience input from the LC, which acts to modulate its responses. However, in addition, the PPC is an important point of convergence for various other types of information: sensory, motor, and goal-related. Indeed, recent evidence suggests that the IPL is a “structural core” region of the human cerebral cortex, being one of the most densely interconnected cortical regions (Hagmann et al., 2008). This connectivity places it in an ideal position for different types of information—sensory, motor, goal-related, and motivational—to compete; with other brain areas, including the LC, biasing the outcome of such competition.

In summary, we argue that *phasic* bursts of LC noradrenergic activity (on a background of moderate tonic levels) induce, via parietal cortex, a goal-focused task-engaged state, enhancing sustained attention to task demands and facilitating the detection of task-relevant events. In contrast, increases in LC *tonic* activity shift behavior toward a more distractible and exploratory state, favoring responses to novel environmental stimuli. These two complementary aspects of attention—maintaining attentive control on current task goals and responding to salient new or alerting stimuli in the world around us—and switching between them is, in our view, a crucial aspect of right IPL function that is not captured by traditional views of the specialization of this area for visuospatial functions.

### Concluding Remarks

There is little doubt that the right hemisphere plays a major role in processing visuo-spatial information and in the distribution of spatial attention. In particular, observation of patients with neglect—the syndrome that often occurs after right PPC damage—makes this abundantly clear. However, our review of the findings in this field lead us to conclude that the right PPC does not seem to be concerned purely with spatial aspects of attention; the situation is more complex.

Examination of the neglect syndrome and the results of functional imaging studies in healthy control subjects (for reviews, see Husain & Nachev, 2007; Nachev & Husain, 2006; Singh-Curry & Husain, 2009) suggests that this region is also critical for sustaining attention and for the detection of novel or behaviorally salient events—wherever they may occur in space. It is our contention that this combination of attentional functions leaves the right PPC poised to play a crucial role in flexibly reconfiguring behavior: between a state where attention is focused on current task goals and one which is primed to respond to salient new events in the surrounding environment. Damage to such processes contributes to the syndrome of visuospatial neglect, a multicomponent disorder consisting of both spatial and nonspatial cognitive deficits.

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## **19 Hemispheric Asymmetry in Pediatric Developmental Disorders: Autism, Attention-Deficit/Hyperactivity Disorder, and Dyslexia**

**Deborah W. Moncrieff**

Neuroimaging techniques over several decades have opened windows into the brains of children diagnosed with a variety of developmental disorders. In conjunction with earlier efforts that used postmortem specimens, these techniques have widely expanded our potential to understand structural and functional differences in a growing number of individuals across a broader array of disabilities. Magnetic resonance imaging (MRI) is less invasive than the earlier methods of computed tomography and positron emission topography (PET) and can be safely used to study children of all ages. As a result of these advances in imaging techniques, more researchers have examined the brains of children and reported on the presence or absence of hemispheric asymmetries within specific diagnostic categories. As this information has accumulated, however, it has been apparent that similarly abnormal structures in regions of the brain may be evident in children diagnosed with different developmental disorders. Overlapping findings could potentially be due to errors in diagnostic classification of study subjects, or they may represent systematic and similar alterations occurring in neural systems across several pediatric disorders. Phenotypically, children with developmental disorders often share a number of common traits which complicate efforts to differentially diagnose them, prevalent among which are behavioral symptoms related to language and cognitive skills. Assessment strategies used to clinically diagnose these types of pediatric disorders are often limited in sensitivity and specificity, primarily because they employ stimuli that activate multiple sensory, attentional, and cognitive pathways in the brain.

Because of the many deleterious effects of pediatric developmental disorders, extensive research into the biological underpinnings of risk factors that may lead to each particular disorder and to subsequent behavioral and cognitive deficits has been warranted. Outward manifestations of pediatric disorders have been linked to a complex interaction of multiple genes and epigenetic factors, especially those related to language function (Hyman, 2000; Bishop, 2001). Chief among these is an abnormal cerebral asymmetry, identified as a shared phenotype that is linked to two chromosomal regions in children diagnosed with autism, attention-deficit/hyperactivity

disorder (ADHD), and dyslexia (Smalley et al., 2005). The same regions of linkage overlap were also identified in individuals with other traits or disorders associated with abnormal hemispheric asymmetry, including schizophrenia, bipolar disorder, specific language impairment (SLI), and handedness (Lewis et al., 2003; Segurado et al., 2003).

Evidence of common risk genes in pediatric developmental disorders supports an emerging view that abnormal hemispheric asymmetry may represent a functionally important but epigenetically downstream consequence of alterations in neural substrate or in the interactions of neurochemicals throughout development. These aberrant cerebral asymmetries have been characterized by volumetric analysis of neural tissue through a variety of imaging techniques and have also been inferred through behavioral assessment strategies, especially the dichotic listening test. The dichotic listening test is an important tool in the behavioral armamentarium for examining hemispheric specialization for language and auditory processing skills. Results from dichotic listening tests can reflect an abnormal balance in function between the left and right hemispheres within the temporal lobe as detailed in studies with patients with lesions on the left or right side of the brain (Hugdahl, 1995). Abnormal results are often due to an abnormally large degree of asymmetry between the right and left hemispheres following specific damage to one side of the brain. Information from dichotic listening tests and other behavioral measures aimed at quantifying a deficit, together with results from structural and functional magnetic resonance imaging and electrophysiology, may one day lead to a more comprehensive understanding of whether and how hemispheric asymmetry is altered in each particular developmental disorder.

A prevalent goal of research in hemispheric asymmetry has been to identify specific regions of neural tissue that are abnormally asymmetrical in children with developmental disorders, whether that abnormal asymmetry is the result of greater volume on one side of the brain than is typically observed or from a reduced volume of neural tissue on one side compared to that seen in normal children. A specific goal of many research initiatives has been to ultimately identify an abnormal asymmetry that is unique to one particular developmental disability, but this goal has been elusive. Some early reports of specific anatomical differences for children with one particular developmental disorder (which will be discussed in detail in this chapter) have been discounted when improved techniques for measuring neuroanatomical volumes have failed to support evidence of abnormal asymmetry, and others have been challenged by different results in new studies that have carefully controlled subject populations. Sorting out the conflicting evidence and developing an empirical basis for claiming a neuroanatomical marker for any particular developmental disorder have represented an enormous challenge to researchers in this important clinical area.

Another complication is that children with developmental disorders do not always have only one particular disability. Some children may be simultaneously diagnosed

with dyslexia, attention deficit disorder, language disorder, and auditory processing disorder, or with any other possible combination of the disorders that commonly occur in childhood. Identification of multiple disabilities may occasionally be the result of inadequate assessments for differential diagnosis of overlapping processes within sensory, attentional, and cognitive processing domains. In other cases, it may be due to a real co-morbidity of multiple factors within a particular child. Children may display a variety of functional asymmetries when assessed through a battery of behavioral tests. Even with purportedly objective electrophysiological and functional neuroimaging measures, a significant amount of variability in the results reported from pediatric studies has undermined the establishment of standard diagnostic procedures. Researchers in this field share a desire for accurate, sensitive, and specific assessment strategies to clarify the diagnosis and treatment of children with developmental disabilities. Despite the number of twists and turns taken by research initiatives, there is a significant body of evidence to suggest that real progress is being made on this important objective.

### **Hemispheric Asymmetry and Autism**

Hemispheric asymmetry has not been a centerpiece of studies investigating the neuropathology of autism. Relatively few autistic brains have been examined by the imaging methods that have been so widely used in other developmental disorders, and of those, most have been done on the brains of adults with autism. Despite the relative paucity of anatomical studies, there has been some evidence of abnormal asymmetry that may occur in the brains of children with autism.

### **Structural Differences in Autism**

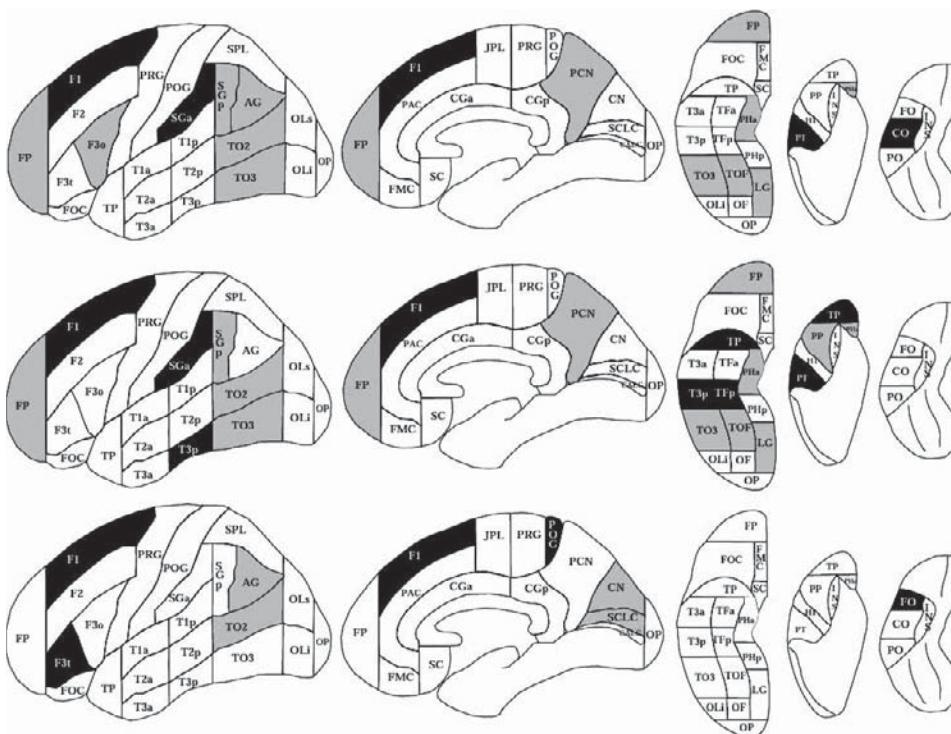
Compared to controls, children with autism were found to have several structural differences in the cerebellum, corpus callosum, hippocampus, amygdala, and brain-stem, but none of these differences were evidenced by any degree of abnormal asymmetry (Hendren et al., 2000). One study with single photon emission computed tomography reported abnormally low regional cerebral blood flow (rCBF) in temporal and parietal regions of the left hemisphere in autistic children under anesthesia (Mountz et al., 1995). Similarly, Chiron and colleagues (1995) reported reduced resting rCBF in the left sensorimotor and auditory cortices and in Broca's area in children with autism. While both circumstances led to a rightward shift in asymmetry during rest, there appeared to be a decrease in overall cerebral blood flow in children with autism (Chiron et al., 1999).

A third study noted that in adolescent children with Asperger's syndrome, right-hemisphere abnormalities were present in temporal, frontal, and occipital lobes and in the cerebellum (McKelvey et al., 1995). Because autistic disorders range from mild

to severe deficits in social interaction and communication, it seems likely that children representing different degrees of severity across the spectrum of autism may also reflect dissimilar cerebral morphology in imaging studies. Asperger's syndrome is considered by many to represent a milder form of autism, often referred to as "high-functioning autism," and thereby may not share genetic or epigenetic factors with severe types of autism that have a more dramatic impact on a child's language abilities. The widespread nature of autism and the inclusion of children whose characteristics span across the spectrum may have potentially complicated studies investigating anatomical anomalies in this population.

More recently, MRI scan volumetric analyses revealed a 27% larger right-side language-related area of the cortex (inferior lateral frontal and posterior superior temporal regions) in boys with autism compared to a 17% larger left-side area in controls (Herbert et al., 2004). In another MRI study, a similar reversal of the normal leftward asymmetry in language-related areas of cortex was reported in boys diagnosed with both autism and language disorder and in boys diagnosed with SLI, but neither in boys diagnosed only with autism who had normal language nor in boys with none of these disorders (DeFosse et al., 2004). These results suggested that reversed asymmetry in frontal language areas of the brain, with larger volumes on the right than on the left, may be differentially related to pediatric language disorders but not necessarily to autism. A follow-up MRI study specifically compared boys with autism to boys with developmental language disorders (DLD), however, and reported a similarly larger aggregate volume of right-asymmetrical cortex in both disorders (Herbert et al., 2005; see also figure 19.1 and table 19.1). They noted that higher order association areas were most vulnerable in both groups of children and that when examined in terms of cortical parcellation units, specific regions with asymmetry unique to each disorder could be separately identified. Children with autism showed a leftward asymmetry in the central operculum, which was not found in the boys with DLD, but also showed a strong rightward asymmetry in the pars opercularis and the angular gyrus that resulted in an overall rightward hemispheric asymmetry.

In general, boys with either autism or DLD were remarkably different from controls and similar to each other in patterns of hemispheric asymmetry across many shared regions of the brain, with an increase in the number and volume of cortical parcellation units toward the right and with little or no loss of leftward gray-white matter. The large number of asymmetries that are nearly identical in both of these groups of disordered children reinforces the possibility that the two groups may share genetic factors that predispose their brains to common abnormal courses of language development. These results were consistent with other reports of enlarged areas of white and gray matter in developing brains of individuals with autism and DLD (Lainhart, 1997; Courchesne et al., 2003) and appear to be greater in areas that myelinate later in development (Herbert et al., 2004). Evidence of greater differences in myelinated



**Figure 19.1**

Asymmetry in each parcellation unit by group. Black indicates units with significant leftward asymmetry, and gray indicates significant rightward asymmetry. Nonshaded units were not significantly asymmetrical in either direction. DLD = developmental language disorders; for definitions of abbreviations for regions showing larger aggregate volume in children with autism and DLD, see table 19.1.

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regions has led some to speculate that the altered cortical asymmetry may be due to an adaptation to an abnormal brain and white matter growth trajectory. One proposition of a positive feedback loop is that increased hemispheric volume is reinforced by poor interhemispheric connectivity, which in turn favors increased lateralization and a local processing of sensory input. The few differences between the two groups related to hemispheric asymmetry, possibly within parietal regions of the brain, may stem from unidentified genetic factors or to epigenetic factors that lead to the unique phenotypic characteristics that clinicians use to separate autism from DLD. Whether unique features of each disorder arise from variations in the expressivity of the primary genetic factors, from other biological traits that interact with genetic predispositions,

**Table 19.1**

Abbreviations used in figure 19.1

Abbreviation	Definition
<i>Primary sensory and motor cortex</i>	
CP	Central operculum
POG	Postcentral gyrus
<i>Unimodal association cortex</i>	
F3o	Pars opercularis
FO	Frontal operculum
PT	Planum temporale
T3p	Posterior inferior temporal gyrus
TO2	Middle temporo-occipital gyrus
TO3	Inferior temporo-occipital gyrus
TOF	Temporo-occipital fusiform gyrus
<i>Higher order association cortex</i>	
F3t	Pars triangularis
FP	Frontal pole
AG	Angular gyrus
SGa	Anterior supramarginal gyrus
SGp	Posterior supramarginal gyrus
PHa	Anterior parahippocampal gyrus
PP	Planum polare
TP	Temporal pole
<i>Unclassifiable</i>	
F1	Superior frontal gyrus
LG	Lingual gyrus
PCN	Precuneus
TFp	Posterior temporal fusiform

or from environmental influences early in the child's development is currently not known.

### Effects of Serotonin on Brain Development in Autism

The role of serotonin has been identified as one possible mechanism for altered brain development in children with autism (Cook et al., 1997; Piven & Palmer, 1999). Serotonin is important for prenatal and postnatal brain development and has been recently implicated in cortical column development through innervations of Cajal-Retzius cells (Janusonis et al., 2004). In the normal brain, minicolumnar organization differs between the two cortices with greater distances between columns that are wider and

with a greater number of large pyramidal cells evident on one side than the other. Different patterns of asymmetry within anterior and posterior brain regions that are involved in language function may be related to specific functional roles within those areas (Buxhoeveden & Casanova, 2002; Hutsler & Galuske, 2003). Significant abnormalities in cortical columns that may be important for hemispheric specialization and language function have been reported in postmortem brains of children with autism (Casanova et al., 2002). Digitized images of cortical laminae revealed smaller and more numerous cell columns in the brains retrieved from children with autism, but these were not reportedly more or less evident on one side of the brain. In addition, the cellular configuration within each column was more widely dispersed, leaving less neuropil space in the peripheral areas. The areas studied were the middle temporal gyrus, the superior and middle frontal gyrus, and the tempoparietal auditory area. Because the cytoarchitecture of cortical columns is linked to processing efficiency (Rakic, 1991), this result suggested that the brains of autistic children may have a greater number of processing units than normal. Casanova and colleagues (2002) hypothesized that the increased number of minicolumns leads to greater activation in these cortical areas and that the brains of children with autism may therefore be overtaxed by a chronic state of overarousal.

The hypothesis that children with autism experience chronically heightened arousal has led some to speculate that appropriate lateral inhibition has failed to develop in these children, thereby implicating possible interactions between serotonin, glutamate, and GABA during early development. Modulatory effects of serotonin across GABA-mediated inhibitory neurotransmission and glutamateric excitatory neurotransmission are involved in sensory processing, learning, and memory. While some supposed that overarousal is due to limitations in the function of GABAergic neuronal systems within the cortex (Casanova et al., 2002), others have suggested that an early loss of serotonergic fibers may have contributed to a hypoglutamatergic condition in the developing brain (Ciranna, 2006). Studies in animal models of autism have demonstrated that through negative feedback in early development, high levels of serotonin can induce a loss of serotonin terminals and produce autism-like symptoms (Whitaker-Azmitia, 2005). Rats given dietary changes to increase serotonin during development have been shown to have altered auditory processing, suggesting that changes in serotonin concentration may alter activity in the auditory cortex (Manjarrez et al., 2005). These results lend support to earlier reports of altered cortical innervation patterns in thalamocortical projections in rodents, possibly due to glutamatergic expression of serotonin transporter mechanisms (D'Amato et al., 1987; Bennett-Clarke et al., 1996). In these animal studies, it was thought that increased levels of serotonin led to greater tangential arborization of axons and that the greater number of fibers resulted in a blurring of the boundaries within cortical regions (Cases et al., 1996).

High levels of blood serotonin have been regularly reported in children with autism. Up to age 2 years in normally developing children, whole brain serotonin synthesis capacity is more than 200% greater than adult values and then drops off throughout development. This capacity is reportedly disrupted in children with autism for whom the capacity grows more slowly through early development until adolescence when the blood levels are 1.5 times greater than in normal adults (Chugani et al., 1999). As indicated in the animal studies, higher levels of blood serotonin lead to decreased cortical serotonin synthesis. The effects of serotonin appear to be different within the right and left hemispheres of the brain in children with autism. When studied with PET for the presence of a serotonin synthesis tracer, children with autism who displayed right cortical decreases in serotonin synthesis were more likely to have mild language impairment while those who displayed left cortical decreases in serotonin synthesis had a higher incidence of severe language impairment (Chandana et al., 2005). This would suggest that hemispheric differences in cortical serotonin synthesis may account for some of the severity differences observed in language skills across children with autism.

### Dichotic Listening Findings in Autism

Dichotic listening was used in the past as a technique to probe hemispheric specialization for language and to explore similarities between autism and language impairment. Only a few studies examined children, and most used everyday words as the dichotic stimuli. An early study hypothesized that children with autism suffered from a central cognitive deficit that led to severe language impairment (Prior & Bradshaw, 1979). The children with autism were assessed for handedness and were found to show either right-handedness or mixed dominance with no strong preference for either hand. On the dichotic listening test, the children with autism performed at the same overall level as the control children, but they did not exhibit an average right-ear advantage (REA). This led to speculation that for some of the children with autism, language specialization may have been in the right rather than the left hemisphere. Further analysis showed that language lateralization was related to whether the child had acquired normal speech skills by the age of 5 years and to the child's intelligence.

A few other studies probed dichotic listening in children with autism with mixed results. One group found that children with autism performed similarly to controls (Arnold & Schwartz, 1983). Another reported that children with autism performed normally on two commonly used dichotic listening tests unless they also suffered from echolalia (Wetherby et al., 1981). The study tested only 6 subjects, who ranged in age from 8 to 24 years and whose language and echolalia symptoms covered a wide range as well. A recent study reported a higher incidence of a left-ear advantage (LEA) and

poorer scores overall among children with autism and further noted that the children with autism also had relatively low intelligence (Hayashi et al., 1989).

Clinicians and researchers rarely include dichotic listening techniques for standard assessment of children with autism. Past studies have provided only mild support to the morphological evidence of larger volumes in the right hemisphere that has been reported for children with autism and language impairment (Herbert et al., 2004; DeFosse et al., 2004). It seems possible that an evaluation with behavioral dichotic listening techniques using standard clinical tests that are currently available may add important behavioral information about hemispheric specialization and degree of asymmetry in this population.

### **Summary of Results in Autism**

Children with autism may have abnormal hemispheric asymmetry with larger representation on the right than on the left side in language areas of the cortex. This effect may reflect an adaptation to an abnormal brain and white matter growth trajectory in thalamocortical, interhemispheric, or intrahemispheric projections early in development. Cortical minicolumns in children with autism may have a greater number of neuronal cells, especially within the right hemisphere, leading to increased activations and a higher state of arousal. These altered cortical areas may have been due to higher than normal levels of brain serotonin during prenatal and postnatal periods, which may have contributed to an increase in the number of processing units within the right hemisphere.

### **Hemispheric Asymmetry and ADHD**

By the 1990s, ADHD had become the most common psychiatric disorder of childhood. Parents and physicians became increasingly concerned about the widespread use of pharmaceutical stimulants in the treatment of children diagnosed with the disorder. Impulsivity, distractibility, and deficits in vigilance are the behavioral descriptors most commonly used to diagnose children with ADHD. These traits are usually identified through questionnaires given to the parents and teachers of children suspected of ADHD rather than through more rigorous and direct cognitive measures of inattention. Most of the behaviors are common in children who have difficulties sustaining attention, but many of the same behaviors could potentially be due to sensory processing deficits or problems with language. The absence of a specific biological construct for ADHD has not prevented widespread diagnosis of the presumed disorder, but it has prompted a significant quantity of research into neurobiological markers that could be specifically linked to deficits in attention. Several hypotheses have emerged regarding the etiology and pathophysiology of ADHD, many of which are

largely dependent upon neuroanatomical differences observed in children diagnosed with the disorder.

### **Right-Hemisphere Deficits in ADHD**

One current theory of ADHD is that the disorder should be viewed as a right-hemisphere syndrome (Stefanatos & Wasserstein, 2001) following supportive evidence of diminished neural activity in right-hemisphere prefrontal regions of the brain during behavioral tasks, especially in the caudate nucleus (Vaidya et al., 2005). This theory was initially suggested by the observation that right-hemisphere brain damage produced symptoms that were similar to ADHD (Heilman et al., 1986). It has been advanced by multiple findings of structural differences in the brains of children with ADHD, especially in prefrontal and frontostriatal regions. A problem with the theory, however, is that for every study that has reported abnormalities in regions on the right side of the brain, there are as many that have failed to report differences at all or that report differences in homologous regions on the left side of the brain. A recent review of anatomical evidence in this population has noted that small sample sizes and a variety of measurement methods make it extremely difficult to compare results across different studies (Seidman et al., 2005).

Reports of a smaller right-hemisphere frontal lobe in children with ADHD (Hynd et al., 1990; Castellanos et al., 1996) have been supported by evidence of reduced right-hemisphere dorsolateral prefrontal volume (Yeo et al., 2003). Investigators measuring gray and white volume in children with ADHD have reported reduced gray matter in both prefrontal cortices, especially on the right (Mostofsky et al., 2002) and in the right-hemisphere posterior cingulate gyrus, superior frontal gyrus, and putamen (Overmeyer et al., 2001). Reductions in white matter, however, were also noted for the left hemisphere in both of these studies. Sowell and colleagues (2003) reported evidence of increased gray matter density in the right occipital lobes of children with ADHD. These researchers compared distances between the center of the brain and the cortical surface and reported that brain surfaces of children with ADHD were reduced overall in the anterior temporal cortices and in the inferior dorsolateral prefrontal cortex, with reduced volumes noted on the right in the parietal cortex. This variability in evidence of anatomical differences in the right hemisphere of children with ADHD is difficult to resolve at this time, but with advanced methods for analysis of neuroimaging results, it is hoped that some of this confusion may be resolved.

### **Basal Ganglia Differences in ADHD**

One region that has been widely studied among children with ADHD is the basal ganglia, with several reports of anatomical differences in the caudate nucleus. Findings have indicated nearly every possible combination of symmetry and asymmetry in the caudate nucleus in children with ADHD, including reduced and symmetrical caudate

nuclei, leftward asymmetrical caudate nuclei due to larger left-sided or smaller right-sided volume, and rightward asymmetrical caudate nuclei due to larger right-sided or smaller left-sided volume (Krain & Castellanos, 2006). Several studies have reported altered asymmetry of the basal ganglia due to a reversed right greater than left volume of the caudate nucleus, suggesting that deficient synaptic pruning during early development may have prevented the decrease in caudate volume that is seen in typically developing children (Castellanos et al., 2002). In an earlier study that compared the larger caudate nucleus volume in boys with ADHD to performance on discrimination tasks, it was noted that the immature degree of asymmetry did not interfere with automatic responses during a low-level stage of attentional processing but that the boys with the larger right-side caudate nucleus produced slower responses on a higher level response execution task (Casey et al., 1997).

The caudate nucleus was originally thought to be primarily involved in motor planning and execution but is now understood to also be necessary for learning and memory. Its role in language function is likely due to its close proximity to the thalamus and to the multiple inputs it receives from the association cortices, including those related to complex auditory and visual information. Some recent studies have also made comparisons between anatomical findings and behavioral results to determine whether abnormal morphology can predict deficits in behaviors that are typically weak in children with ADHD. When caudate nucleus volume asymmetry was measured in children not yet diagnosed with ADHD and results were compared to the severity of parent-reported behaviors commonly linked to the diagnosis of ADHD, the degree of rightward asymmetry significantly predicted the cumulative severity ratings of inattentive behaviors (Schrimscher et al., 2002). This meant that children with greater asymmetry toward the right were more likely to demonstrate inattentive behaviors in this population. Since none of these children had yet been diagnosed with ADHD, it raises the possibility that the greater rightward asymmetry may be linked to subclinical manifestations of attention deficits and that children with more severe traits may differ in structural morphology. Asymmetry measurements of the caudate nucleus among children whose parents reported few of the ADHD behaviors were slightly leftward, but the degree of leftward asymmetry was considered too small to categorically establish directionality for normal children. These results may suggest that the brains of some children with ADHD are possibly lateralized to a greater degree toward the right side in prefrontal striatal systems that may play an important role in language and cognitive functions throughout development.

There is currently no consensus that anatomical differences in children with ADHD are abnormally lateralized to any extent. Evidence of anatomical differences in frontal and extrastratal regions of the brain tend to suggest that frontal lobe volumes are likely reduced in children with ADHD, but the inconsistency across the studies makes it difficult to interpret them with confidence. It has been suggested that improvements

in morphometric procedures, together with careful subgrouping of individuals with ADHD into phenotypic subtypes, may lead to more precise localization of group differences to inferior aspects of prefrontal regions (Sowell et al., 2003). These researchers speculated that the inclusion of normal volumes in dorsal aspects of the prefrontal cortex in earlier studies may have led to conclusions that abnormalities were greater on the right side of the brains in children with ADHD. Despite the earlier evidence that caudate nucleus size on the right side of the brain may be related to deficits in response execution tasks and limited reports that some children with ADHD may have abnormal right-sided asymmetry in this region of the basal ganglia, they suggest that improved methods of analyzing structural differences within and across groups of children may significantly challenge the hypothesis that ADHD is a right-hemisphere syndrome.

### **Corpus Callosum and Dichotic Listening in ADHD**

In addition to reports of abnormal asymmetry for the caudate nucleus in children with ADHD, there have also been reports of possible underdevelopment of the corpus callosum (Roessner et al., 2004). Researchers investigating the corpus callosum in children with ADHD have also used several different measurement methods that may have led to variations in defining boundaries of the rostrum, splenium, and genu. Long-standing evidence that callosal deficits lead to poor regulation of attention (Witelson, 1989) have led some researchers to suggest that children with ADHD may lack normal integrative functions between the two hemispheres that are involved in language. One group has theorized that when engaged in cognitive activities, children with ADHD rely more heavily on anatomical structures that process visual, spatial, and motoric information rather than on those that are normally utilized for linguistic processing (Hale et al., 2009). The recruitment of alternative brain regions for compensatory activation may facilitate efforts during some cognitive tasks in these children, but weaknesses in traditional neural pathways may be more evident in studies that examine hemispheric asymmetry during behavioral tasks that are known to depend upon normal interhemispheric transfer of information. Hale and colleagues (2009) used dichotic listening techniques that involved simultaneous presentation of consonant-vowel pairs (DCV) or two-syllable words and reported that children with ADHD had significantly poorer performance on word identification than age-matched control children. Comparisons between dichotic listening performance and measures obtained from a variety of standard cognitive tasks also revealed strong correlations between reduced dichotic listening performance in the left ear and poorer measures of similarities, reading recognition, spelling, trails making, information, vocabulary, arithmetic, word attack, and block design.

Presentations to the left ear during the DCV and the dichotic word tasks require activation of the right hemisphere, together with interhemispheric transfer through

the corpus callosum, for correct identification. Presentations to the right ear require only activation of the left hemisphere via the dominant contralateral auditory pathway. Weaknesses in left-ear performance are often attributed to deficits in the interhemispheric transfer of information from the right hemisphere to the left hemisphere for linguistic processing. When the same children were asked to identify the emotion "sad" during dichotic presentations of the two-syllable words, performance in the right ear was similarly reduced and also strongly correlated with two psychiatric co-morbidity measures (oppositional defiant disorder and mood disorder). The right hemisphere is presumed to be specialized for processing the suprasegmental features of linguistic input which would be needed to correctly interpret the emotional valence of the incoming word. The authors concluded that because the children with ADHD performed normally on tasks that involved lateralized hemispheric specialization, that is, word identification measures following right-ear presentations and emotional identification measures following left-ear presentations, ADHD may reflect abnormal right-hemisphere function in support of interhemispheric interaction rather than impoverished right-hemispheric function alone. Adequate processing of linguistic and emotional information arriving directly from the contralateral ear suggests that each hemisphere functions normally in these children. Weaknesses for information presented to the ipsilateral ear, however, suggest that the transfer of information through callosal pathways may be interrupted or disordered.

The corpus callosum is a massive bridge of commissural fibers that interconnects cortical regions of the two cerebral hemispheres. Connections through the corpus callosum may be to homologous regions on both sides of the brain or fibers may be heterolateral, connecting one primary cortical area to a secondary or supplementary cortical area on the other side of the brain. Throughout childhood, the callosum thickens with increasing myelination, with a burst of growth during the first four years of life. Functionally, the corpus callosum was thought to be mature by age 12 years, but with continued myelination throughout adolescence, it is probable that interhemispheric transfer of information may improve into early adulthood. Because the corpus callosum is the largest and most important bridge of fibers connecting the cerebral hemispheres, reduced volumes within this important corticocortical pathway in children with ADHD may be related to impaired functions within other brain regions.

### **Functional Connectivity and ADHD**

An analysis of network activations across multiple regions of the brain during specific tasks can now be accomplished through measurements of functional connectivity during fMRI experiments. Unlike standard fMRI techniques that describe and contrast activation patterns across multiple regions of the brain during cognitive tasks, functional connectivity studies seek to illuminate which brain regions work together in

an integrated, cooperative manner during specific tasks. These methods seek to establish functional links between brain regions that subserve skilled performance in order to then characterize where in the integrated network activation may differ in individuals with task-related disabilities.

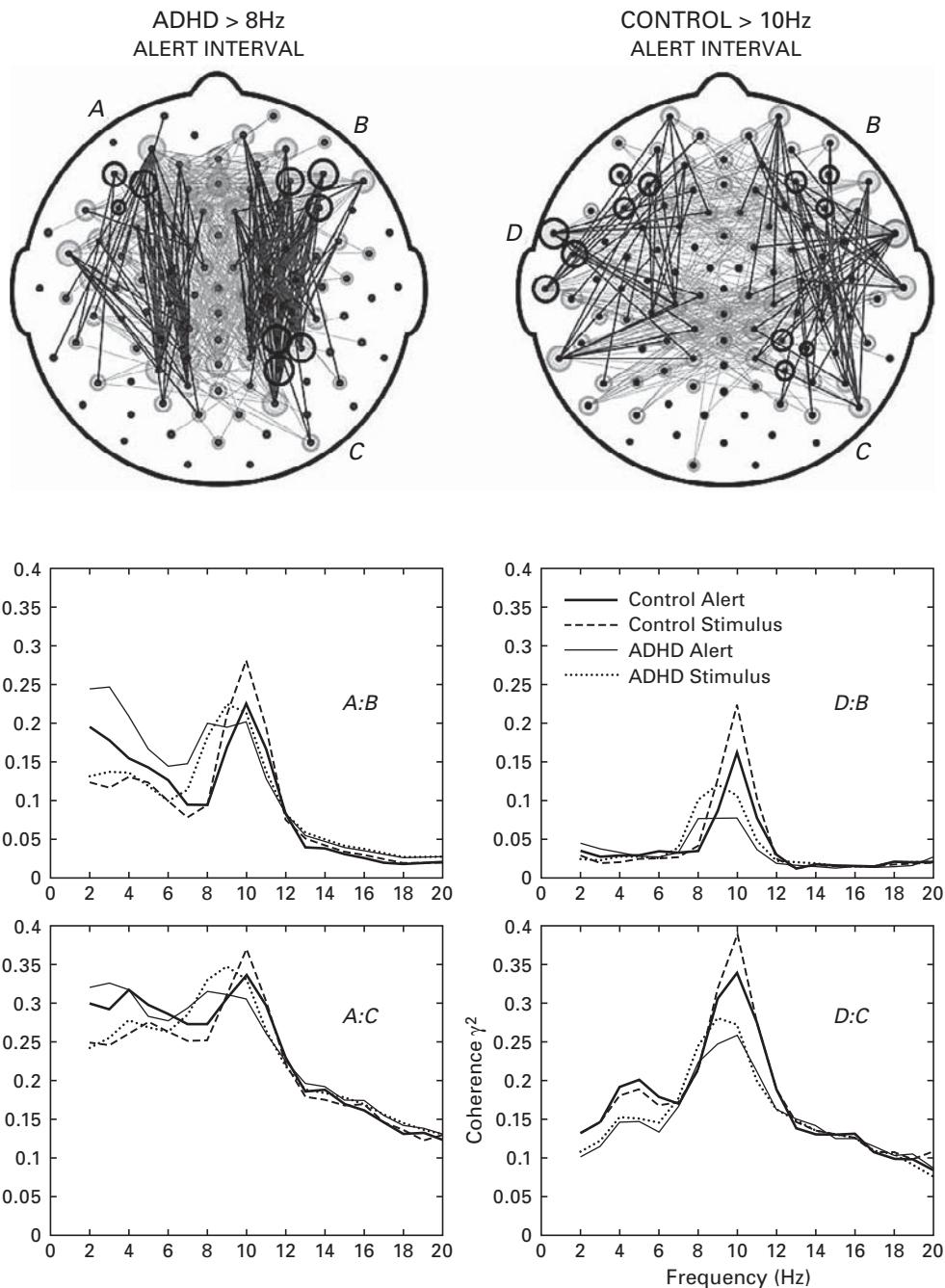
A recent study investigating functional connectivity through electroencephalogram (EEG) coherence reported evidence of significantly different coherence patterns in children with ADHD in both hemispheres in the region of the frontal cortex (Murias et al., 2007; see also figure 19.2/plate 8). Using a denser array of 128 electrodes than previous studies of EEG coherence in ADHD, these researchers found reduced coherence in the upper alpha band (10 to 11 Hz) across electrode pairs linking prefrontal with anterior temporal, central, and parietal areas and across pairs linking temporal areas with central and parietal areas. These reductions in upper alpha band coherence were independent of task, suggesting that they represent a static condition in the brains of children with ADHD. Comparisons between children with ADHD who were receiving medication and those who were not showed a trend toward smaller coherences in the children on medication. These researchers noted that their study was not designed to test the effects of medication, but many researchers are now suggesting that structural and functional evidence in unmedicated children may be more valid as neurobiological markers of ADHD.

They also reported significant elevations in coherence in the lower alpha band (at 8 Hz), most of which occurred between hemispheres at frontal electrode sites with stronger evidence of elevated coherence in the right hemisphere than in the left. The interhemispheric nature of the reduced coherence was thought to reflect differences in corpus callosum connectivity in the children with ADHD, since reduced coherence has been observed in patients with lesions of the corpus callosum (Knyazeva & Innocenti, 2001). The elevations in coherence are somewhat paradoxical, but these researchers suggest that the lower volume of white matter reported

#### **Figure 19.2 (plate 8)**

(Upper left) Topography of attention-deficit/hyperactivity disorder (ADHD) group coherence elevation at 8 Hz in the alert interval. (Upper right) Control group coherence elevations at 10 Hz. Within-hemisphere electrode pairs are plotted in blue and between hemisphere pairs in green. (Lower) Example spectra for both groups in the alert and stimulus intervals. Spectra are averages of the labeled electrode clusters, each representing averages across nine electrode pairs. The left frontal cluster "A" includes AF7 (Geodesic Sensor Net electrode No. 27), AF3 (24), and F5 (28). The right frontal cluster "B" includes AF8 (2), AF4 (3), and F6 (123). The right posterior cluster "C" includes P4 (87), P6 (93), and P04 (86). The left anterior temporal cluster "D" includes F9 (39), FT7 (40), and T9 (45).

(Geodesic Sensor Net 10-10 electrode equivalents from Luu and Ferree, (2000. Reprinted with permission from Murias et al., 2007.)



in children with ADHD reflects a lower number of interhemispheric axons. They hypothesize that this limited number of axons is thereby induced to increase connections into the contralateral cortex in an altered way as suggested by similar work in patients with schizophrenia (Innocenti et al., 2003) and that these alterations result in activation patterns that lead to the elevations in coherence. The study also reported on elevated coherences in the delta and lower theta bands (2 to 4 Hz) in interhemispheric pairs spanning frontal areas that were more evident in the left hemisphere. These elevations in coherence were dependent upon task because when the children with ADHD were responding to the presentation of words, their coherences in these lower frequency bands were similar to those in the control children, but during the interval prior to the presentation of the word, their coherences were significantly higher.

### **Frontostriatal Connections and ADHD**

Many have theorized that connectivity throughout frontostriatal circuits may be abnormal in children with ADHD. The frontostriatal circuits connect the prefrontal cortex and the striatum, the part of the basal ganglia that contains the caudate nucleus and putamen. Despite the failure of anatomic studies to reveal consistent findings regarding volume or asymmetry differences in these structures, evidence is emerging that functional connectivity in the frontostriatal pathways may be deficient in children with ADHD and that some of the deficiencies may be related to myelination of fibers within those circuits as well. Children must engage specific neural pathways in order to suppress inappropriate and irrelevant activations in favor of ones that are necessary for a given cognitive task. This ability to suppress is referred to as cognitive control and is associated with the neural circuits linking the prefrontal cortex and the striatum (Koechlin et al., 2003). These circuits develop slowly throughout childhood, and compared to adults, children are generally more susceptible to interference when performing tasks that require inhibition of a response. Functional neuroimaging has been used to examine the activation patterns in frontostriatal pathways during these attention-related tasks in children with and without ADHD. In an early study, adolescents with ADHD had lower levels of activation in right mesial prefrontal cortex both when asked to inhibit a motor response and when asked to time their motor response to a sensory cue (Rubia et al., 1999). Others have also reported significantly lower activation in the ventral prefrontal cortex and the inferior parietal cortex in children with ADHD during a go/no-go task (Durston et al., 2003). A recent meta-analysis confirmed that frontostriatal networks are consistently underactivated during task-relevant response selection when children with ADHD must resist interference from irrelevant stimuli and engage appropriate executive function (Dickstein et al., 2006). One group reported that lower levels of activation may be more prevalent in the right hemisphere during one type of task

(switching) and in the left hemisphere during another (go/no-go) in children with ADHD who are not being medicated, raising the possibility that previous failures to control for medication may have contaminated earlier results (Smith et al., 2006). Right-hemisphere deficits in activation were also reported among children with ADHD during similar response inhibition tasks in the superior temporal lobe and the right precuneus, together with decreased activity in the left-hemisphere inferior prefrontal cortex (Rubia et al., 2009). In this study, children with ADHD were compared to children with conduct disorder, and only the children with ADHD showed deficiencies in the left inferior prefrontal cortex. These researchers intend to investigate further to determine whether this left-hemispheric underactivation may be a specific biomarker for ADHD.

Without evidence of absolute structural abnormalities within the striatum and/or the prefrontal cortex, some researchers have hypothesized that failures in development and refinement of projections within frontostriatal circuits may lead to inappropriate executive control (Casey et al., 2007). In order to investigate this proposal, Casey and colleagues produced functional imaging maps while children with ADHD and their parents engaged in a go/no-go task. They noted that functional activity in the right prefrontal region (inferior frontal gyrus and caudate nucleus) strongly correlated with behavioral performance on the go/no-go task. They added that lower prefrontal activity levels also strongly correlated with fractional anisotropy, an index of white matter tract myelination produced by diffusion tensor imaging techniques. In both the children and their parents, fractional anisotropy evidence of reduced white matter was evident in the regions of the right hemisphere where lower levels of functional activity had been observed. The strong association between results from children and their parents is consistent with many studies that have demonstrated familial transmission of these traits, mostly consistent with an autosomal dominant pattern (Faraone & Doyle, 2001; Hechtman, 1994).

### **Summary of the Results in ADHD**

The theory that ADHD may represent a deficit in structure and/or function of the right hemisphere continues to receive support with evidence of alterations affecting prefrontal and basal ganglia regions and the frontostriatal circuits that connect them. There is also evidence that interhemispheric connections through the corpus callosum may be underdeveloped in children with ADHD and that alterations in these pathways may interfere with normal activation patterns in both the right and left hemispheres, especially across frontal regions of the brain. Results from dichotic listening studies have supported evidence of poor interhemispheric transfer of information in children with ADHD, suggesting that differential diagnosis between ADHD and auditory processing disorder may be particularly challenging.

### Hemispheric Asymmetry and Dyslexia

Among all pediatric developmental disorders, dyslexia has received the greatest amount of attention for evidence of abnormal hemispheric asymmetry. Children diagnosed with dyslexia are unable to read at an appropriate level for their chronological age despite normal intellectual ability, normal hearing and vision, and adequate environmental resources to develop reading skills (Snowling, 2000). In 1900, Hinshelwood reported on a heritable difficulty with reading which was termed “word blindness” and which he hypothesized stemmed from defects in cortical language areas of the brain—specifically, within the angular gyrus on the left side. Throughout the first half of the twentieth century, research into reading disability focused on altered physiological activities within visual sensory processing regions of the brain and short-term memory (Orton, 1925) until psychologists and educators began to advocate that reading disability arose from adverse environmental conditions, an idea that was part of the widespread “nature versus nurture” debate. By mid-century, the Orton–Gillingham approach was one of many remediation programs that used a multisensory approach, integrating auditory, visual, and kinesthetic information for developing strong language skills in individuals with dyslexia.

In the second half of the century, researchers proposed associations between reading disorders and problems in the auditory system (Myklebust, 1954) and phonological deficits (Critchley, 1970), leading to a flurry of research into the linguistic determinants of dyslexia (Liberman et al., 1971). Dichotic listening techniques were widely used to characterize the brain’s auditory processing of differing stimuli presented simultaneously to the two ears and to index hemispheric dominance for language (Shankweiler & Studdert-Kennedy, 1975; Repp, 1977). Around the same time, Geschwind and Levitsky (1968) reported larger left than right planum temporale in a majority of normal individuals. Subsequent analyses of postmortem specimens reported greater symmetry of the planum temporale in brains of dyslexic subjects, attributed to larger plana than normal on the right side of the brain (Galaburda, 1989; Galaburda et al., 1985). Since then, a number of researchers have used neuroimaging techniques to measure and compare the plana temporale in brains of children with dyslexia. Comprehensive reviews of the research endeavors in this important area of hemispheric asymmetry were produced in a previous volume in this series on asymmetry (Eckert & Leonard, 2004; Habib & Robichon, 2004). In both of those chapters, results are provided for adults and children, and the reader is encouraged to read those for detailed evidence of neuroanatomical differences in children with dyslexia.

Analyses of MRI brain scans from children have suggested that structural abnormalities may differ in both directions around a normal degree of cerebral lateralization that involves a small degree of asymmetry, with some children demonstrating more symmetrical plana than normal and others demonstrating significantly larger than

normal degrees of asymmetry. In several studies, measures of asymmetry in planum temporale, planum parietale, cerebrum, and cerebellum, together with overall size measurements of the cerebellum and primary auditory cortex, have been used to demonstrate that children with reading disabilities may fall into subgroups along a continuum (Leonard & Eckert, 2008). Children with low cerebral volume and normal degrees of leftward asymmetry were found to have multiple deficits, including SLI and reading comprehension difficulties. Others with higher overall cerebral volume, large Heschl's gyri, asymmetrical plana, and reversed cerebral and cerebellar asymmetries were more often characterized by dyslexia or phonological deficits (Leonard et al., 2006).

### **Association with Phonological Processing**

A current working definition of dyslexia suggests that alterations in neurobiology have led to deficits in phonological processing that are uncharacteristic in relation to other cognitive abilities and environmental resources (Lyon et al., 2003). The presumed link between phonological processing deficits and reading disability has been tested by a variety of methods, some of which have also included additional information about structural differences in the brain. Variations in the temporal bank of the perisylvian region have been related to differences in receptive language and phonological processing (Hiemenz & Hynd, 2000), leading some to examine the relationship between coding and storage of phonologic, semantic, and syntactic information with leftward asymmetry in children. Kibby and colleagues (2004) reported on moderate correlations between leftward asymmetry of the posterior superior temporal lobe (planum temporale) and better coding and storage of semantic and syntactic information, but they did not find correlations with phonological processing. They did report, however, that an extra gyrus in the region was associated with reduced phonological working memory on a digit span backward task. This result was similar to earlier evidence of a duplicated Heschl's gyrus in college students with phonological processing deficits and dyslexia (Leonard et al., 2001).

In addition to the continuing evidence of abnormalities in the planum temporale in children with dyslexia, researchers have investigated other regions of the brain for evidence of abnormal asymmetry. A cerebellar deficit hypothesis was supported by evidence of significantly smaller right anterior lobes of the cerebellum among children with dyslexia (Eckert et al., 2003). Another group that reported no differences in cerebral volume in the children with dyslexia also reported lower rightward asymmetry of the cerebellum that could be potentially related to about one-third of the individual cases (Kibby et al., 2008). Another study with adults rather than children reported reduced phonological decoding abilities among individuals with more symmetrical cerebellums (Rae et al., 2002). These results are consistent with the underpinnings of the original cerebellar deficit hypothesis (Nicolson et al., 1999), which has

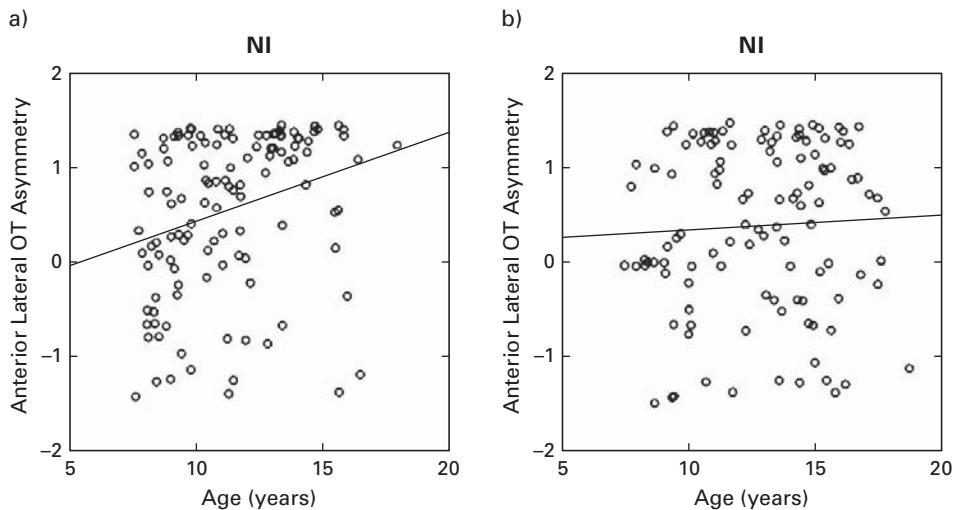
been criticized for a failure to establish strong correlations with core phonological processing deficits in children with dyslexia. The authors of the hypothesis now suggest that dyslexia may stem from deficiencies in a procedural learning system that depends upon multiple interconnections in a network that includes cerebellar structures as well as the basal ganglia and parietal regions (Nicolson & Fawcett, 2007).

### **Functional Neuroimaging Results during Phonological Tasks**

Many studies have investigated neurobiological associations with phonological processing tasks in children with reading disabilities. A fairly consistent result has been that children with reading disorders demonstrate lower levels of activation in a number of left-hemisphere sites, including the inferior frontal gyrus, superior temporal gyrus, regions of the inferior parietal lobule, middle temporal gyrus, and middle occipital gyrus (Aylward et al., 2003; Hoeft et al., 2007; Shaywitz & Shaywitz, 2005). In a recent study, Shaywitz and colleagues (2007) examined age-related changes in neural systems for reading in a large sample of children with and without dyslexia. When reading pseudowords, older children without reading disabilities showed greater activation within the left anterior lateral occipitotemporal region than younger children without reading disabilities, but children with dyslexia failed to demonstrate the same age-related increases in activation within anterior regions. Instead, the older children with dyslexia showed greater activation in the left posterior medial occipitotemporal region, similar to the younger children without reading disabilities, suggesting that a shift in activation from posterior medial to anterior lateral is a hallmark of skilled reading that is lacking in children with dyslexia. With respect to the significance of hemispheric asymmetry, the study also showed that the anterior lateral occipitotemporal region was the only area that showed a significant difference in asymmetry with age (see figure 19.3).

The left occipitotemporal cortex, also known as the fusiform cortex or Brodmann's area 37, has been termed the "visual word form area" because it plays a significant role in recognition of words as well as color, face, body, number, and abstractions (Cohen et al., 2000). Its role in the development of skilled reading has been supported by a number of recent functional imaging studies. Hypoactivation in the left parietal and bilateral fusiform cortices was reported to be the signature finding for dyslexia when children with dyslexia exhibited this pattern of hypoactivation compared to age-matched children with normal reading skills and reading-matched children who were younger (Hoeft et al., 2007). The researchers noted further, however, that the gray matter volume within the left parietal region (but not within the fusiform cortex) was smaller in the children with dyslexia compared to children in both of the other groups.

Hypoactivation in the left fusiform gyrus was reported when children with dyslexia were reading words in a phonological task (Bolger et al., 2008). In this experiment,



**Figure 19.3**

Asymmetry in the anterior lateral occipitotemporal (OT) region in (a) nonimpaired (NI) and (b) dyslexic (DYS) readers. Higher scores represent more lateralization (positive, left lateralized; negative, right lateralized), whereas lower scores represent less lateralization. Older NI readers are more left lateralized than are younger NI readers. There is no difference in lateralization in older and younger DYS readers.

(Reprinted with permission from Shaywitz et al., 2007.)

each word was paired with another word that matched for orthography and phonology (dime–lime), differed for both (staff–gain), or conflicted on phonology (pint–mint) or on orthography (jazz–has). The researchers were interested in measuring the neural correlates of consistency, calculated as the ratio of “friends” to “friends plus enemies” for each word where the number of “friends” depended upon how many other words were similar to each token phonologically or orthographically. What they found was that normal readers demonstrated stronger activation in bilateral inferior and middle frontal gyri, bilateral anterior cingulate cortex, and left fusiform gyrus when reading more challenging word pairs with lower orthographic and phonological consistency. In most of these same regions, the children with reading impairments who demonstrated better phonological awareness and nonword decoding skills showed stronger activation during higher consistency word pairs. In the reading impaired children, activation increased only in the bilateral anterior cingulate cortex during lower consistency word pairs. These results suggest that among the children with dyslexia, more resources were potentially needed for mapping phonology and orthography for higher consistency words, leaving resources unavailable for the more demanding lower consistency words. Other studies have reported similar evidence of stronger activation in

left occipitotemporal regions in children with better reading fluency together with evidence of stronger activation in right-hemisphere supramarginal gyrus and superior temporal gyrus among children with poorer skills in these important areas of reading (Rimrodt et al., 2009).

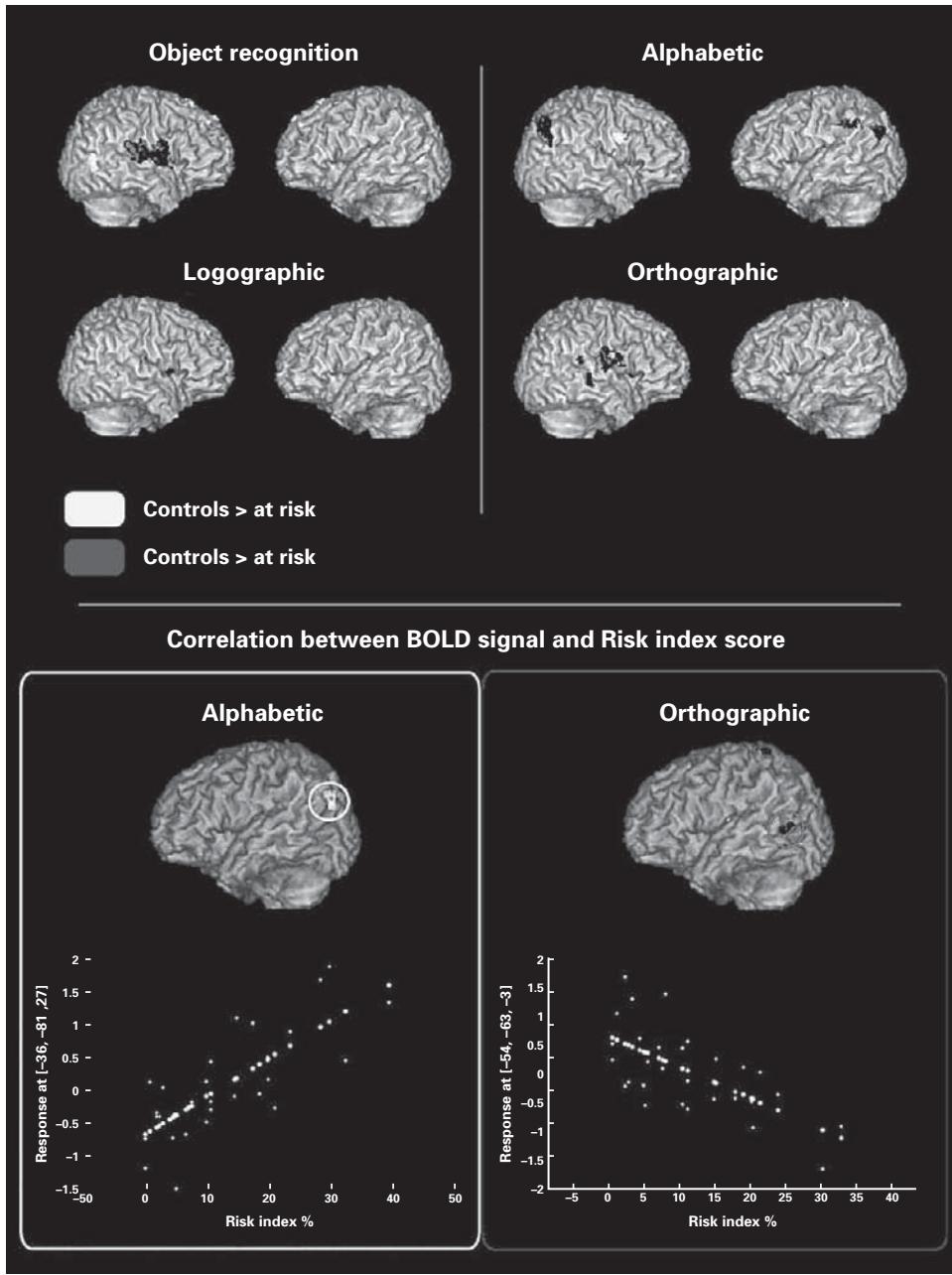
These results support the theory that visual word recognition requires normal activity in the left parietal and fusiform cortices and that this activity is fundamental to reading skill (or fluency). How children learn to link letters to sound and integrate these parallel processes into an ability to read normally is still unclear. What these results suggest is that good readers who successfully integrate these processes then utilize fewer resources within left-hemisphere regions, shifting activation to a more anterior lateral engagement for what has essentially become automatized reading, saving resources for more complicated tasks that require greater decoding skills. Poorer readers, on the other hand, appear to require greater resources in order to engage in phonological decoding tasks even when presented with relatively simple words. One hypothesis is that poor readers work hard to essentially memorize words, converting what should be easily decoded orthographic representations into sight words for better recognition. Intriguing parallels have been made between poor and skilled readers and individuals who use the Kana or Kanji writing systems in Japan. Strong activation patterns within anterior lateral occipitotemporal areas observed in skilled readers have also been reported from users of the Kana writing system that represents phonemes symbolically as in alphabetic languages (Shaywitz et al., 2007). Activation within posterior medial occipitotemporal regions seen in the children with reading disabilities has also been noted from individuals reading the Kanji writing system that uses ideographs and must be essentially memorized for understanding. While this may suggest that children with reading disabilities need to memorize words because of a neurologically based inability to decode them, it does not resolve the complex issues surrounding the means by which normal readers effectively engage neural networks to develop phonological skills.

Some researchers have hypothesized that links between the left-hemisphere angular gyrus of the inferior parietal lobule and visual association areas in the occipitotemporal area are critical for reading (Horwitz et al., 1998). Some regard this pathway as primary for phonologic assembly, the decoding process necessary for integrating graphemes with phonemes. In a recent study, children with poor reading skills showed lower levels of activation when reading sentences for comprehension in a number of left-hemisphere regions, including the angular gyrus, the postcentral gyrus, the superior occipital gyrus, and the middle frontal gyrus (Meyler et al., 2008). They also showed reduced activation in the right-hemisphere supramarginal gyrus and inferior parietal lobe. After reading remediation that included a specific phonological auditory training task, the children with poor reading continued to show reduced activation in the left-hemisphere superior occipital and middle frontal gyri, but their activations

in the left-hemisphere angular gyrus were similar to activations from the normal reading children. One year after the remediation, the only region that remained underactivated in the children with the initial reading disabilities was the left cuneus, bordering the superior occipital gyrus. At that time, the poor readers showed stronger activation in multiple areas across the medial frontal cortex. These results suggested that effective reading remediation can increase activation in cortical regions that are essential for good reading with the greatest effect found in the left angular gyrus. Because this study utilized a sentence comprehension task, the researchers speculated that the left angular gyrus may operate together with other parietal and temporal structures to effectively integrate linguistic information in a verbal working memory, not only for word-level assembly but also for sentence-level assembly.

Many of these studies have focused on brain activation patterns in school-age children, often in their adolescent years. There have been relatively few studies that have investigated patterns of activation in younger children in order to characterize developmental differences in early years. One study, however, compared activation patterns in 6-year-old children across a range of factors related to a risk for dyslexia, including familial heredity, language and motor skills development, inclusion for special education services, handedness, and general health (Specht et al., 2009; see figure 19.4, plate 9). The children were engaged in a semantic categorization task with visual stimuli that ranged in linguistic complexity from object recognition to logo-graphic to alphabetic to orthographic. Activation was strongest for all of the children during alphabetic tasks, and there were differences between children identified as being at risk and those not identified across all four tasks, especially during the two reading tasks. During the alphabetic condition, the control children produced more activation in several subcortical regions of the right hemisphere, and at-risk children produced more activation in bilateral angular gyrus, right cuneus and precuneus, and left supramarginal gyrus. During the orthographic condition, the control group produced greater activation in the typical occipitotemporal area (right inferior temporal gyrus, left middle temporal gyrus, and left superior parietal lobe and occipital gyrus). Post hoc analyses revealed that at-risk children with the highest risk scores produced the strongest activation patterns within the left angular gyrus during both the alphabetic and orthographic conditions. There was also a trend toward a positive correlation with risk in the right superior temporal gyrus and a negative correlation with risk in the left middle temporal gyrus, superior parietal lobe, and cerebellum.

This study demonstrated a greater differentiation between groups during the orthographic condition. Stronger activations by at-risk children in the parietal area compared to stronger activations by the control children in the frontal area suggested to these researchers that children in the at-risk group may have been processing words more as objects rather than reading single letters. They noted that this finding is consistent with recent evidence that parietal activation increases when individuals are



**Figure 19.4 (plate 9)**

The upper panel displays the significant differences between the groups, rendered onto the lateral view of a child's brain (nonparametric SnPM analysis, alpha level = .005, cluster threshold = 10). The lower panel displays the correlation with the risk index score for the two literacy conditions (threshold  $p(\text{FDR-corrected}) < .05$ , cluster threshold = 10, left: whole brain threshold, right: small volume correction for the occipitotemporal area). BOLD, blood oxygen level dependent; SnPM, SPM2 software package; FDR, false discovery rate.

(Reprinted with permission from Specht et al., 2009.)

processing words that become degraded from their normal forms (Cohen et al., 2008). These results are also consistent with weaknesses in occipitotemporal regions observed in children with dyslexia during many other studies as discussed above. The researchers also noted increased activation in the anterior insula by the at-risk group during the orthographic but not the alphabetic condition, suggesting that the control children were processing phonologically during the alphabetic condition whereas the at-risk children may have been using a phonological strategy during the orthographic condition as well.

### **Functional Connectivity Studies**

A number of functional connectivity studies have been conducted to examine network activation during reading tasks. An early examination reported that dyslexic children showed lower levels of functional connectivity during nonword reading tasks that demanded increasing phonologic assembly (Pugh et al., 2000). Compared to normal children, who showed significant correlations in left-hemisphere activation between the angular gyrus and the superior temporal gyrus and regions in the visual lobe, children with dyslexia showed none of these correlations. Correlations between the right-hemisphere angular gyrus and these other regions were similar in both groups, evidence that the deficit during phonological processing tasks is occurring in activation levels within the left hemisphere only.

Another study examined functional connectivity between the supramarginal cortex and the inferior frontal cortex within the left hemisphere and reported significantly different patterns of connectivity in children with dyslexia during a pseudoword reading task (Quaglino et al., 2008). These researchers used structural equation modeling in order to establish causal relationships between activity levels in these regions of the brain. By comparing children with dyslexia to age-matched and reading-matched controls, these researchers were able to characterize the relative strengths of reciprocal connections between these areas based on either chronological age or on reading ability. Children with dyslexia and those matched for reading skill showed similarly higher levels of connectivity between the fusiform cortex and the left inferior frontal cortex, suggesting that these connections may be strongly related to reading skill level. The other main difference for the children with dyslexia was in the lower connectivity observed between the left inferior frontal cortex and the supramarginal cortex, which was similar in the two groups of children who could read normally. These results were interpreted to mean that the dorsal temporoparietal pathway from the supramarginal cortex that is important for phonological processing is deficient in children with dyslexia and that a ventrobasal pathway from fusiform cortex may be overutilized by children with poorer reading skills.

Significant differences in functional connectivity between the left inferior frontal gyrus and the bilateral middle frontal gyri, supplementary motor areas, left precentral

gyrus, and the right superior frontal gyrus were also reported in another study of children with dyslexia (Richards & Berninger, 2008). There were no significant differences for connectivity between any regions and the cerebellum. After these same children received specific reading instruction in phonemic awareness, grapheme–morpheme associations, decoding, and spelling, the patterns of connectivity were similar to those obtained from children who could read normally.

During a noun–verb association task, children with dyslexia did demonstrate significant differences in cerebellar activation, however (Baillieux et al., 2009). In this study, the control children demonstrated activation within both the right and left cerebellar cortices with a slight rightward asymmetry. The children with dyslexia, however, demonstrated more diffuse and widespread activation throughout cerebellum, leading these researchers to hypothesize that children with dyslexia may be deficient in intracerebellar distributions of neural activity. They noted that these results were supported by evidence of larger Purkinje cells in the posterior cerebellar cortex of dyslexic subjects (Finch et al., 2002) and smaller right anterior lobes of the cerebellum among children with dyslexia (Eckert et al., 2003). They add that the cortical overactivation observed during this study and many others in children with dyslexia may be due to a decreased inhibitory influence from Purkinje cells in the cerebellum.

### Dichotic Listening and Dyslexia

The ability of dichotic listening to probe for hemispheric lateralization for language has made it a reasonable approach to look for behavioral evidence of abnormal asymmetry in children with dyslexia. Some dichotic listening studies have reported more or less asymmetry among children with dyslexia, and others have reported correlations between dichotic listening results and measures of planar asymmetry in the temporal lobe. Table 19.2 lists dichotic listening studies that have used verbal material to test children with dyslexia. Several differences across these studies should be noted. Some researchers asked the children to repeat everything that was presented, which makes the task a test of binaural integration (BI). Others asked the children to ignore one ear and repeat what had been presented in the other ear, which is a test of binaural separation (BS). Because the listener must repeat more information, the BI task involves a higher verbal workload than the BS task. The workload in dichotic listening is made higher when an open set of stimuli is used as with single syllable words and when the number of stimuli presented to each ear is increased, so the studies that utilized four pairs of words were the most challenging among the BS tasks (Swanson, 1986; Swanson & Cochran, 1991) and the studies that utilized quadruple pairs of digits were potentially the most challenging among the BI tasks (Kershner, Henninger, & Cooke, 1984).

Results have varied during BI dichotic listening tasks with reports of poorer performance overall with a normal REA (Dermody, Mackie, & Katsch, 1983; Kołtuska &

**Table 19.2**  
Dichotic listening results in children with dyslexia

Author(s)	Year	Ages	Stimuli	Results for dyslexics
<i>Binaural integration tasks</i>				
Thomson	1976	9–12	Digits, words, reversible words, similar words, and reversible nonsense syllables CVs	Symmetry or LEA
Dermody, Mackie, & Katsch	1983	10–13	1, 2, 3, and 4 pairs of digits	Fewer double correct responses
Kershner, Henninger, & Cooke	1984	10–12	Double pairs of words at high intensity; single pairs of words at low intensity	Written responses resulted in an LEA
Koltuska & Grabowska	1992	8–9	Digits, words	Poorer performance but similar laterality; at low intensity level, dyslexic children with "language disorder" performed better in LE; those with "phonetic disorder" had an REA
Lamm & Epstein	1994	3rd to 10th graders	CVs	"Surface" dyslexics had larger laterality with words; "phonological" dyslexics showed poorer performance overall
Brunswick & Rippon	1994	7–11	CVs	No difference
Martinez & Sanchez	1999	9–13 and 6–8 reading-matched	CVs	Poorer REA linked to phonological deficits
Moncrieff & Musiek	2002	11	CVs, digits, and words	Poorer LE performance with words
Moncrieff & Black	2008	11	CVs, digits, and words	Lower scores in LE with digits and words and in RE with CVs
<i>Binaural separation tasks</i>				
Aylward	1984	6–12	Triple digit pairs	Larger REA
Swanson	1986	9–13	Four pairs of words	Lower scores overall, especially when dividing attention
Hugdahl et al.	1989	15–17	CVs	REA in both left- and right-handed dyslexic boys

**Table 19.2**  
(continued)

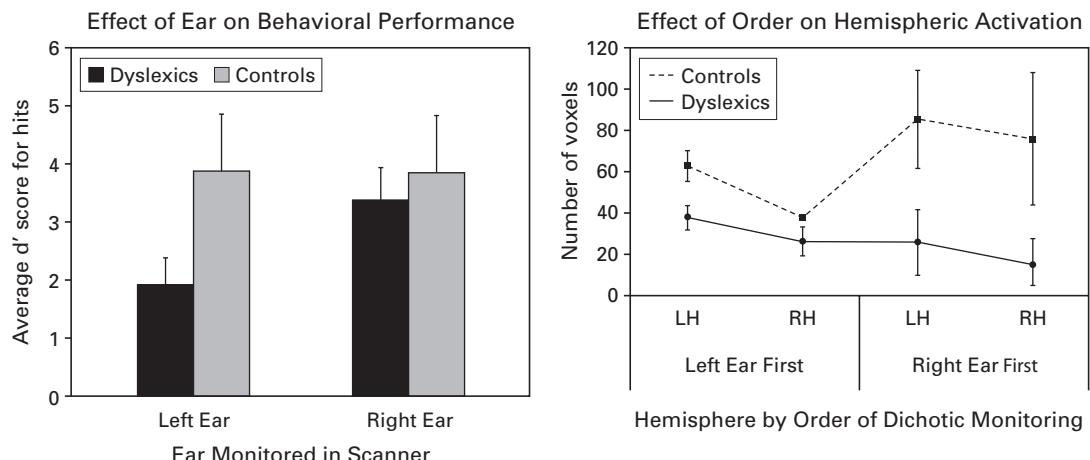
Author(s)	Year	Ages	Stimuli	Results for dyslexics
Kershner & Morton	1990	Mean = 12.3	Quadruple pairs of digits	Larger lateralities suggesting problems with selective attention
Morton & Siegel	1991	7–12	CVs and digits	Lower LE for digits; higher LE for CVs during free recall only; priming effects interfered with performance for both digits and CVs
Swanson & Cochran	1991	Mean = 10	Four pairs of words	Lower recall and poorer selective attention
Morton & Kershner	1991	Mean = 12.2	Quadruple pairs of monosyllabic digits	Symmetrical responses in morning, in those directed to report RE first
Morton	1994	9–12	CVs	Stronger REA with comprehension difficulties; stronger LEA with word-attack and reading comprehension difficulties
Kershner & Graham	1995	Mean = 13.4	Single, double, triple and quadruple pairs of monosyllabic digits	Weaker REA in LE first order, stronger REA in RE first order
Hugdahl et al.	1995	11–17	CVs	No REA
Asbjørnsen & Bryden	1998	9–14	CVs	Unable to shift attention
Heiervang et al.	2000	10–13	CVs	No difference in REA; no correlation between planum temporale asymmetry and lateralization
Helland & Asbjørnsen	2001	Mean = 12.7 and 12.1	CVs	Lower performance in RE; symmetrical with no language impairment; LEA with language impairment
Foster et al.	2002	8–12	CVs	Same as children with ADHD; LEA in those with larger right bank lengths in planum temporale
Hugdahl et al.	2003	10–12	CVs	Significant correlation between planum temporale and dichotic listening asymmetry
Asbjørnsen et al.	2003	Mean = 12.11	CVs	Lower laterality
Helland et al.	2008	12	CVs	Similar for those who respond to intervention, no REA for those who did not

Note. LEA, left-ear advantage; CV, consonant-vowel; LE, left ear; REA, right-ear advantage; RE, right ear; ADHD, attention-deficit/hyperactivity disorder.

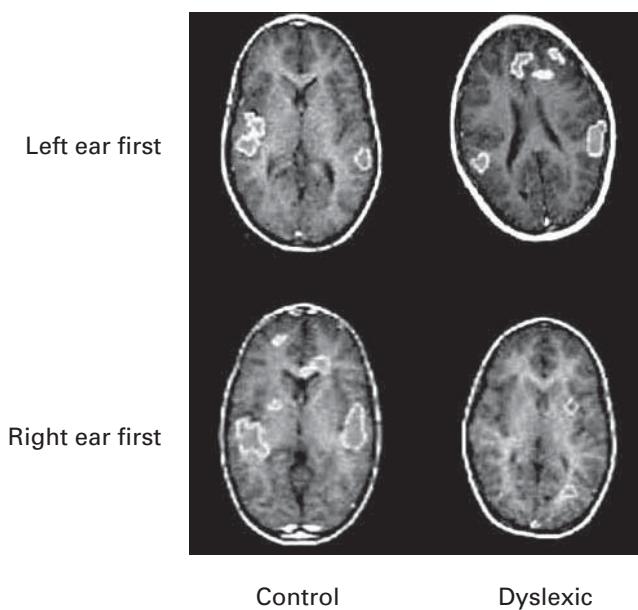
Grabowska, 1992), symmetry or an abnormal LEA (Thomson, 1976; Kershner, Henninger, & Cooke, 1984), and no difference (Brunswick & Rippon, 1994). Other studies have reported that children with dyslexia produced an REA but with a larger difference between the two ears than normal because of poorer performance in their left ears, especially when the verbal workload was increased (Lamm & Epstein, 1994; Moncrieff & Musiek, 2002). A larger REA was also reported from early BS dichotic listening studies (Aylward, 1984; Kershner & Morton, 1990) when testing with digits (Morton & Siegel, 1991), especially in the directed right-ear-first condition (Kershner & Graham, 1995). When testing with CVs in the BS task, a pattern has emerged that children with dyslexia perform more poorly in their right ears (Morton & Siegel, 1991; Hugdahl et al., 1995; Helland & Asbjørnsen, 2001; Asbjørnsen et al., 2003), especially those who demonstrate difficulties with phonological processing and comprehension (Morton, 1994) or who fail to respond well to reading intervention (Helland et al., 2008).

Comparisons between dichotic listening performance and structure of the planum temporale have differed. One reported no correlation between behavior and brain asymmetry (Heiervang et al., 2000) and another reported a significant correlation between behavioral and structural asymmetries (Hugdahl et al., 2003). Another group reported that during the BS task with CVs, children with lower performance in their right ears also tended to have larger right bank lengths in the planum temporale (Foster et al., 2002). Current theories suggest that the impaired phonological processing seen in children with dyslexia may stem from structural or functional deficits in the left temporal lobe that reduce the children's ability to process auditorily presented information. Several candidate genes have been identified in children with dyslexia, most of which are involved in neuronal migration very early in development (Fisher & Francks, 2006). Genetic alterations in migration of thalamocortical neural fibers in children with dyslexia (Galaburda, 2005) have been tested in an animal model and were shown to cause auditory processing and cognitive deficits (Galaburda et al., 2006). This new line of evidence suggests that children with dyslexia may suffer from genetically induced disruptions in auditory processing of verbal information through ascending neural pathways and that these disruptions may interfere with normal development of phonological processing skills.

A larger than normal REA in children with dyslexia occurs from significantly poorer performance in the left ear and normal performance in the right ear during dichotic listening tasks with words and digits (Moncrieff & Black, 2008). This result suggested that these children do not suffer from a global language deficit per se but that they may have a weakness in processing information from the left ear when it is placed in competition with the right ear. Many have suggested that this deficit may be related to poor selective attention during dichotic listening tasks (Kershner & Morton, 1990; Swanson & Cochran, 1991), evidenced by a failure among children with dyslexia

**Figure 19.5**

(Left) Average number of correct “hits” during monitoring of left and right ears during binaural separation task. (Right) Number of activated voxels in the right-hemisphere (RH) and left-hemisphere (LH) regions contrasted for whether the child monitored the left ear first or the right ear first.

**Figure 19.6 (plate 10)**

Activation observed during the binaural separation task for a representative child in each monitoring condition. Left hemisphere is on the right and right hemisphere is on the left in the images.

to shift attention when directed (Asbjørnsen & Bryden, 1998) and by evidence of stronger than normal priming effects for presentations of verbal material (Morton & Siegel, 1991). One study suggested that this effect may be reduced by presenting the verbal information to the nondominant left ear first (Kershner & Graham, 1995). A recent study used fMRI techniques to examine priming effects during a BS dichotic listening task in children with and without dyslexia. In this study, children were asked to ignore one ear and focus for semantically incongruous words embedded in segments from a familiar fairy tale. Results from the study demonstrated that children with dyslexia were less able to focus on and identify information presented to their left ears in general, and those who were asked to monitor their right ears first produced the lowest levels of activation overall. Control children who monitored their right ears first demonstrated the highest levels of activation overall (Moncrieff et al., 2008, see figures 19.5 and 19.6). These results seem to support the notion that in children with dyslexia, priming of the dominant right ear during dichotic monitoring tasks may inhibit the child's ability to switch attention to information arriving at the left ear.

### **Summary and Conclusion**

Children with autism, ADHD, or dyslexia have been shown to have structural and functional asymmetries that are different from their age-related peers. Despite current evidence of shared genotypes and overlapping phenotypic characteristics across these developmental disorders, information regarding structural and functional asymmetries may be helpful in making differential diagnoses of these disorders in the clinical setting. It appears that children with autism are more likely to display greater rightward asymmetry in cortical regions, possibly due to altered levels of serotonin early in development that resulted in reduced inhibition throughout cortical regions and a chronic state of overarousal for these children. Children with ADHD appear to have a reversed rightward asymmetry in the caudate nucleus and lower levels of activity in right-hemispheric regions, possibly due to a failure in synaptic pruning early in development. Another possibility is that children with ADHD may have deficits in development of white matter pathways, especially in the corpus callosum, which may be related to differences observed in low-frequency-band EEG coherence measures. Leftward asymmetry within temporal lobe regions and the cerebellum have been implicated in children with dyslexia, together with functional deficits in a variety of left-sided temporal, occipitotemporal, and frontotemporal regions. In the future, evidence from behavioral, electrophysiological, and functional neuroimaging studies will assist our understanding of how these developmental disorders differ so that accurate differential diagnoses and appropriate targeted techniques can be effectively applied for remediation.

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## **VIII Asymmetry in Schizophrenia and Psychosis**



## 20 Lateral Differences in the Default Mode Network in Schizophrenia

Nathan Swanson, Tom Eichele, Godfrey Pearlson, and Vince D. Calhoun

The human brain's default mode network (DMN) has been the focus of much study in recent years (Bai et al., 2008; Buckner, Andrews-Hanna, & Schacter, 2008; Raichle et al., 2001; Zhou et al., 2007). The DMN has been identified as consisting of regions including ventral medial prefrontal cortex, posterior cingulate–retrosplenial cortex, inferior parietal lobule, and dorsal medial prefrontal cortex (Buckner et al., 2008). This network consistently shows signal decreases during evoked responses. While the DMN is primarily identified during rest, it also manifests itself with systematic task- or event-related deactivations that are related to behavioral variability (Eichele et al., 2008; C. S. Li, Yan, Bergquist, & Sinha, 2007; Weissman, Roberts, Visscher, & Woldorff, 2006). While resting state activity has long been known in neurophysiology, the first imaging evidence of spatially organized brain activity at rest originated with Ingvar (1979). DMN activity was not fully revealed until higher resolution positron emission tomography yielded images consistently showing DMN activity (Mezrow et al., 1995).

However, the nature of the DMN remained relatively unexplored until Raichle's seminal work (Raichle et al., 2001). This opened a broad range of related topics—from the standpoint of understanding the intrinsic nature of the DMN, the interaction between intrinsic and evoked activity (Fox, Corbetta, Snyder, Vincent, & Raichle, 2006; Fox et al., 2005), the relationship between electrophysiological and hemodynamic activity (Eichele et al., 2005; Laufs et al., 2003; Mantini, Perrucci, Del Gratta, Romani, & Corbetta, 2007; Scheeringa et al., 2008), and associations with various clinical states (Bai et al., 2008; Calhoun, Maciejewski, Pearlson, & Kiehl, 2008; Garrity et al., 2007; Greicius, Srivastava, Reiss, & Menon, 2004; Kim et al., 2009).

Since then, the DMN has been examined in more detail using functional magnetic resonance imaging (fMRI), taking a variety of approaches, including seed-based correlation (Vincent et al., 2006) and independent component analysis (ICA; Calhoun et al., 2001; Calhoun, Kiehl, & Pearlson, 2008) as well as concurrent electroencephalography–fMRI (Eichele et al., 2005; Laufs et al., 2003; Mantini et al., 2007; Scheeringa et al., 2008). While the majority of fMRI studies look at evoked responses, the DMN,

by contrast, has higher energy consumption when a subject is resting quietly (Calhoun, Maciejewski, et al., 2008; Kim et al., 2009; Raichle et al., 2001).

The focus of this chapter is to examine the lateral differences between DMN regions in the left and right hemispheres of the brain. Since DMN is a relatively new approach to laterality research, we report novel empirical data, specifically looking at hemisphere differences in DMN activation. Laterality continues to be investigated as available techniques to quantify brain activity evolve. The human body shows considerable symmetry with some marked symmetry differences that have been widely studied (e.g., dominant eye, handedness). There are marked structural brain asymmetries, especially in regions that play a significant role in cortical areas specialized for language perception and production (Barta, Pearlson, Powers, Richards, & Tune, 1990; Frederikse et al., 2000; Tervaniemi & Hugdahl, 2003). Many functional regional networks, such as those mediating motor, speech, working memory, and attentional functions, are organized in a lateralized fashion as well, where activation is consistently stronger in one hemispheric region than in its contralateral homologue.

Disturbances in hemispheric lateralization have been widely reported in schizophrenia, both in behavioral tests (Løberg, Hugdahl, & Green, 1999) and electrophysiological data, as well as structural magnetic resonance imaging (MRI; Gruzelier, Wilson, & Richardson, 1999; Schlaepfer et al., 1994) and fMRI (Pearlson, Petty, Ross, & Tien, 1996; Ross & Pearlson, 1996) domains. There has been a long-standing hypothesis linking schizophrenia with a lateral dysfunction between the two hemispheres (Barnett, Kirk, & Corballis, 2005). However, the relevance of how the lateral cortical and midline regions of the DMN may be lateralized has not been addressed. The laterality differences in blood-oxygen-level-dependent (BOLD) signals acquired during two fMRI paradigms, during an auditory oddball (AOD) task and during rest, within hemodynamic responses from the DMN in 28 healthy control subjects (HC) and 28 patients with schizophrenia (SZ), is investigated.

As the DMN spans both brain hemispheres, it is natural to inquire whether significant laterality effects exist in these neural circuits for HC and/or SZ for each of the above paradigms and whether significant between-groups laterality differences are detectable. In particular, observing and understanding the behavior of lateral DMN differences across various paradigms and groups may provide better insight into the nature and overall function of the DMN. These differences between HC and SZ may provide further insight into this and other intrinsic, lateralized mental activities, which include language, that appear impaired in schizophrenia.

We focus on examining the voxelwise lateral differences (Stevens et al., 2005) of independent component maps that reflect the DMN in these groups. Previous schizophrenia studies have reported cognitive dysfunction in domains linked to the DMN (Bluhm et al., 2007; Garrity et al., 2007; Harrison, Yucel, Pujol, & Pantelis, 2007; Zhou et al., 2007). There have been reports of lateral differences in areas within the DMN

(Stevens et al., 2005; Wimber et al., 2008). However, to date no one has specifically examined lateral differences among these areas in the context of the DMN.

We hypothesized that HC would show an L > R DMN lateral bias and that SZ would show a reduced bias due to impairments in higher order cognitive functions that are localized to the left hemisphere, in particular language (S. Baron-Cohen, 2000). We also hypothesized that there would be other decreased lateral differences in the DMN in schizophrenia, supporting the hypothesis that patients with schizophrenia have cross-hemispheric disruptions (Andreasen, Calage, & O'Leary, 2008) that interfere with cognitive activity.

### Findings

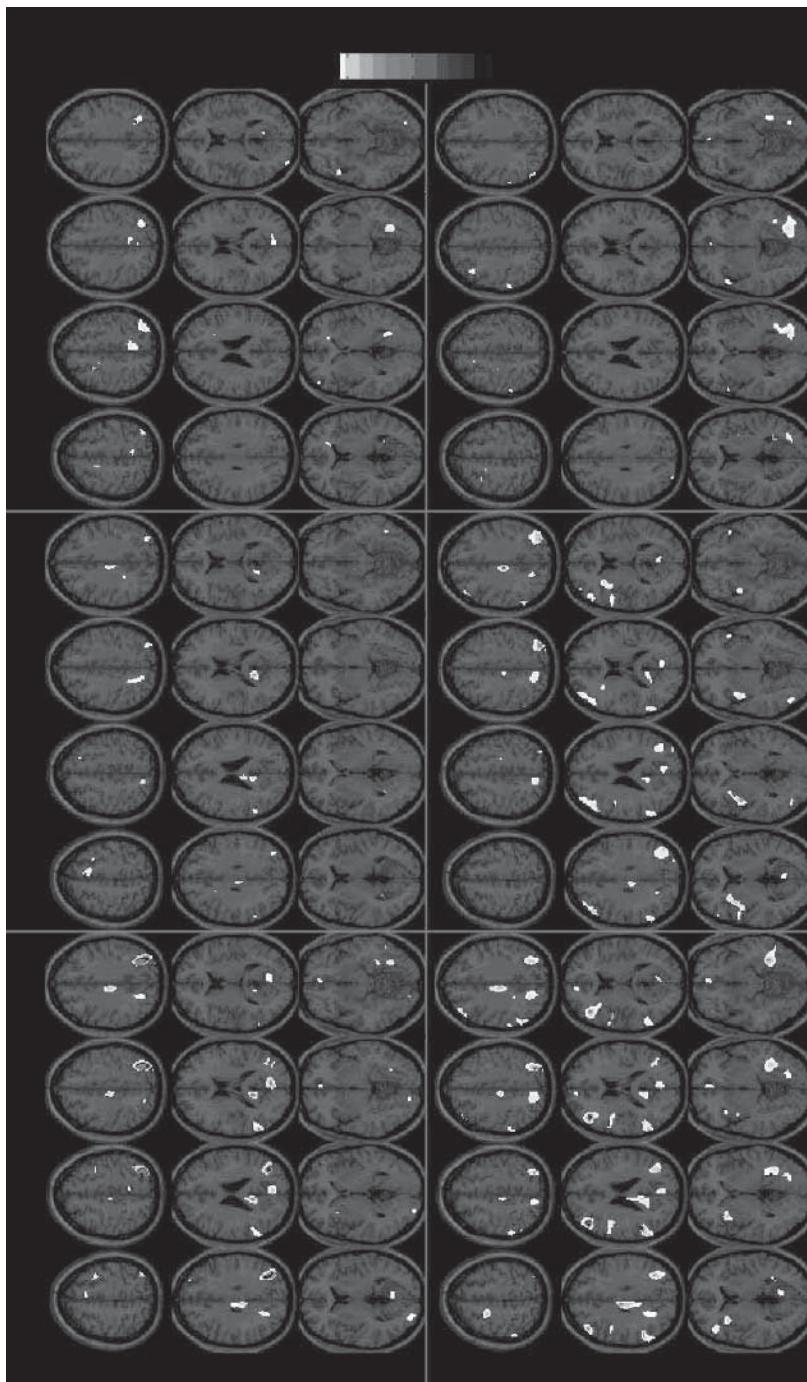
The results show the significant lateralized findings from one-sample (within group) and two-sample (across-groups) *t* tests, both for rest and AOD. In figure 20.1 (plate 11), the significant activation maps of the lateral differences of the DMN, both within group and across groups, for rest and AOD, are given. Note that the hemispheres are R > L on the left side of the brain and L > R on the right side of the brain. See table 20.1 for a full listing of significant activation differences.

In the rest condition, for HC, there were significant L > R activity differences in inferior parietal lobule (IPL), cuneus, and middle temporal gyrus. The IPL had a particularly marked activation difference (see top-left map of figure 20.1/plate 11). For R > L, the superior temporal gyrus and the middle frontal gyrus were also significantly asymmetrical. For SZ, posterior cingulate, cingulate gyrus, and superior frontal gyrus all had significant R > L findings. For HC > SZ (L > R), inferior parietal and superior frontal gyri showed lateral differences between groups.

In the AOD condition, for HC, there were L > R differences in middle and inferior frontal gyri, as well as supramarginal gyrus for R > L. For SZ (L > R), insula and middle frontal gyrus showed lateral differences. For R > L, the cingulate gyrus was significantly asymmetrical. For HC > SZ (L > R), the IPL showed asymmetry and, for (R > L), middle occipital gyrus and cerebellum had significant lateral activation differences.

We now discuss the explored lateral differences of the DMN in HC and SZ during rest and while performing the AOD task. The goals of this chapter are to (1) identify within-group lateral differences in the DMN to help understand its function (2) compare these lateral differences between groups to identify potential disease-related biomarkers (3) use these lateral differences explore the nature of schizophrenia during rest and a defined task, and (4) test the hypothesis for any L > R lateral bias in HC, as well as test for significant lateral differences between groups. Based on the results, one can infer several differences between HC and SZ in non-task-evoked activity, including language and level of wakefulness.

The results shows a significant L > R bias in the DMN of HC, particularly marked in IPL. The left IPL has been shown to be involved in language formulation, and our



**Figure 20.1 (plate 11)**  
Control, patient, and control versus patient laterality maps for the default mode network at rest and during an auditory oddball (AOD) task. The left side shows the R > L significant activations, while the right side shows the L > R significant activations. The maps are sorted according to group and task.

**Table 20.1**

Significant activation regions of the lateral default mode network (DMN) differences

Region	Brodmann's area	Volume	Maximum activation (R/L)
<i>Rest, HC (positive)</i>			
Inferior parietal lobule	39, 7, 40	0.2/1.7	3.5(53,-42,24)/8.7(-36,-62,39)
Middle temporal gyrus	39	0.0/1.9	na/6.6(-39,-66,23)
Posterior cingulate	23, 29, 30, 31	1.0/1.0	5.6(6,-43,21)/4.6(-12,-66,17)
Superior temporal gyrus	22, 39, 13	1.2/0.1	5.5(59,-51,19)/5.3(-36,-57,28)
Cingulate gyrus	23, 31, 24	3.1/0.0	5.2(3,-22,31)/na
Cuneus	18, 30	0.0/1.0	na/5.0(-12,-69,20)
Supramarginal gyrus	40	0.7/0.1	4.9(59,-51,22)/3.7(-36,-54,28)
Medial frontal gyrus	10, 11	0.0/0.4	na/4.5(-9,43,-10)
Inferior temporal gyrus	20	0.1/0.0	4.0(59,-7,-22)/na
Fusiform gyrus	20	0.1/0.0	4.0(59,-7,-25)/na
Anterior cingulate	32	0.0/0.3	na/3.9(-6,40,-10)
Paracentral lobule	31, 6, 5	0.2/0.0	3.7(3,-21,43)/na
<i>Rest, HC (negative)</i>			
Middle frontal gyrus	6	1.0/0.0	5.1(36,6,52)/na
Middle temporal gyrus	37	0.3/0.0	4.4(39,-69,20)/na
Medial frontal gyrus		0.1/0.0	4.4(9,20,46)/na
Fusiform gyrus	37	0.4/0.0	4.3(33,-59,-7)/na
Parahippocampal gyrus	37	0.2/0.0	4.1(33,-38,-8)/na
Precuneus	19	0.1/0.0	4.1(33,-83,37)/na
Middle occipital gyrus	18, 19	0.0/0.6	na/4.0(-21,-96,8)
Inferior temporal gyrus	37, 20	0.2/0.0	3.9(53,-50,-13)/na
Cerebellum		0.0/0.3	na/3.8(-15,-87,-1)
Cuneus	18, 19	0.0/0.4	na/3.7(-21,-96,5)
Superior frontal gyrus	10, 9	0.4/0.0	3.5(6,20,49)/na
Inferior frontal gyrus		0.1/0.0	3.5(18,22,-16)/na
Cerebellum		0.0/0.0	3.2(15,-38,-8)/na
Caudate	Caudate tail	0.0/0.0	3.2(33,-32,2)/na
Inferior parietal lobule		0.1/0.0	3.2(42,-44,55)/na
Postcentral gyrus	2	0.0/0.0	3.1(50,-27,40)/na
<i>Rest, SZ (positive)</i>			
Posterior cingulate	23, 30, 29	0.9/0.0	5.6(6,-43,21)/na
Cingulate gyrus	23, 24, 31	1.2/0.0	5.4(3,-16,31)/na
Supramarginal gyrus	40	0.4/0.0	4.5(56,-45,24)/na
Inferior parietal lobule	40	0.2/0.0	4.3(56,-42,27)/na
Superior frontal gyrus	8	0.0/0.1	na/3.8(-24,25,43)
Middle frontal gyrus	8	0.0/0.0	na/3.5(-21,28,40)

**Table 20.1**  
(continued)

Region	Brodmann's area	Volume	Maximum activation (R/L)
<i>Rest, SZ (negative)</i>			
Superior frontal gyrus	6	1.6/0.0	7.4(6,20,52)/na
Medial frontal gyrus	32	0.2/0.0	4.5(9,20,46)/na
Middle frontal gyrus	6	0.2/0.0	4.5(33,8,49)/na
Parahippocampal gyrus	37	0.0/0.1	3.6(30,-44,-10)/4.3(-24,-49,5)
Fusiform gyrus	37	0.3/0.0	4.3(50,-53,-15)/na
Inferior temporal gyrus	20	0.1/0.0	3.8(50,-56,-12)/na
Cingulate gyrus		0.0/0.1	na/3.8(-18,13,30)
Cerebellum		0.0/0.1	na/3.7(-24,-52,0)
Inferior frontal gyrus		0.0/0.0	3.6(50,23,-6)/na
<i>AOD, HC (positive)</i>			
Inferior parietal lobule	40, 39, 7	0.9/0.6	6.4(50,-39,27)/4.4(-36,-62,39)
Supramarginal gyrus	40	2.8/0.1	5.6(50,-42,30)/3.7(-39,-54,28)
Cingulate gyrus	24, 23, 31	4.7/0.0	5.5(6,-7,28)/na
Superior temporal gyrus	22, 13, 39	2.2/0.1	5.1(59,-54,19)/4.6(-39,-57,28)
Middle temporal gyrus	39, 21	0.1/1.8	4.0(56,-4,-20)/4.9(-39,-60,28)
Anterior cingulate	32	0.0/0.2	na/4.5(-6,40,-10)
Medial frontal gyrus	11, 10, 9, 6	0.6/0.9	4.1(6,56,14)/4.5(-6,40,-12)
Posterior cingulate	23, 30, 29, 31	1.2/1.0	4.4(3,-40,24)/3.7(-15,-61,9)
Inferior temporal gyrus	21	0.2/0.0	4.2(59,-7,-17)/na
Cuneus	18, 30	0.0/0.4	na/3.8(-12,-61,6)
Paracentral lobule	31, 6	0.5/0.0	3.6(3,-21,43)/na
Cerebellum	18	0.0/0.1	na/2.9(-12,-55,3)
Fusiform gyrus		0.0/0.0	2.8(56,-4,-23)/na
<i>AOD, HC (negative)</i>			
Middle frontal gyrus	46, 10, 9, 6	0.0/4.4	na/6.8(-42,36,18)
Inferior frontal gyrus	46, 47, 6, 44, 9, 13	0.0/3.6	na/5.7(-42,33,12)
Fusiform gyrus	37	0.8/0.0	5.0(36,-44,-8)/na
Parahippocampal gyrus	19, 37	0.8/0.0	4.9(36,-44,-5)/na
Inferior parietal lobule	40	0.0/1.4	na/4.8(-53,-41,52)
Medial frontal gyrus	6	0.0/0.3	na/4.8(-21,6,52)
Insula	47, 13	0.0/1.5	na/4.6(-33,17,-1)
Superior frontal gyrus	9, 6	0.0/0.4	na/4.3(-42,37,31)
Cerebellum	18, 19	0.5/0.0	4.3(21,-70,1)/na
Middle temporal gyrus	37	0.5/0.0	3.9(56,-50,-10)/na
Postcentral gyrus	40	0.0/0.1	na/3.8(-56,-35,49)
Precentral gyrus	6, 44	0.0/0.4	na/3.7(-45,1,28)
Middle occipital gyrus		0.4/0.0	3.7(24,-73,4)/na
Cingulate gyrus	24	0.0/0.1	na/3.6(-18,-1,47)
Inferior temporal gyrus	20	0.1/0.0	3.3(56,-50,-13)/na

**Table 20.1**  
(continued)

Region	Brodmann's area	Volume	Maximum activation (R/L)
<i>AOD, SZ (positive)</i>			
Cingulate gyrus	23, 24, 31	1.4/0.0	6.0(3,-19,31)/na
Precuneus	19, 39, 7, 31, 23	2.7/3.0	4.5(12,-65,45)/5.3(-39,-71,42)
Inferior temporal gyrus	20, 21	0.4/0.0	5.1(59,-7,-22)/na
Fusiform gyrus	20	0.2/0.0	5.0(59,-7,-25)/na
Inferior parietal lobule	39, 40, 7	0.3/0.5	3.8(59,-51,38)/4.7(-42,-68,39)
Superior temporal gyrus	22, 39, 13	0.8/0.1	4.6(62,-51,19)/4.2(-42,-57,28)
Supramarginal gyrus	40	1.6/0.1	4.6(59,-51,33)/3.2(-42,-54,28)
Middle temporal gyrus	39, 21	0.0/1.3	3.9(56,-4,-20)/4.4(-42,-60,28)
Posterior cingulate	30, 23, 29, 31	0.6/0.9	3.9(9,-46,22)/3.9(-3,-58,8)
Cuneus	30, 18	0.0/0.2	na/3.4(-6,-61,9)
Middle frontal gyrus		0.0/0.1	na/3.1(-36,19,38)
Cerebellum	18	0.0/0.0	na/3.1(-9,-58,3)
<i>AOD, SZ (negative)</i>			
Insula	13, 47	0.0/2.8	na/5.4(-39,3,0)
Middle frontal gyrus	46, 9, 10	0.0/4.7	na/5.1(-45,33,26)
Superior occipital gyrus	19	0.3/0.0	4.2(42,-80,26)/na
Superior temporal gyrus	38, 22	0.1/0.2	3.7(50,17,-11)/4.1(-39,2,-13)
Superior frontal gyrus	9, 10	0.0/0.8	na/4.1(-45,37,31)
Inferior frontal gyrus	47, 46, 45, 44	0.2/1.3	3.8(50,20,-9)/3.9(-50,36,12)
Precentral gyrus	44, 6	0.0/0.8	3.5(24,-15,48)/3.6(-50,6,8)
Inferior temporal gyrus	37	0.0/0.2	na/3.6(-45,-70,1)
Middle occipital gyrus		0.0/0.5	na/3.4(-45,-73,1)
Precuneus	19	0.2/0.0	3.4(27,-80,34)/na
Middle temporal gyrus	19	0.1/0.0	3.4(42,-80,23)/na
Cerebellum		0.1/0.0	3.2(15,-41,-8)/na
Cuneus	19	0.2/0.0	3.1(27,-83,35)/na
Inferior occipital gyrus		0.0/0.0	na/3.0(-45,-76,-1)
Parahippocampal gyrus	37	0.0/0.0	3.0(27,-44,-8)/na
<i>Rest, HC &gt; SZ (positive)</i>			
Inferior parietal lobule	7, 40, 39	0.0/0.8	na/3.1(-39,-65,47)
Cuneus	18	0.0/0.4	na/2.5(-3,-72,17)
Cingulate gyrus	31	0.0/0.1	na/2.5(-12,-45,41)
Middle frontal gyrus		0.1/0.0	2.4(39,19,38)/na
Paracentral lobule	5	0.1/0.0	2.4(3,-32,54)/2.3(-9,-41,49)
Posterior cingulate	31	0.0/0.2	na/2.3(-12,-58,14)
Medial frontal gyrus	6	0.0/0.0	na/2.2(-3,-21,51)
Anterior cingulate	32	0.0/0.0	2.1(3,36,23)/na
Superior temporal gyrus	22	0.0/0.0	2.1(62,-49,16)/na

**Table 20.1**  
(continued)

Region	Brodmann's area	Volume	Maximum activation (R/L)
<i>Rest, HC &gt; SZ (negative)</i>			
Cerebellum	19	0.2/0.0	3.5(24,-52,0)/na
Superior frontal gyrus	6, 8, 9	0.1/1.0	2.2(33,51,28)/3.4(-6,20,54)
Parahippocampal gyrus	19	0.2/0.0	3.3(24,-49,5)/na
Middle occipital gyrus	19, 18	0.0/0.2	2.5(27,-58,3)/3.0(-33,-92,16)
Superior temporal gyrus	38	0.0/0.2	na/3.0(-48,17,-13)
Cingulate gyrus	24, 32	0.0/0.1	na/2.7(-12,2,47)
Medial frontal gyrus	6	0.0/0.2	na/2.6(-12,2,50)
Inferior frontal gyrus	10	0.1/0.1	2.2(53,36,12)/2.5(-45,20,-11)
Fusiform gyrus		0.0/0.0	2.2(33,-62,-7)/na
Postcentral gyrus	1	0.0/0.0	2.2(56,-15,45)/na
Inferior occipital gyrus		0.0/0.0	2.1(30,-79,-6)/na
<i>AOD, HC &gt; SZ (positive)</i>			
Cingulate gyrus		0.1/0.0	3.1(12,-19,26)/na
Middle frontal gyrus	8	0.3/0.0	3.0(36,22,38)/na
Medial frontal gyrus	10, 11	0.0/0.3	na/3.0(-9,40,-10)
Anterior cingulate	32	0.0/0.1	na/2.9(-6,40,-10)
Precentral gyrus	9	0.1/0.0	2.9(36,22,35)/na
Fusiform gyrus	20	0.0/0.0	na/2.9(-59,-7,-25)
<i>AOD, HC &gt; SZ (negative)</i>			
Middle occipital gyrus	19	2.1/0.0	4.0(30,-70,3)/na
Cerebellum	19, 18	1.0/0.0	4.0(24,-70,1)/na
Inferior parietal lobule	40	0.0/0.8	na/3.5(-56,-33,40)
Inferior occipital gyrus	18, 19	0.4/0.0	3.4(33,-73,-4)/na
Middle temporal gyrus		0.2/0.0	3.4(39,-49,8)/na
Inferior temporal gyrus		0.2/0.0	3.2(45,-73,-1)/na
Cuneus	19	0.0/0.4	na/3.1(-24,-86,29)
Inferior frontal gyrus	47	0.0/0.4	na/3.1(-53,17,-6)
Superior temporal gyrus	38, 22	0.1/0.3	2.9(39,2,-13)/3.1(-53,14,-6)
Fusiform gyrus	37	0.3/0.0	3.1(36,-44,-8)/na
Parahippocampal gyrus	19	0.1/0.0	2.8(36,-44,-5)/na
Insula		0.1/0.0	2.8(39,3,3)/na
Postcentral gyrus	40	0.0/0.1	na/2.7(-56,-35,49)
Middle frontal gyrus	6	0.0/0.1	na/2.7(-30,8,47)
Medial frontal gyrus		0.0/0.1	na/2.6(-9,20,46)

*Note.* The positive columns are positively correlated with the DMN, while the negative columns are anticorrelated with the DMN. HC, healthy control group; SZ, schizophrenia group; na, not applicable.

finding is consistent with the prediction and suggests that HC may be involved in higher order cognitive functions during rest, including language formulation (Cohen, Dehaene, Chochon, Lehericy, & Naccache, 2000; S. Baron-Cohen, 2000). Also, the finding that SZ displayed significantly less of this asymmetry compared to HC may reflect a compensatory need for SZ to draw on the right hemisphere secondarily to compensate for left-hemisphere deficits in the DMN regions, consistent with a hypothesis that SZ is associated with dysfunctional interhemispheric connectivity (Andreasen et al., 2008).

The DMN is also to be correlated with theory of mind (TOM; Spreng, Mar, & Kim, 2009). TOM refers to the ability to infer the thoughts or intentions of other people. An R > L hemisphere activation bias has been shown in SZ compared to HC (Andreasen et al., 2008) in tasks invoking TOM. The results are consistent with this finding in showing that HC have a significant left-hemisphere bias, but SZ do not. This may suggest that, as with language, there may be significantly less TOM activity in SZ. Both impaired language and TOM activity may suggest overall reduced internal thought generation or inner dialogue during rest for SZ or disruption of these processes by hallucinations.

(Olbrich et al., 2009) reported BOLD activation patterns similar to ours comparing HC to SZ when comparing different stages of sleep. Furthermore, the right (but not left) posterior cingulate significantly deactivates while under sedation (Greicius et al., 2008), which resembles our results comparing HC > SZ. This particular lateral difference was verified as the right posterior cingulate's hemodynamic response being less in SZ than in HC. This might suggest that SZ are less attentive to their surroundings during AOD and rest—being in a more “restful” or “sedated” state than HC. This may well be explained by the antipsychotic medications taken by all of the SZ patients. A similar conclusion was drawn by Calhoun, Kiehl, and Pearlson (2008).

The IPL and posterior cingulate asymmetry differences suggest that there may be specific impairments in SZ that manifest during rest as language formulation and wakefulness abnormalities. Further research in resting state/DMN differences should be carried out to explore this. In particular, the notion of differing levels of internal dialogue may illuminate the mechanism of certain SZ symptoms. For example, hallucinations in SZ may be allied to dreams, or to “daydreaming,” but appear more real than in HC. Similarly, the auditory hallucinations in SZ may stem from disruptions in processes that produce internal dialog in HC. Numerous other asymmetry differences were detected that deserve further investigation.

## Conclusion

The lateral asymmetries between HC and SZ in the DMN were examined, both during rest and during an AOD task. There are significant lateral differences in the L > R IPL

for HC, and this pattern differs significantly from SZ, both during rest and during the AOD task. Asymmetries between HC and SZ are also evident in the posterior cingulate ( $L > R$ ). These results suggest that HC may have significant language activation (internal dialogue) during rest, that SZ involves a deeper "restful" state than HC. The results also support the theory that SZ is linked to hemispheric dysfunction.

### **Additional Methodological Matter**

All participants were scanned during both an auditory AOD task and while at rest. The AOD consists of detecting an infrequent sound within a series of regular and different sounds. The task consisted of two runs of auditory stimuli presented to each participant by computer using the visual auditory presentation package (VAPP) via insert earphones embedded within 30-dB sound attenuating magnetic-resonance-compatible headphones. The standard stimulus was a 500-Hz tone, the target stimulus was a 1000-Hz tone, and the novel stimuli consisted of nonrepeating random digital noises (e.g., tone sweeps, whistles). The target and novel stimuli each occurred with a probability of .10; the standard stimuli occurred with a probability of .80. The stimulus duration was 200 milliseconds with a 1,000-, 1,500-, or 2,000-millisecond interstimulus interval. All stimuli were presented at 80 dB above the standard threshold of hearing. All participants reported that they could hear the stimuli and discriminate them from the background scanner noise. Prior to entry into the scanning room, each participant performed a practice block of 10 trials to ensure understanding of the instructions. The participants were instructed to respond as quickly and accurately as possible with their right index finger every time they heard the target stimulus and not to respond to the nontarget stimuli or the novel stimuli. An MRI-compatible fiber-optic response device (Lightwave Medical, Vancouver, BC) was used to acquire behavioral responses for both tasks. The stimulus paradigm, data acquisition techniques, and previously found stimulus-related activation are described more fully elsewhere (Kiehl et al., 2005). Participants also performed a 5-minute resting state scan and were instructed to rest quietly without falling asleep with their eyes open (eyes were open to avoid the possibility that participants would fall asleep).

Participants consisted of 28 HC and 28 chronic SZ outpatients, all of whom gave written, informed, internal-review-board-approved consent at Hartford Hospital and were compensated for participation. Schizophrenia was diagnosed according to the *Diagnostic and Statistical Manual of Mental Disorders* (4th ed., text revision; DSM-IV-TR) criteria on the basis of a structured clinical interview, the Structured Clinical Interview for DSM-IV (First, 1995), administered by a research nurse and by review of the medical records. Exclusion criteria included auditory or visual impairment, mental retardation (full-scale IQ < 70), traumatic brain injury with loss of consciousness greater than 15 minutes, and presence or history of any CNS neurological illness. Participants were

also excluded if they met criteria for alcohol or drug dependence within the past 6 months or showed a positive urine toxicology screen on the day of scanning. All participants were able to perform the AOD task successfully during practice prior to the scanning session. However, only participants that performed the AOD task with 80% correctness or higher were selected for analysis. Healthy participants were free of any *DSM-IV-TR* Axis I disorder or psychotropic medication.

Scans were acquired at the Olin Neuropsychiatry Research Center at the Institute of Living/Hartford Hospital on a Siemens Allegra 3T dedicated head scanner equipped with 40 mT/m gradients and a standard quadrature head coil. The functional scans were acquired transaxially using gradient-echo echo-planar-imaging with the following parameters: repeat time, 1.50 seconds; echo time, 27 milliseconds; field of view, 24 centimeters; acquisition matrix,  $64 \times 64$ ; flip angle, 70; voxel size,  $3.75 \times 3.75 \times 4$  mm $^3$ ; slice thickness, 4 millimeters; gap, 1 millimeter; 29 slices, ascending acquisition. Six "dummy" scans were acquired at the beginning to allow for longitudinal equilibrium, after which the paradigm was automatically triggered to start by the scanner. The AOD consisted of two 8-minute runs, and the resting state scan consisted of one 5-minute run.

Data was preprocessed using the SPM5 software package (<http://www.fil.ion.ucl.ac.uk/spm/software/spm5/>). Data were motion corrected using INRIalign—a motion correction algorithm unbiased by local signal changes (Freire, Roche, & Mangin, 2002), spatially normalized into the standard Montreal Neurological Institute space using a symmetric template (Stevens, Calhoun, & Kiehl, 2005) and spatially smoothed with a  $10 \times 10 \times 10$  mm $^3$  full width at half-maximum Gaussian kernel. For reporting in tabular form, coordinates were converted to the standard space of Talairach and Tournoux (Talairach, 1988). Following spatial normalization, the data (originally acquired at  $3.75 \times 3.75 \times 4$  millimeters) were resliced to  $3 \times 3 \times 3$  mm $^3$ , resulting in  $53 \times 63 \times 46$  voxels. Group spatial ICA (Calhoun, Kiehl, & Pearlson, 2008) was used to decompose all the data into components using the group ICA of fMRI toolbox (GIFT) software (<http://icatb.sourceforge.net/>) as follows. Dimension estimation, to determine the number of components, was performed using the minimum description length criteria, modified to account for spatial correlation (Y. O. Li, Adali, & Calhoun, 2007). Using this approach, the AOD and the resting data were both estimated to have 19 components. Once the estimate of the number of components was determined, we applied ICA to the data using group ICA (Calhoun, Kiehl, & Pearlson, 2008) as follows. Data from all subjects were concatenated, and this aggregate data set was reduced to 19 temporal dimensions using principal component analysis, followed by an independent component estimation using the infomax algorithm (Bell & Sejnowski, 1995).

For each participant, spatial maps were then reconstructed and converted to Z values; hence, the intensities of the image provide a relative strength of the degree to which the component contributes to the data (Beckmann et al., 2005). For each data

set, each of the 19 components was manually inspected to identify the default component. The default mode component was identified by spatially correlating all components with a default mode mask generated by WFU Pickatlas, developed at Wake Forest Pharmaceuticals University (<http://www.fmri.wfubmc.edu/>; Maldjian, Laurienti, Kraft, & Burdette, 2003). This mask contained the posterior parietal cortex (Brodmann's area 7), the frontal pole (Brodmann's area 10), and the occipitoparietal junction (Brodmann's area 39), as well as the posterior cingulate and precuneus (Raichle et al., 2001). This template was smoothed with a  $3 \times 3 \times 3 \text{ mm}^3$  full width at half-maximum Gaussian kernel. The component that (spatially) correlated most significantly with the template was selected as the default mode component. For each subject, default mode components from each run of the task were then converted to z values and averaged to produce one default mode component.

A voxelwise laterality map was created for each of the respective images by subtracting the image from itself after flipping in the left-right direction (Stevens et al., 2005). Only in-brain voxels were included in the analysis. Next, a voxelwise one-sample *t* test was computed for the lateralized images for each group, both for auditory and rest (Calhoun, Adali, Pearlson, & Pekar, 2001). Note that the voxelwise laterality map avoids the problem of a laterality index (which requires voxel counting and thus is sensitive to the threshold). Two-sample *t* tests were also calculated across tasks. All results were tested using a significance threshold of  $p < .05$  corrected using the false discovery rate (FDR). Note that both the correlated (positive) and anticorrelated (negative) DMN regions (Fox et al., 2005) were included in our results (see table 20.1 for details).

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## **21 The Origins of Psychosis and the Evolution of Language: Cerebral Asymmetry, Sex Chromosomes, and Speciation**

**Timothy J. Crow**

### **Historical Background**

The history of asymmetry in relation to psychosis is long and erratic but approaches a genetic denouement. This chapter summarizes the case that cerebral asymmetry (the torque) is necessary to an understanding of psychosis and argues that it can be understood only in terms of the origins of humans and the evolution of language.

The first to propose that the role of the two hemispheres had psychiatric implications was the medical practitioner Arthur Wigan (1844) in his book *A New View of Insanity: The Duality of Mind*. His idea was that the two hemispheres could function independently, that thoughts could occur in either separately, and that thoughts in one hemisphere could intrude on the other and generate conflict. The concept preceded Darwin's (1859) theory and Broca's (1861) discovery of the role of the left hemisphere in language.

Although it created considerable interest, the book had few empirical consequences and failed to generate a subsequent literature. Broca's discovery that a component of language was located in the frontal lobes and on the left side proved more fertile; it may be considered a major origin of hemispheric theories of mental illness as well as language.

Interestingly, Broca's report shortly preceded the debate between Thomas Huxley and Richard Owen on whether the hippocampus minor was the defining feature of the human brain. Huxley (1863) argued that it was present in the chimpanzee and had no particular significance. Although it was brought to the attention of the English-speaking world by Hughlings Jackson (1932), neither Huxley nor Owen was apparently aware of the relevance of Broca's finding to the dispute, a fact of some note since Huxley had urged on Darwin that he had "too readily embraced the axiom that *Natura non facit saltum*" (see Gould, 2002, p. 151) In other words, Huxley was a saltationist. One may ask what would have happened had he appreciated the nature of the claim that Paul Broca had made? Could it be that discussion concerning the mechanism of human origins was brought forward a century?

### Early Evolutionary Thoughts

In a report on his postmortem studies at the West Riding Asylum in Wakefield, James Crichton-Browne (1879) inserted the following into the discussion: "it is not improbable that the cortical centers which are last organized, which are the most highly evolved and voluntary, and which are supposed to be located on the left side of the brain, might suffer first ... in insanity. ..." (p. 42). Thirty-five years later his thoughts were echoed by Southard (1915):

the atrophies and aplasias when local show a tendency to occur in the left cerebral hemisphere ... aside from the left-sidedness of the lesions very striking is their preference for the association centres of Flechsig ... for this there is probably good a priori reason in the structure, late evolutionary development and relatively high lability of these regions. (pp. 662–663)

Thus, Crichton-Browne and Southard, both engaged in postmortem studies, reached an evolutionary conclusion implicating laterality as the latest development in *Homo sapiens*, but on the basis of theory rather than empirical evidence. Crichton-Browne found no evidence for asymmetry in weight of the two hemispheres, and the findings on which Southard based his conclusion regarding left-sidedness of the lesions are not stated.

These papers straddled the origin of the concept of schizophrenia. Kraepelin (1899) formulated the concept of dementia praecox in the last decade of the nineteenth century, to be followed by Bleuler's (1950) concept of schizophrenia in the early twentieth century. Both were treated as categorical entities to be distinguished from manic-depressive illnesses, but by 1920 Kraepelin had developed doubts. Intermediate ("schizoaffective") states challenged the distinction that has nevertheless dominated the textbooks ever since. Lately, there is recognition in the research literature that psychiatric disease entities are continuously variable rather than categorical. Attempts have been made to address the consequences, especially in the context of the genetic predisposition.

These developments in nosology can be considered in relation to the state of evolutionary theory. The *Origin of Species*, published in 1859, included minimal reference to man. Thomas Huxley took on the task in his book *Evidence of Man's Place in Nature* in 1863.

### Evolutionary Paradox

Although a genetic contribution was recognized from 1920 onwards, this was not formulated in an evolutionary framework until the paradox was appreciated (Essen-Moller, 1959) of persistence of a condition that is genetically determined but associated with a fecundity disadvantage. Few papers considered psychosis as an evolutionary question before the seminal contribution of Huxley, Mayr, Osmond, and Hoffer (1964) that proposed a balancing advantage for the genetic disadvantage

of schizophrenia. The first two authors—Julian Huxley and Ernst Mayr—are notable as two of the four “synthesists” of evolutionary theory with Mendelian genetics, generally considered to have taken place in the 1940s and 1950s. The answer they gave—that the advantage lies in resistance to wound shock and stress—is not supported by empirical evidence and is implausible on the expectation that the balance of advantage will be in the same physiological systems as the disease-related disadvantage (Kuttner & Lorincz, 1966). The question had been framed, but no adequate answer proposed. The question raises issues in evolutionary theory unsolved today (Crow, 2007), including the one that Thomas Huxley was concerned with, the nature of transition between species. What happened in the speciation event is what defines the species. If directional asymmetry is the feature that defines *Homo sapiens*, then the genetic event that introduced this characteristic is the focus of our attention.

### Evidence for Anomalous Asymmetry

The paper that reintroduced the issue of asymmetry was Pierre Flor Henry's (1969) studies of the psychoses associated with temporal lobe epilepsy. In 1969 he reported that when the lesion was on the left side, the psychosis was schizophrenia-like in form, whereas when the lesion was on the right side, the psychosis was affective. From this paper stems the subsequent literature on laterality in relation to psychiatric disease. It was a landmark that, together with the studies of Marian Annett (1985) of the genetics of handedness, points the way to understanding human nature.

### Studies of Handedness

Gur (1977) first reported that a population of 200 patients with schizophrenia was less strongly right-handed on a laterality index than a control population of similar size. This, she concluded, was evidence of dysfunction in the left hemisphere.

Subsequent studies have confirmed and generalized the finding. Sommer, Ramsey, Kahn, Aleman, and Bouma (2001) meta-analyzed 19 studies and found evidence of an increase in mixed and left-handedness in patients relative to controls with an odds ratio of 1.61, and relative to other psychiatric patients with an odds ratio of 1.51 ( $p < .01$  in each case). In a later review of 40 studies Dragovic and Hammond (2005) concurred that there was an increase in left-handedness as well as mixed handedness relative to the general population.

The change is not attributable to onset of disease because in the UK National Child Development cohort , an excess of ambidexterity was found in response to the question “Which hand does your child write with?” posed to the mother at child's age 7 in children who developed psychosis in adult life (Crow, Done, & Sacker, 1996). In

addition, a measure of relative hand skill at age 11 years indicates that children at risk of psychosis are lateralizing later or less than the general population.

### Anatomical Studies

**Planum Temporale** If psychosis represents a failure of lateralization of language deviations of anatomical asymmetry are predicted. These might be local, affecting, for example, the asymmetry of the planum temporale, the asymmetry rediscovered by Geschwind and Levitsky (1968), or global. In the latter case they may affect the torque, a deviation from right frontal to left occipital described by Yakovlev and Rakic (1966), or the converse deviation from left frontal to right occipital described as a developmental gradient by Gratiolet and Leuret (1839).

Loss or reversal of planum temporale asymmetry has been described by a number of workers (Rossi, Serio, et al., 1994; Rossi, Stratta, et al., 1994; Petty et al., 1995; Barta et al., 1997); see meta-analyses by Shapleske, Rossell, Woodruff, and David (1999) and Sommer et al. (2001), although there have been some failures to observe this change (Kleinschmidt et al., 1994; Kulynych, Vladar, Fantic, Jones, & Weinberger, 1995). One explanation of the discrepancies, notable in the context of the subsequent literature, was that surface area rather than volume was the critical variable (Barta et al., 1997). According to Harasty, Seldon, Chan, Halliday, and Harding (2003), the left planum temporale is longer and thinner than the right, with the implication that the asymmetry represents a shape deformation. In first-episode patients, DeLisi et al. (1994) employed length measures of the sylvian fissure and found loss of asymmetry ( $R > L$  in controls) of the anterior portions and a trend for loss of asymmetry ( $L > R$ ) in female patients in the posterior portion, corresponding to the planum temporale. Atypical asymmetry of the lateral sulcus in this series was associated with better cognitive function, particularly in schizophreniform patients (Hoff, Neale, Kushner, & DeLisi, 1994). Such findings indicate that the interactions between illness status, sex, and laterality are complex.

**Temporal Gyri Volumes** Somewhat similar discriminations of the anterior and posterior portions of the superior temporal gyrus (STG) were reported by Rajarethnam, DeQuardo, Nalepa, and Tandon (2000), who found that patients had a significantly smaller left anterior STG and that the volume of this region correlated negatively with the severity of hallucinations. The left posterior STG was not significantly smaller, but its volume was negatively correlated with severity of thought disorder.

In a voxel-based morphometry study of four groups of 30 subjects (male and female schizophrenia and control subjects), Kawasaki et al. (2008) found a consistent pattern of gray matter asymmetry over all groups but a significant difference in lateralization in the *pars triangularis* (of Broca's area) with a skew toward rightward asymmetry and

a reduction in leftward asymmetry in the planum temporale in patients relative to control subjects.

The same group (Takahashi et al., 2007) found a significant negative correlation between duration of untreated psychosis (DUP) and the volume of gray matter in the left planum temporale after controlling for age, age at illness onset, and duration and dosage of neuroleptic medication. When subjects were divided into two groups around the median DUP, the long-DUP group had a significantly smaller planum temporale gray matter volume than the short-DUP group. The authors suggest this reflects a progressive pathological process in the gray matter of the left planum temporale during the initial untreated phase. Others have reported progressive change. Kasai, Shenton, Salisbury, Hurayasu, et al. (2003) reported patients with first-episode schizophrenia showed significant decreases in gray matter volume over time in the left STG compared with patients with first-episode affective psychosis or healthy subjects, the progressive decrease being more pronounced in the posterior portion of the gyrus (mean = 9.6%).

Kwon et al. (1999) reported that gray matter volume was significantly reduced in the left planum temporale (28.2%) in schizophrenic patients compared with normal controls. Heschl's gyrus (primary auditory cortex) showed no differences between the left and right sides in either group. Reduced left planum temporale volume was associated with suspiciousness and persecution subscale ratings on the Positive and Negative Syndrome Scale.

Loss of asymmetry in a related area, the angular gyrus in the inferior parietal lobe, has also been reported (Niznikiewicz et al., 2000): Lobule volumes showed a leftward asymmetry (left 7.0% larger than right) in comparison subjects and a reversed asymmetry (left 6.3% smaller than right) in schizophrenic subjects.

Thus, there are number of magnetic resonance imaging (MRI) studies that suggest left-sided losses of volume, but there are also negative findings. Moreover if the losses were as consistently left-sided and volumetric as many of these reports suggest, it seems that they would be more obvious. The left hemisphere would be clearly smaller than the right, and this is not the case.

Some postmortem findings are relevant. In a series of 30 brains of patients with schizophrenia and 30 controls, consistent changes of asymmetry were observed in three gyri—superior temporal (Highley et al., 2001), parahippocampal, and fusiform (McDonald et al., 2000). In each case, an asymmetry of volume to the left was observed in the control population that was absent or reversed in patients. The change was present in female and male patients, but the relationship to age of onset differed—in female patients the anomaly was greater with earlier age of onset, as might be expected, but in male patients the reverse was the case—the anomaly was greater with later ages of onset. Thus, subtle and sex-dependent deviations in cortical morphology require explanation.

In this series of brains, the application of similar techniques to the frontal lobes did not reveal significant asymmetries (Highley et al., 2001), but histological investigation revealed striking asymmetries in Brodmann's area 9 of dorsolateral prefrontal cortex (Cullen et al., 2006). There were asymmetries to the left in cell density, size, and shape in controls that were either reversed or absent in patients. These findings raise the question how does the cellular structure of the cortex relate to surface morphology?

**Paracingulate Region** The paracingulate sulcus has been reported as markedly asymmetrical, sometimes with a sex difference and variable in relation to psychosis. Le Provost et al. (2003) found asymmetry of the paracingulate sulcus to the left in controls that was absent in male patients with schizophrenia. In 63 people at ultra-high risk of developing psychosis compared with 75 healthy volunteers, Yucel et al. (2003) found significantly fewer people in the ultrahigh-risk group with a well-developed cingulate sulcus, and significantly more had an interrupted sulcus on the left. In 53 individuals with schizophrenia compared to 68 controls, Wang et al. (2007) found smaller cingulate gray matter volume in patients with a significant L > R asymmetry in thickness of the anterior and significant L < R asymmetry in the surface area of the posterior cingulate gyrus but no significant group by interhemisphere interaction. This is in some contrast with a meta-analysis (Honea, Crow, Passingham, & Mackay, 2005) which found that the anterior cingulate volume as assessed by voxel-based morphometry was asymmetrical to the right in the literature surveyed.

In 40 first-episode patients and 40 healthy controls, Fornito et al. (2008) found that patients with schizophrenia displayed a bilateral reduction in thickness of paralimbic regions with an increase in surface area of both the limbic and paralimbic anterior cingulate cortex. The same group found that ultrahigh-risk individuals who developed psychosis displayed bilateral thinning of the rostral paralimbic cingulate cortex, which was negatively correlated with negative symptoms, whereas individuals who did not develop psychosis displayed a relative thickening of dorsal and rostral limbic areas. The authors concluded that anterior cingulate differences may predict psychosis. In another series, Koo et al. (2008) found that first-episode patients with schizophrenia showed progressive gray matter decreases in cingulate regions compared with healthy controls; these patients also differed from patients with first-episode affective psychoses in whom the changes were confined to the subgenual cingulate region. Patients with schizophrenic illnesses also showed a less asymmetrical paracingulate pattern than healthy controls.

Thus, there are systematic changes in the paracingulate and cingulate regions that are sex dependant, may progress in relation to disease, and in some instances are asymmetrical.

**Cortical Surface and Gyrification** In first-episode cases, Kasai, Shenton, Salisbury, Onitsuka, et al. (2003) found a reduction in left temporal lobe gray matter and absence of normal left-greater-than-right asymmetry of the temporal pole gray volume in both schizophrenia and bipolar disorder. Narr et al. (2004) found significant increases in cortical folding in the right superior frontal cortex in male but not female patients compared with male controls as were also reported by Harris et al. (2004). Furthermore, there are reports of anomalies or absence of asymmetry of the internal capsule (Clark et al., 2006).

There are also reports of a *reduction in gyral folding* on the left side (e.g., Sallet et al., 2003). These are compatible with a normal excess of gyrification on the left side as proposed by Gratiolet, and that this asymmetry is lost in patients with schizophrenia. Wiegand et al. (2005) measured the complexity of the gray matter boundary and found it to be increased on the left in normal controls but lost in schizophrenic patients, with a group of bipolar patients intermediate between schizophrenic individuals and controls.

Rightward asymmetry and abnormal cortical folding has also been found in the *pars triangularis* of the inferior frontal gyrus (Wisco et al., 2007). Some studies have demonstrated decreased fractional anisotropy in cases of schizophrenia relatively selective to the arcuate bundle (Burns et al., 2003; Douaud et al., 2007). Early childhood onset psychosis significantly lowered global sulcal complexity indices. In a group of 33 individuals with schizophrenia and 30 healthy and age- and sex-matched controls, sulcal depth was found to be significantly reduced in patients (Csernansky et al., 2008). Significant bilateral symmetry was observed in patients across occipital, parietal, and temporal cortices, and sulcal depth in the left hemisphere was correlated with severity of impaired performance of working memory and executive function.

Each of these areas of investigation suggests that there are critical findings at the level of cortical folding and that these have the potential to reveal the geometry of the torque and its pathophysiological implications.

**The Torque** First attempts to assess the torque in relation to schizophrenia employed width measurements of single axial sections. Loss of torque was reported by Crow, Colter, Frith, Johnstone, and Owens (1989), Falkai, Schneider, Greve, Klieser, and Bogerts (1995), DeLisi et al. (1997), and Maher, Manschreck, Yurgelun-Todd, and Tsuang (1998), and in two of these studies (Crow, Colter, Frith, Johnstone, & Owens, 1989; Maher, Manschreck, Yurgelun-Todd, & Tsuang, 1998), loss of asymmetry was related to earlier age of onset.

It might be predicted that cerebral torque was the variable with which interindividual and disease-related variation is associated. However, the findings of different studies have been in apparent conflict.

Bilder et al. (1994) reported that assessing the total volumes of the hemispheres divided into four coronal sections along the anteroposterior axis revealed a torque that was systematically reduced in patients with schizophrenia. With the same technique, they found that individuals with mood disorders showed reductions in torque intermediate between those of patients with schizophrenia and controls (Bilder et al., 1999). By contrast with these findings, Chapple et al. (2004), using volumetric measurements of prefrontal, premotor, sensorimotor, and occipitoparietal regions, found no significant differences in torque between 59 patients with schizophrenia, 78 unaffected relatives, and 76 controls. Applying a new image analysis technique that demonstrates the torque including a marked sex difference in favor of males posteriorly, Barrick et al (2005) found significant brain torque in male and female control and patient groups. Patients tended to have reduced torque (left frontal right occipital asymmetry), but although 3 out of 26 patients showed an apparent reversal of torque, overall there was no significant difference between patients relative to controls.

A possible resolution of this discrepancy is that the key variable is not volume but surface area.

**Ventricular Enlargement** Enlargement of the ventricles, first reported using computerized tomography by Johnstone, Crow, Frith, Husband, and Kreel (1976), is perhaps the most consistent and largest morphological change. Selectivity to the left side, particularly in the temporal horn, was reported by Crow et al. (1989) in a radiographic postmortem study. Although subsequent MRI findings have not been as consistently left sided, three studies that have looked at morphology in detail report similar findings. Degreef et al. (1992) found enlargement of the left but not the right horn to be correlated with indices of clinical severity. Kawasaki et al. (1993) also found a correlation with positive symptoms, and Yotsutsuji et al. (2003) found the most substantial increase in the left temporal horn, more marked in males than in females. Thus, late changes in the left anterior temporal lobe are more closely related to the disease process than those on the right side.

**Neurochemical Asymmetries** In a postmortem study, Reynolds (1983) found dopamine concentration in amygdala increased in schizophrenia selectively on the left side, interpreting the increase as secondary to a deficit of corticoamygdaloid connections on the left. Deficits in glutamatergic function were reported by Deakin et al. (1989), who found these to be localized in the frontal cortex and left temporal pole. Later Law and Deakin (2001) reported reductions of the hippocampal N-methyl-D-aspartate glutamate receptor as assessed by messenger RNA in dentate gyrus and CA3 region of the hippocampus in both affective disorders and schizophrenia, but with selectivity to the left side in the latter case.

Most striking is the report (Hsiao, Lin, Liu, Tzen, & Yen, 2003) that for dopamine uptake as studied by Tc-99m-TRODAT-1 as a single photon emission computed tomography (SPECT) ligand there were no overall changes in patients with schizophrenia by comparison with controls, but when studied by hemisphere, uptake was reduced in the right striatum and increased in the left in patients compared to controls. An asymmetry index showed the control group to be increased to the right in both caudate nucleus and putamen, but the patient group was symmetrical, with the groups being clearly separated by this criterion. The finding can be interpreted as an interaction between cortical afferents and the incoming dopaminergic nigrostriatal pathway, perhaps involving D2 receptors located on the terminals of the corticostriatal afferents. The finding of an interaction between asymmetry variation in the cortex and ascending dopaminergic (incentive) mechanisms is relevant to the mechanism of the anti-psychotic effect.

With positron emission tomography, Early and colleagues (1987; Russell et al., 1997) found that never-medicated patients with schizophrenia had abnormally high blood flow in the left globus pallidus compared to normal controls, and, with SPECT, they found that blood flow to the left temporal lobe was reduced in 22 individuals with schizophrenia by comparison with age- and sex-matched controls. Posner, Early, Reiman, Pardo, and Dhawan (1988) found that these blood-flow anomalies were associated with asymmetries of attentional control.

### **Electrophysiological Investigation**

Electrophysiological studies have revealed evidence of anomalous lateralization and deviations of interhemispheric transmission.

Thus, Endrass, Mohr, and Rockstroh (2002), using a lateralized lexical decision task, found that controls, but not schizophrenia patients, showed significantly faster interhemispheric transmission time (IHTT) from the right to the left hemisphere for words, while IHTT from the left to the right hemisphere did not differ between groups and stimuli. Comparable findings were reported by Barnett, Kirk, and Corballis (2005), measuring evoked potentials in a reaction time experiment. While controls showed faster information transfer from the right-to-left hemisphere, this asymmetry was not present in the schizophrenia group, which also exhibited a decrease in the amplitude of the N160 in the right hemisphere. These findings suggest a loss of rapidly conducting myelinated axons in the right hemisphere in schizophrenia. Neither study differentiated anterior from posterior in terms of the shift of direction that might be expected in relation to the torque.

When stimuli are presented simultaneously to both hemispheres, there is an advantage (termed “bilateral field advantage”) in performance relative to presentation to either hemisphere independently. In three recent studies, the bilateral field advantage has been shown to be missing in patients with schizophrenia:

1. In a tachistoscopic study comparing words and pseudowords, Mohr, Pulvermüller, Cohen, and Rockstroh (2000) found that healthy controls showed a right-visual-field advantage (RVFA), indicating left-hemispheric dominance for language, and patients showed a RVFA similar to that of controls, consistent with normal left-hemispheric language dominance. However, controls performed much better on words presented in the bilateral condition, when copies of the same word appeared twice, compared to stimulation in only one of the visual hemifields. This bilateral advantage, interpreted as evidence for cooperation between the hemispheres, was absent in schizophrenic patients.
2. In a lexical decision task, Barnett, Kirk, and Corballis (2007) found that controls exhibited the expected decrease in latency when words were presented bilaterally, but this effect was not observed in the schizophrenia group.
3. Mohr, Pulvermüller, Rockstroh, and Endrass (2008) used event-related (brain) potentials (ERPs) and source localization in a lexical decision task on words and pseudowords presented tachistoscopically. Healthy controls exhibited a significant bilateral redundancy gain (BRG) for words, absent for pseudowords. Schizophrenia patients failed to show the bilateral redundancy gain, consistent with a deficit in interhemispheric information exchange, and a significant increase in ERP amplitude approximately 180 milliseconds after stimulus onset, occurring specifically for words in the bilateral stimulation condition. Source localization using minimum norm estimates demonstrated BRG-related enhanced activity in the left temporal cortex for healthy controls but not schizophrenia patients. The authors concluded that the findings provide evidence for reduced interhemispheric cooperation which may be due to impaired information transfer from the right to the left hemisphere.

In an ERP experiment, Angrilli et al. (2009) matched word pairs in three tasks: rhyming-phonological, semantic judgment, and word recognition. Slow evoked potentials were recorded from 26 scalp electrodes, and a laterality index was computed for anterior and posterior regions during the interstimulus interval. During phonological processing, individuals with schizophrenia failed to achieve the left-hemispheric dominance consistently observed in healthy controls. The effect involved anterior (frontotemporal) brain regions and was specific for the phonological task; group differences were small or absent when subjects processed the same stimulus material in a semantic task or during word recognition, that is, during tasks that typically activate more widespread areas in both hemispheres.

These experiments show how the deficit of lateralization in the schizophrenic brain is selective to the phonological component of language. This loss of hemispheric dominance can explain typical symptoms, for example, when an individual's own thoughts are perceived as an external intruding voice. The change can be interpreted

as a consequence of "hemispheric indecision," a failure to segregate phonological engrams in one hemisphere.

### Meaning of Asymmetry

Annett and Kilshaw (1984) formulated the concept that lateralization is a major determinant of cognitive ability. Two large cohort studies now support this contention:

1. In the UK National Child Development Survey, Crow, Crow, Done, and Leask (1998) derived an index of relative hand skill from measures of square ticking taken at age 11 years with the left and right hands. This measure proved to be a predictor of verbal and nonverbal ability as well as mathematical and reading skills at age 11. There were substantial sex differences in favor of females for verbal and males for nonverbal ability, but the form of the relationship to hand skill was similar in each case. There were deficits at the extremes of right and left hand skill, but also deficits close to ambidexterity (referred to as the "point of hemispheric indecision") that were at least as marked.
2. Closely similar findings were obtained in the BBC Internet survey (Peters, Reimers, & Manning, 2006) that included almost a quarter of a million volunteers following a *Horizon* program on sex differences. Subjects completed a questionnaire in which they classified themselves as strongly right- or left-handed, moderately right- or left-handed, or ambidextrous. They also completed simple tests of verbal and spatial ability. The findings were consistent across a wide age range. There were deficits in those who described themselves as ambidextrous, particularly for spatial ability, and there were also deficits at the extremes of hand skill relative to those who described themselves as moderately right- or left-handed with the right-handers having an advantage in verbal ability.

Thus, the findings in the BBC Internet survey strongly reinforce and add to the main conclusions of the UK National Child Development Survey. There are major interactions between sex and the variable of lateralization that are manifested in the course of development and present at all adult ages. They relate particularly to verbal ability, arguably the core of human cognitive capacity, but are seen also in other aspects of ability.

The two surveys reveal a powerful variable, if reflected only indirectly in relative hand skill, that constitutes a major determinant of human cerebral capacity. One can ask what other variable, genetic, psychometric, or physical, has the potential to interact with these key human abilities in this instructive way? Here, surely, is a variable that points the way to understanding the genetic basis of human ability.

The functional correlates of the valleys in the M-shaped curve are of interest. The trough around ambidexterity clearly indicates that failure to lateralize is associated

with reading delays and perhaps dyslexia. Individuals who later developed schizophrenic or affective psychoses were closer to ambidexterity than the rest of the population and, for a given level of lateralization, had fewer words (Leask & Crow, 2006).

### Lateralization of Language

#### Speech Production

Li et al. (2007) found that lateralized activation discriminated words from pseudo-words in controls but not in patients or their siblings. Those at genetic risk of schizophrenia are thus less strongly lateralized for symbol discrimination tasks.

In a verbal task, Spaniel et al. (2007) found increased activation in the right homologue of Broca's area in patients with schizophrenia by comparison with healthy controls. Concordant twins, surprisingly, showed intrapair differences in lateralization significantly higher than controls.

In a series of experiments, Sommer et al. (2001) have investigated language lateralization using functional MRI (fMRI). In a word generation and semantic precision task, they found language lateralization was reduced in male patients relative to controls with a significant hemisphere by group interaction ( $F = 11.2, p < 0.01$ ), signifying increased activation in the right hemisphere of patients. These authors repeated this study with essentially the same findings in females (Sommer, Ramsey, Mandl, & Kahn, 2003). Again, loss of asymmetry was due to increased activity in the right hemisphere. In a series of 12 right-handed monozygotic twin pairs discordant for schizophrenia and 12 healthy right-handed psychotic twin pairs matched for gender, age, and education (Sommer, Ramsey, Mandl, van Oel, & Kahn, 2003), these authors found that the groups did not differ in activation of the left hemisphere, but activation of the right hemisphere was significantly higher in the discordant than the healthy pairs. Within the discordant twin pairs, language lateralization was not significantly different between patients with schizophrenia and their cotwins, suggesting that the difference between ill and well is related to genetic predisposition.

#### Speech Perception

Dollfus et al. (2005) used functional imaging to investigate the perception of speech in familiar or unfamiliar languages. By comparison with controls, they found in patients that lateralization to the left middle temporal gyrus, left angular gyrus, and left inferior frontal gyrus was decreased. Seventy-six percent of patients exhibited less leftward asymmetry than their matched control subjects, and six of 21 patients showed a predominately rightward asymmetry.

With a similar design, Razafimandimbry et al. (2007) found reduced leftward lateralization for language which was stable over time but not related to specific symptoms

or deficits. These authors concluded that abnormal organization of language was characteristic of schizophrenia as an entity. Dollfus et al. (2008) found that in only five of 23 patients compared to 21 of 23 sex- and age-matched controls there was activation of an area in the medial prefrontal cortex on the left side that these authors relate to the "theory of mind." Thus, failure of lateralization can be related to the more abstract concept of the social brain.

### Auditory Hallucinations

McGuire, Shah, and Murray (1993) reported with SPECT that 12 males with schizophrenia had increased blood flow in Broca's area during the hallucinating phase relative to the recovery state, with blood flow also increased in the left anterior cingulate cortex and left temporal lobe. The authors concluded that auditory hallucinations are associated with *increased* activity in the network of areas normally specialized for language. However, in an fMRI study, Woodruff et al. (1997) examined seven patients experiencing severe auditory verbal hallucinations and assessed them again after the hallucinations diminished. Hallucinations were associated with reduced responsivity of the temporal cortex, especially the right middle temporal gyrus, to external speech. These authors concluded that schizophrenia is associated with a reduced left and increased right temporal cortical response to auditory perception of speech, and that the auditory hallucinating state is associated with *reduced* activity in the temporal cortex region that overlaps with those that normally process speech.

Plaze et al. (2006) examined 15 patients with chronic hallucinations while they were listening to sentences in French or an unknown language and found that activation in the left superior temporal region was negatively correlated with the presence of auditory hallucinations. They concluded that auditory hallucinations compete with normal external speech processing within the temporal cortex.

Sommer et al. (2008) examined the issue with fMRI in 24 psychotic patients experiencing auditory verbal hallucinations and in another session when they silently generated words. They concluded that during auditory verbal hallucinations, Broca's area on the right is activated, and degree of lateralization is correlated with the degree to which the hallucinations had a negative emotional valence.

### Thought Disorder

In a small sample of patients with severe thought disorder, Kircher et al. (2002) used MRI to investigate the amount of speech that these patients produced in response to a Rorschach ink blot. In control subjects, the amount of speech was correlated with activation of the left STG; within the patient group, the main correlations were with the right STG. The authors concluded that the findings were consistent with perturbed (reversal of) hemispheric interaction.

### The Structure of Language and Its Decomposition in Psychosis

It has been argued (Crow, 1998, 2004) that the nuclear symptoms of schizophrenia cast light on the neural structure of language. The nuclear (core) symptoms of schizophrenia, according to Kurt Schneider, are defined by the glossary of the Present State Examination (Wing, Cooper, & Sartorius, 1974) as follows:

1. Thought echo or commentary—the subject experiences his own thought as repeated or echoed with very little interval between the original and the echo.
2. Voices commenting—a voice or voices heard by the subject speaking about him and therefore referring to him in the third person.
3. Passivity [delusions of control]—the subject experiences his will as replaced by that of some other force or agency.
4. Thought insertion—the subject experiences thoughts *which are not his own* intruding into his mind. In the most typical case the alien thoughts are said to have been inserted into the mind from outside, by means of radar or telepathy or some other means.
5. Thought withdrawal—the subject says that his thoughts have been removed from his head so that he has no thoughts.
6. Thought broadcast—the subject experiences his thoughts actually being shared with others.
7. Primary delusions—based upon sensory experiences (delusional perceptions) the patient suddenly becomes convinced that a particular set of events has a special meaning.

Schneider (1959) considered that, when present, these symptoms identify illnesses to which we will agree to attach the label schizophrenia. That these symptoms do aggregate together and can be used to define a core syndrome ("nuclear schizophrenia") was well established in the World Health Organization Ten-Country Study of the Incidence and Manifestations of Schizophrenia (Jablensky et al., 1992).

#### **de Saussure, Chomsky, and the Meaning of Nuclear Symptoms**

The theory outlined here is that the asymmetry of the human brain (the torque) is the foundation of the faculty of language—and that these are primary disorders of the structure of language, that they reveal its constituent elements and the way in which these elements are segregated within the four quadrants of heteromodal association cortex.

**Language Is Bihemispheric** de Saussure (1916) maintained that the linguistic sign (the word) was characteristically bipartite, comprising a signal (the sound pattern or phonological engram) and a signaled (the associated concept or meanings). The asso-

ciation between the sound pattern and its meanings, according to de Saussure, is arbitrary—any sound pattern can be associated with any concept or meaning (the first principle). Somewhat similar, although the parallel is seldom noted, is Chomsky's (1995) distinction between phonemic and logical form as components of the *structural derivation* in the minimalist theory.

In de Saussure's system, there is a two-way relationship between the components—with movement from the sound pattern to meanings in speech reception, and from the concepts to sound patterns in speech production. One can ask what is the neural basis of the separation of the two components? A parsimonious hypothesis is that one component is segregated to one hemisphere.

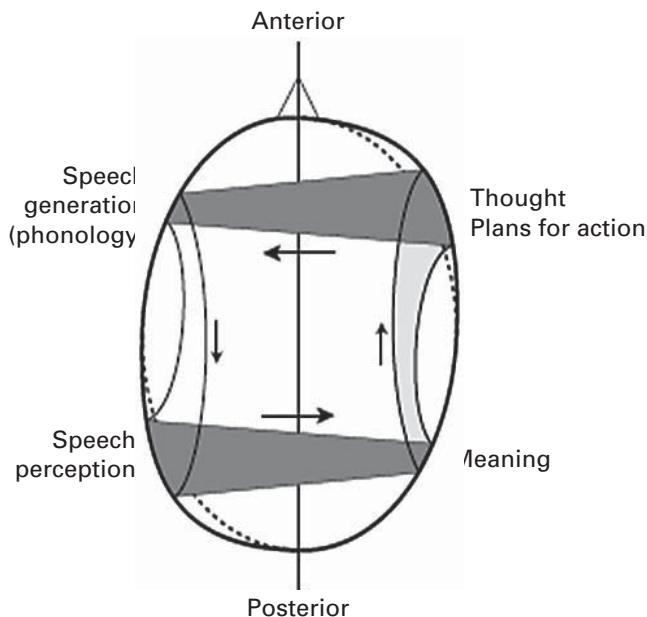
From Broca's observations, it is clear that what is localized in the dominant hemisphere is the phonological engram. It follows that some part of the signifieds must be assumed to be located in the nondominant hemisphere. For each phonological engram, there must be a corresponding engram—a mirror image—in the nondominant hemisphere, but one that is systematically transformed by the differing terminations of the interhemispheric connections in that hemisphere.

de Saussure's second principle is that speech is linear—just a “ribbon of sound.” Allied to this is the notion that there must be a speaker and a hearer—speech is necessarily communicative—and the “ribbon of sound” is what travels between them.

One envisages, therefore, that speech is encoded, bihemispherically, by the speaker from his or her concepts or thoughts into phonological engrams that are then transformed into the ribbon of sound, that this is received by the hearer and decoded into his or her own meanings or concepts, and that this encoding and decoding takes place in part by interaction between the hemispheres.

**Deixis and the Significance of the Indexical** The system works well so long as the speaker refers to the world outside himself and the hearer. However, a complication arises when he or she refers to himself or herself. As Hurford (1992) points out, such a referral necessitates further decoding on the part of the hearer—that the “I” that the speaker refers to relates not to the “I” of the hearer but to the “you” (to him or her) of the speaker. This class of symbols—the “indexicals”—referring to the speaker or hearer belongs to the wider class of “deictic” symbols that include reference to the “here” of the present place and the “now” of the present moment in time. According to Buehler (1934), this triad of terms is the coordinate origin around which language is structured—this place, at the present moment in time, defined by the “I” of the speaker, without which language has no point of reference, and loses its capacity to convey meaning.

The concept of the indexical provides a clue to the nature of psychotic symptoms. While there is no general misuse of the first-person pronoun in individuals with psy-



**Figure 21.1**

The four quadrants of heteromodal association cortex as the basis of the “language circuit.”

chosis, those with early onset developmental disorders such as autism and Asperger’s syndrome often have difficulty in acquiring the distinction between the use of “I” and “you.” The more general significance is that these symbols relate to what is self-generated in speech and what is other-generated—that there is a fundamental dichotomy between speech production and speech perception—and that this dichotomy can be understood in terms of the brain torque (see figure 21.1).

**The Human Brain Is a Four-Chambered Organ** It is often overlooked that the asymmetry of the human brain is not a simple left-right difference but a deviation across the fronto-occipital axis that transforms the brain from the standard primate and vertebrate pattern of two chambers (anterior and posterior corresponding to motor and sensory compartments) into a four-chambered organ within which motor and sensory compartments are differentiated by side.

The association cortex on one side is “ballooned” (thinned and broadened) relative to the homologous cortex on the other side. A clue to the nature of the torque and its functional significance comes from a postmortem study of the planum temporale by Harasty et al. (2003)—relative to the structure on the right side, the planum on the left is thinner and longer in the anteroposterior dimension but the volume is

unchanged. It is as if the cortex on the left side is ballooned. The conclusion is reinforced by two studies of a single set of MRI scans: (1) When the technique of Barrick et al. (2005) was applied, the torque, including the occipital sex difference, was clearly demonstrated (Mackay et al., 2003), but (2) when volumes were assessed by a point-counting stereological technique after the lobes had been demarcated no differences between gray matter volumes on the two sides were demonstrable in frontal or occipito-parieto-temporal regions (Highley et al., 2003). Thus, the essence of the torque is that the cortex on one side is thinned and broadened relative to its contralateral partner, and the polarity of the contrast changes along the anteroposterior axis.

What has changed relative to other primates is that the cortex is thinned or broadened on one side relative to the other and that the direction of this gradient differs along the anteroposterior axis. The effect must be assumed to be that the distribution of interhemispheric connections differs on the two sides, and it is this that allows the spread of neural activity to be systematically different on one side compared to the other. However, the direction of the difference is opposite in the motor and sensory halves of the brain—converging from right to left anteriorly and from left to right posteriorly (see figure 21.1).

The core feature of the torque is that it crosses the anteroposterior axis in a way that separates left and right motor, and left and right sensory functions, in the opposite sense. Thus, if we assume that the signifier is located in the left hemisphere and that it has two representations, one motor in Broca's area and one sensory in Wernicke's area, we must also assume that the signifieds have two forms, one motor in right dorsolateral prefrontal cortex (DLPFC) and one sensory in right occipito-parieto-temporal cortex (OPTC). Thus, the "abstract concept" center of Lichtheim is located in the right hemisphere and divided into two parts. It is not difficult to see that the quadripartite schema thus arrived at corresponds to Chomsky's (1995) distinction in *The Minimalist Program* between articulatory-perceptual and conceptual-intentional, with the specification that the articulatory component is anterior as also is the intentional component but on the opposite side, and the conceptual component of the signifieds is posterior and on the right. Thus, the anatomy of the torque dictates that there are four and only four compartments of language.

If we assume further that each "sign" or "structural derivation" has two parts—a signifier and a signified, on the one hand, and phonetic form and logical form, on the other—and that these forms are represented differentially in the two hemispheres according to the above principles, we have a hypothesis that imposes the following significant constraints on the structure of language:

1. Speech perception and production are homologous processes but take place in opposite directions.

2. Phonological engrams are localized to the left hemisphere but have a neural basis that is subtly different in Broca's and Wernicke's areas.
3. The principles of transfer between the compartments of language are the rules that govern transfer of neural activity between areas of heteromodal association cortex.

Thus, functions can be distinguished in humans that are not present in other mammals, and this, it is argued, gives us a route to the neural basis of language. The first consequence is that transmission between areas of association cortex has directionality. If we assume that transmission is predominantly from the area of greater to lesser size, then the direction is from left to right posteriorly, that is, in sensory association cortex, and from right to left anteriorly in relation to motor function. Thus is identified a circuit from left to right OPTC to right DLPFC and then to left DLPFC. This is the *sapiens*-specific language circuit.

To this concept can be added the proposal that there is an isomorphism between the fiber tracts connecting heteromodal association areas of cortex and the components of linguistic competence. Thus, the frontal inter-hemispheric (callosal) connection can be conceived as mediating syntax, the left antero-posterior (arcuate and uncinate bundles) as mediating phonology, the posterior inter-hemispheric connection as providing a framework for semantics, and the right-hemispheric posteroanterior fiber tracts (from perceived meaning to intention) can be seen as the structural basis of pragmatics.

The key to language is the separation of a phonological engram from its associations. Thus, if we assume that what is segregated in the dominant hemisphere is the phonological engram—a collection of simple but heavily interconnected motor sequences—this leaves open the possibility that each of these motor patterns has connections with engrams that are systematically different (either more diffuse if motor or more restricted if sensory) in the non-dominant hemisphere.

What happens in the dominant hemisphere? The sensory phonological engram is distinct from the motor engram, these engrams being located in Wernicke's and Broca's areas, respectively. However, the form must be different—the motor engram can have relatively direct access to motor neurons and the output, but the sensory engram is one step removed from the acoustic input—word traces have to be filtered out from the totality of incoming sensory information.

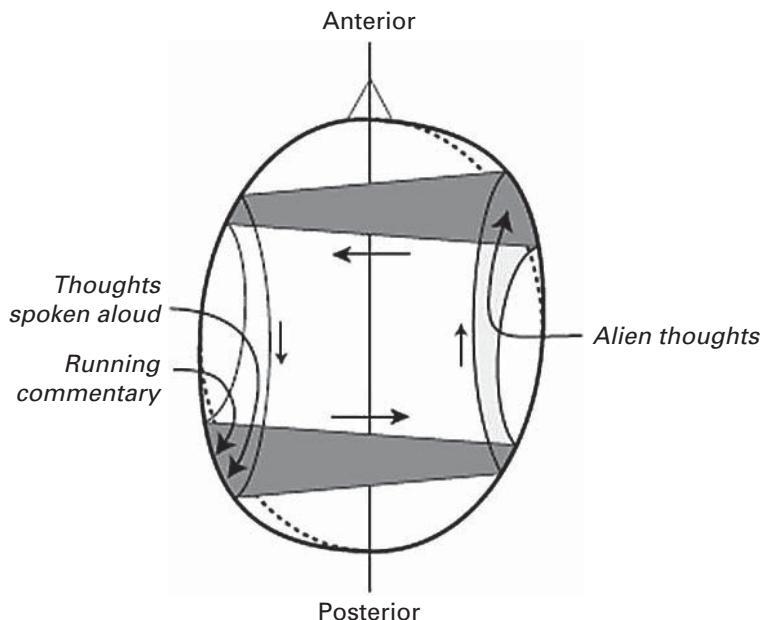
Nonetheless, there is a relationship between the two. Words that are heard are recognized as related to, if not identical to, those that are spoken. The form of the relationship presumably is what is established in the course of language acquisition. Conversely some aspect of the distinction between the two is what is lost in the case of auditory hallucinations—what is intrinsically generated (whether in the process of thought or in motor planning) has activated engrams that are normally accessible only to incoming acoustic stimuli.

The simplest assumption is that contiguous functions are dealt with in anatomically related areas. Thus, if the phonological engrams of the output are assembled in association areas focused on Broca's area in the left hemisphere, one must assume that the processes that are related to this assembly but differ from it in the crucial respect that they confer upon it its arbitrariness and flexibility are located in the homologous regions in the right hemisphere. In functional terms, these engrams can be loosely referred to as "thought"—the precursor of, or the plans for, speech.

In the occipito-parieto-temporal junction association areas the convergence is in the opposite direction. From the phonological engrams that have been extracted from the primary acoustic signal in auditory association areas on the left there is a convergence to a smaller area of homologous cortex on the right. Thus, the many-to-one transition in this case is from left to right, and the process of simplification may be identified as the distillation of "meaning" from the linear sequence of phonology on the left.

While de Saussure (1916) argued that what is characteristic of human language is the separation of the signifier, a phonological engram, and its associations, the signifieds or concepts and meanings, later linguists, for example, Paivio (1991) and Wray (2002), have spoken of a duality of patterning or "a duality of representation in the brain." Paivio distinguished between logogens and imagens, that is, between phonological and graphic representations, the key point being that for a given "sign" they are related and alternate forms of representation. A rather similar concept is incorporated in popular models of working memory, that a "phonological loop" is coupled with a "visuospatial sketch pad" to form a whole controlled by an "executive." However, few theories have been related to hemispheric lateralization, and none, it seems, have taken account of the torque. Here it is argued that a simple formulation is possible and couples de Saussure's distinction between the signifier and the signified with specialization of hemispheric function.

The nuclear symptoms of schizophrenia tell us about the deictic frame and what happens when the distinction between compartments breaks down (see figure 21.2). Thought, the precursor of speech, loses its characteristic independence from the outside world—thoughts are inserted into or removed from the individual's mind—while retaining the features of thought these mental phenomena have lost the self-generativity that defines thought as a precursor of speech. The obvious interpretation is that they are influenced by activity in posterior association cortex in a way that differs from the "normal" exchange between posterior and anterior regions. Conversely, auditory hallucinations such as thoughts spoken aloud or running commentary must be supposed to represent self-generated neural activity (thoughts or plans for action in right DLPFC) that activates phonological engrams (perhaps in the superior temporal cortex on the left side) that are normally activated by speech from another individual. In each case there is a loss of the boundary in symbolic represen-



**Figure 21.2**

Schematic representation of the hypothetical origin of nuclear symptoms.

tation (words) between what is self- and what is other-generated. In each case we can see that the boundary has something to do with what is anterior and what is posterior in association cortex. One possibility is that “counterflow” (reverse flow within the language circuit) is the basis of symptoms.

J. L. Austin’s (1962) thesis entitled *How to Do Things with Words* and the performative hypothesis (Ross, 1970) bear a relationship to Buehler’s notion of a deictic origin to the coordinate frame of language. Without the deictic frame, Buehler insists, the structure of language disintegrates. This may be what happens in the case of thought disorder—the determining focus is lost. What the nuclear symptoms of schizophrenia are telling us is what happens when the distinction between the indexicals “I” of the speaker and “you” of the hearer begins to dissolve. The nuclear symptoms tell us that the phonological engram for the perception of speech is quite separate from the phonological engram for speech production. They tell us that “thoughts” as the precursor to speech are distinct from the meanings that are extracted from perceived speech in the nondominant hemisphere. They draw attention to the obscure process of interaction between the motor and sensory elements of the associations (the signifieds) that takes place in the non-dominant hemisphere (Mitchell & Crow, 2005). In each case the phenomena of psychosis yield evidence on the neural organization of language.

Through the structure of the torque and what happens when the mechanism goes wrong, we begin to understand the components of language.

### Overview of the Torque, Language, and Psychosis

Despite controversy, there are clear indications that the anatomical torque from right frontal to left occipital is specific to the human brain and that the asymmetry of gross structure reflects a thinning and broadening of heteromodal association cortex on one side relative to the other. These asymmetries are reflected at the cellular level. The torque establishes that the human *speech circuit* has directionality and comprises four and only four compartments, each with a distinct function; the nuclear symptoms of schizophrenia reveal the differences of function between compartments within a deictic frame. The elements of language (*signs* or *structural derivations*) are held to be represented with characteristic shape deformation in homologous form in the two hemispheres. No other anatomical basis for the evolution of language has been identified.

### The Genetics of Asymmetry: The Big Bang

#### Darwinian Gradualism and the Mueller-Huxley Challenge

In 1873, within two years of the publication of *The Descent of Man* (Darwin, 1871), Friedrich Max Mueller wrote as follows:

There is one difficulty which Mr Darwin has not sufficiently appreciated. ... There is between the whole animal kingdom on the one side, and man, even in his lowest state, on the other, a barrier which no animal has ever crossed, and that barrier is—Language. ... If anything has a right to the name of specific difference, it is language, as we find it in man, and in man only. ... If we removed the name of specific difference from our philosophic dictionaries, I should still hold that nothing deserves the name of man except what is able to speak ... a speaking elephant or an elephantine speaker could never be called an elephant ... and (quoting Schleicher) "If a pig were ever to say to me 'I am a pig' it would ipso facto cease to be a pig" (Mueller, 1873).

What is the nature of a species? Darwin was anxious to establish continuity and the links between species. In his "Recapitulation and Conclusion" to *The Origin*, he wrote:

Hereafter we shall be compelled to acknowledge that the only distinction between species and well-marked varieties is, that the latter are known, or believed, to be connected at the present day by intermediate gradations, whereas species were formerly thus connected. (Darwin, 1859)

Thus, gradualness of change and the principle that there is no difference other than a quantitative one between varieties and species were fundamental.

However, on publication of *The Origin* T. H. Huxley wrote to Darwin that he hoped that Darwin had not loaded himself “with an un-necessary difficulty in adopting Natura non facit saltum so unreservedly” (cited in Gould, 2002). Thus was initiated a division of opinion among evolutionists between those, on the one hand, who follow Darwin in strict gradualism, and those, on the other hand, who following Huxley take a saltational view of the transitions and therefore a more discrete and categorical view of the nature of species.

But what *is* a species? One attempt at a definition is the biological or isolation species concept: A species is a “group of actually or potentially interbreeding natural populations that are reproductively isolated from other such groups” (Mayr, 1963). A more specific and functional definition is that a species is “the most inclusive population of individual biparental organisms which share a common fertilisation system” (Paterson, 1985). Thus, according to Paterson, a species is defined by a “specific mate recognition system.” I will argue that this concept is necessary to answer the question raised by Mueller and to the doubt that Huxley expressed to Darwin.

### Saltations Modulated by Sexual Selection

The theory of punctuated equilibria (Eldredge & Gould, 1972) was preceded by a long history of challenges to the gradualist version (Bateson, 1894; De Vries, 1901), and particularly by Goldschmidt (1940), who formulated the concept of the “hopeful monster,” the outcome of a “macromutation,” doomed to maladaptive failure but that just occasionally might succeed. The case for saltation has been argued at a macro-evolutionary level (Stanley, 1998) on the basis that the amounts of change seen within species and other taxa are simply insufficient to account for the overall pattern of evolutionary change that is seen over time, but all such general arguments come up against the difficulty that Goldschmidt’s (1940) “hopeful monster” encountered: The greater the magnitude of the saltational change, the less likely it is to have survival value, and the greater the difficulty the hopeful monster will have in identifying a mate. The possibility that the monster can identify an individual with the same mutation is clearly dependent on reproduction already having taken place, and even then the new mutation is at a severe statistical disadvantage with respect to the existing population. Thus, a proposal which challenged Darwinian gradualism and appeared to conflict with the principle of natural selection has been widely disregarded.

But here Darwin’s (1871) juxtaposition of *The Descent of Man* and the theory of sexual selection suggests a new possibility. If sexual selection and speciation were in some way interdependent, this might solve the problem of discontinuity and elucidate the significance of mate selection. Darwin himself made no specific proposal. A role for sexual selection in modifying a primary change in a sexually dimorphic feature to establish a new species boundary has been argued in relation to Hawaiian Drosophilid species by Kaneshiro (1980) and Carson (1997). Similar arguments apply in the case

of the prolific speciation of cichlid fishes in the lakes of East Africa (Dominey, 1984) and in birds (Price, 1998).

What is a saltation? Presumably, it is a genetic change of sufficient magnitude or novelty to account for a species difference. Goldschmidt considered that environmentally selected changes in genes were never sufficient to account for species differences. The latter, he suggested, were accounted for by chromosomal rearrangements. Chromosomal theories of speciation (White, 1978; King, 1993) have been criticized on the grounds that chromosomal rearrangements are frequent, often without phenotypic effect, and sometimes present as polymorphisms within a population.

Here it is argued that it is not chromosomal change in general that plays a role in speciation but that change on the sex chromosomes does so. This is because such changes are associated with sexual dimorphisms that themselves are necessary to the construction of a mate recognition system and that are species specific. Furthermore, nonrecombining regions of X-Y homology have a special status because they can account (as in the case of lateralization in humans; see below) for quantitative differences in a characteristic between males and females, such as are plausible substrates for sexual selection. The Y chromosome in mammals (and the W in birds) has a unique role, because it is not necessary for survival. There are interindividual differences on the Y, but there are also large interspecific differences. While the X is the most stable chromosome across species (Ohno's, 1967, law), the Y is by far the most variable.

The mammalian Y therefore can be seen as a test bed of evolutionary change. One possibility is that the primary change in speciation takes place on the Y, and when it is located in a region of homology with the X, there is the possibility of correlated but independent change in the two sexes. Such correlated but quantitatively differing ranges of variation have the potential to explain the type of runaway sexual selection envisaged by Fisher (1930). Thus, a primary and saltational change on the heterogametic chromosome creates a new feature in one sex that occasionally is selected by the members of the other sex to give rise to a phase of sexual selection that defines a new mate recognition system.

In humans, the mate recognition system is defined by the dimension of asymmetry. An important clue to the location of the gene comes from sex chromosome aneuploidies. Individuals who lack an X chromosome (XO, Turner's syndrome) have nondominant hemisphere (spatial) deficits on cognitive testing. Individuals with an extra X (XXY, Klinefelter's, and XXX syndromes) have verbal or dominant hemisphere deficits (see table 21.1). A possible explanation is that an asymmetry determinant is present on the X chromosome. However, then the question arises of why males, who only have one X chromosome, do not have spatial deficits such as are seen in Turner's syndrome. The answer must be that the copy of the gene on the X chromosome is complemented by a copy on the Y, that is, that the gene is in the X/Y homologous class (Crow, 1993). A hormonal explanation will not account for the similarity of the changes in XXY

**Table 21.1**

Neuropsychological impairments associated with sex chromosome aneuploidies

Variable	XX	XY	XO	XXY		
	Normal female	Normal male	Turner's syndrome	Klinefelter's syndrome	XXX	XYY
No. of sex chromosomes	2	2	1	3	3	3
Verbal ability	Normal	Normal	Normal	Delayed	Delayed	Delayed
Spatial ability	Normal	Normal	Decreased	Normal	Normal	Normal

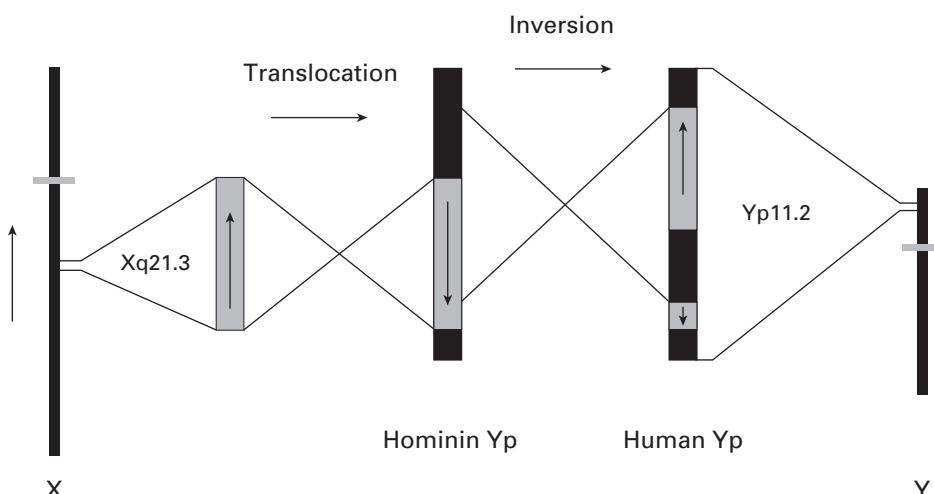
individuals, who are male, and XXX individuals, who are female. The case that the gene is present also on the Y chromosome is strongly reinforced by the verbal deficits and delays that are observed in XYY individuals (Geerts, Steyaert, & Fryns, 2003).

The hypothesis is further strengthened by evidence that Turner's and Klinefelter's syndrome individuals have corresponding deviations in anatomical asymmetry (Rezaie et al., 2004, 2008) and by the demonstration of a same-sex concordance effect—the tendency for handedness and sex to be associated above chance expectation—the hallmark of X–Y linkage (Corballis, Lee, McManus, & Crow, 1996). A role for an X–Y homologous gene is consistent with the presence of a sex difference—brain growth is faster (Darwin, 1859; Kretschmann, Schleicher, Wingert, Zilles, & Loeblich, 1979) and lateralization to the right is stronger (Crow, Crow, Done, & Leask, 1998) in females. Females have greater mean verbal fluency and acquire words earlier (Maccoby & Jacklin, 1975; McGlone, 1980) than males. These facts are related, and they tell us about the nature of the genetic mechanism.

### The Xq21.3/Yp Duplication

When we come to consider where such a gene might be located, there is an important lead. A major chromosomal rearrangement took place in the course of hominid evolution. A 3.5 megabase contiguous block of sequences from the X chromosome was duplicated onto the Y chromosome short arm. That event is now dated at 6 million years ago (Williams, Close, Giouzeli, & Crow, 2006; see figure 21.3). It is therefore a candidate for the transition from a great ape hominid precursor to *Australopithecus*.

The homologous block thus created was later subject to three deletions and was split by a paracentric inversion (by a recombination, presently undated, of LINE-1 elements (Schwartz et al., 1998; Skaletsky et al., 2003) to give two blocks of homology in Yp11.2. Two regions on the human Y chromosome short arm thus share homology with a single region on the human X chromosome long arm (Xq21.3; Lambson, Affara, Mitchell, & Ferguson-Smith, 1992; Sargent et al., 1996). Genes within this region are

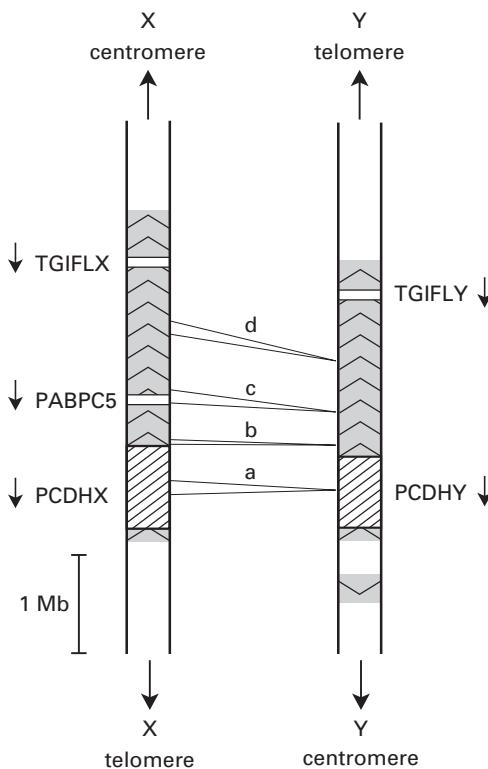


**Figure 21.3**

The Xq21.3/Yp duplication. The first event was a duplication of 3.5 megabases from the Xq21.3 region of the X chromosome long arm to the Y chromosome short arm that has now been dated at 6 million years, that is, coincident with the separation of the chimpanzee and hominid lineages. The second event inverted most of the duplication and some of the preexisting Y short arm but has not been dated.

therefore present on both the X and Y chromosomes in *Homo sapiens* but on the X alone in other great apes and primates.

An explanation for the retention of the duplicated block on Yp can be sought in the gene content of this block (see figure 21.4). Three genes are known to be expressed within this region: PABPC5, a poly (A)-binding protein whose Y gametologue has been lost during hominid evolution, TGIF2LX and Y (homeobox-containing genes with testis-specific expression), and ProtocadherinX (PCDH11X) and ProtocadherinY (PCDH11Y). PCDH11X and Y (each comprising seven extracellular cadherin motifs, a short transmembrane region, and an intracellular cytoplasmic tail; see figure 21.5) that code for cell adhesion molecules of the cadherin superfamily are of note because both forms of the gene have been retained and are highly expressed in both fetal and adult brain (Yoshida & Sugano, 1999; Blanco, Sargent, Boucher, Mitchell, & Affara, 2000) including the germinal layer of the cortex (Priddle, Cranfield., Hewitson, Williams, Groome, Schofield, Esiri, Crow, 2002). The protein products of this gene pair are thus expected to play a role in intercellular communication, perhaps acting as axonal guidance factors and influencing the connectivity of the cerebral cortex. Therefore, this gene pair may have been subject to selective pressure relating to one or more brain characteristics during hominid evolution (Williams et al., 2006; Kalmady & Venkatasubramanian, 2009).



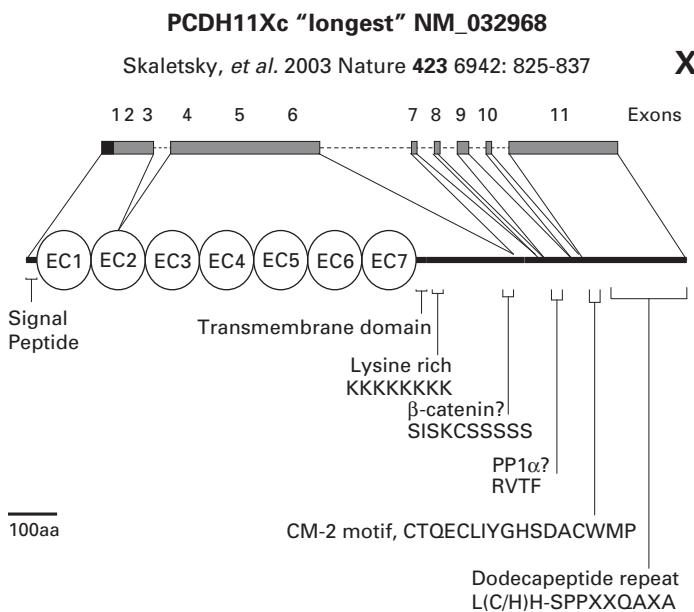
**Figure 21.4**

Alignment of the homologous regions on the X long arm and Y chromosome short arm to show four deletions (a to d) on the Y and the content of genes.

The Y chromosome is described as consisting of strata revealing points in evolution at which blocks were added to the chromosome from the autosomes or the X (Skalsky et al., 2003). Thus, the X chromosome and regions of XY homology have particular significance because they are relevant to sexual dimorphisms and the formation of mate recognition systems.

Three arguments suggest that the X.q21.3/Yp translocation was relevant to hominid evolution:

1. The timing of the original duplication relative to the chimpanzee–hominid bifurcation.
2. The sequence changes in Protocadherin Y, and particularly Protocadherin X since the duplication.
3. The case for an XY homologous determinant of cerebral asymmetry.



**Figure 21.5**

The structure of the Protocadherin XY molecule (figure 21.3) reveals points of interest: (1) the ectodomain comprises seven Protocadherin repeats, structures that interact with the same features on the surface of another cell to generate adhesive forces; (2) a beta-catenin binding site is consistent with the report (Chenn & Walsh, 2003) that this molecule is involved in gyration of the human cerebral cortex; (3) a protein phosphatase 1 $\alpha$  binding site indicates a role in axodendritic formation; and (4) the dodecapeptide repeat motif is specific to this molecule. The protein coded by this gene is the only Protocadherin that includes both beta-catenin and protein phosphatase 1 $\alpha$  binding sites. It is plausible that it acts to form synapses and as an axonal guidance factor.

While argument (1) relates to the *Australopithecus* speciation event, item (3) relates to the sapiens event with the implication that the presence of the homologous block on the Y chromosome created a field for genetic innovation in the hominid lineage, perhaps to be referred to as the “hominid strip.”

#### Species-Specific Variation Is Epigenetic

The key question is the nature and timing of event (3). When did this occur, and what was the critical change? Although it has not been dated, the paracentric inversion is an obvious candidate.

In mammals, genes on one X chromosome are subject to the process of X inactivation, but gene sequences that are also represented on the Y chromosome are protected

from this influence. Such genes are expressed from both X and Y in males and from both Xs in females, a similar dosage thus being maintained in each sex. The mechanism by which this protection is achieved is unknown although pairing in male meiosis has been suspected to be relevant. Recent work on the phenomena of “meiotic suppression of unpaired chromosomes” (Turner, 2007) suggests a possible mechanism. Gene sequences that have been transferred from the X to the Y are in a new situation; a phase of epigenetic equilibration must be assumed. If X–Y pairing in male meiosis plays a role, the orientation of the sequence on the Y matters; and the paracentric inversion could be relevant.

An MRI investigation in monozygotic twins of handedness and asymmetry of the planum temporale (Steinmetz, Herzog, Schlaug, Huang, & Jancke, 1995) suggests an epigenetic influence on cerebral asymmetry, and this may account for the stochastic element incorporated in genetic theories (Annett, 1985; McManus, 1985).

### **Characteristics of Putative Cerebral Dominance Genes in Hominid Evolution**

Other candidates for cerebral asymmetry have been suggested. On the basis of expression comparisons in fetal brain, Sun et al. (2005) suggested LM04. FOXP2 was proposed on the basis of a family study of language abnormalities (Enard et al., 2002) LRRTM1 was identified on the basis of an interpretation of linkage studies in handedness and psychosis (Francks et al., 2007). Table 21.2 summarizes the findings. It can be seen that the claims for the Protocadherin XY gene pair are at least as strong as those for the other candidates and that the timing of the initial duplication is more closely related to hominid evolution.

### **Implications for Evolutionary Theory**

The duplication 5 to 6 million years ago of 3.5 megabases of DNA from the long arm of the X to create a hominid-specific stratum on the Y short arm constitutes a “saltation” and therefore is a candidate for the speciation event for *Australopithecus*. Within the transposed block, a gene pair—Protocadherin X and Protocadherin Y—has been subject to accelerated evolution (in a recent paper, Kalmady and Venkatasubramanian, 2009, have reanalyzed the data with respect to Protocadherin Y and have concluded that this gene has been subject to positive selection) with 16 amino-acid changes in the Y protein and five in the X. The latter are particularly significant in that they include the introduction of two sulfur containing cysteines, which are likely to have changed the function of the molecule, and are expressed in both males and females. The sequence changes are seen as secondary to chromosomal rearrangements on the Y (four deletions and a paracentric inversion), the latter representing the initiating events in successive speciations, and the former representing the sexually selected phase of accommodation that establishes a new mate recognition system. The paracentric inversion, which has not been dated, is a candidate for the sapiens speciation

**Table 21.2**  
Candidate genes as determinants of cerebral asymmetry

Candidate	Will account for a sex difference?	Expressed in germinal cell layer?	Cytogenetic change at six million years ago?	Subsequent change?	Selective pressure?	No. of amino acid changes in hominid evolution	Radical change in protein structure?
FOXP2 (Fnard et al., 2002)	No	No	No	+ve	2	None	
PCDHXY gene pair (Williams et al., 2006)	Yes	Yes	Xq21.3 > Yp duplication	3 deletions on Y and a paracentric inversion (undated)	Accelerated evolution	PCDHX 5 PCDHY 16	2 new cysteine residues added to PCDHX, 1 closely related to 2 other changes in ectodomain 5
LM04 (Sun et al., 2005)	No	Yes	No	No	No	0	None
LRRTM1 (Franks et al., 2007)	If imprinted	n/k	No	No	No	0	None

event. Cerebral asymmetry (the torque) may have been introduced at a late stage, perhaps as recently as 160,000 years ago.

These considerations based on the case of *Homo sapiens* and relating to the faculty of language have implications for the mechanism of speciation in other organisms. The problem raised by saltationists from T. H. Huxley through Bateson, Goldschmidt, Gould, and Eldredge to the present is the absence of a mechanism. No plausible mechanism has been described. The general assumption is that sequence change, equally on an autosome as a sex chromosome, is responsible.

Goldschmidt (1940) maintained that chromosomal rearrangement was responsible, and this has been pursued by some workers (White, 1978; King, 1993). The arguments against this are that such rearrangements are often without effect and may be polymorphic within a species. However, change on the sex chromosomes overcomes some of these objections. In particular it is suggested that sequence change on the Y (the heterogametic chromosome) followed by a change(s) on the X has particular relevance. The Y change introduces a new characteristic in males that is then selected by females. The fact that the heterogametic chromosome is not necessary for survival allows the introduction of a change that may then be subject to sexual selection. Thus, a situation is set up in which change on the X chromosome, particularly in the homologous region, has the potential to generate phenotypic change in both sexes along a dimension related to the change that formerly was confined to males. The fact that the Y gene now varies independently allows the sexual dimorphism to be defined independently in the two sexes. The arbitrariness of the original duplication ensures that the species characteristic is independent of the changes that have led to other and related species.

### Summary

Psychosis is conceived as a species-specific disorder. It is argued that the relevant genetic variation is of a particular type, as Bateson (1894) first claimed, and that it relates to the characteristic that defines the species, the capacity for language. Thus, the nature and form of the symptoms inform us about brain mechanisms specific to *Homo sapiens*, just as the genetic changes constitute a particular example of a general mechanism for species transitions. This, it is proposed, is a two-step process with a change on the heterogametic (in mammals the Y) chromosome followed by compensatory change on the X chromosome to establish a new mate recognition system. Sexual selection and speciation thus are related in a way that is consistent with Darwin's intuition and perhaps addresses the concerns of Thomas Huxley. Paul Broca was the person who first drew attention to the relevant variable—cerebral asymmetry—although the torque (from left frontal to right occipital) had been described by Gratiolet 38 years earlier (Gratiolet & Leuret, 1839).

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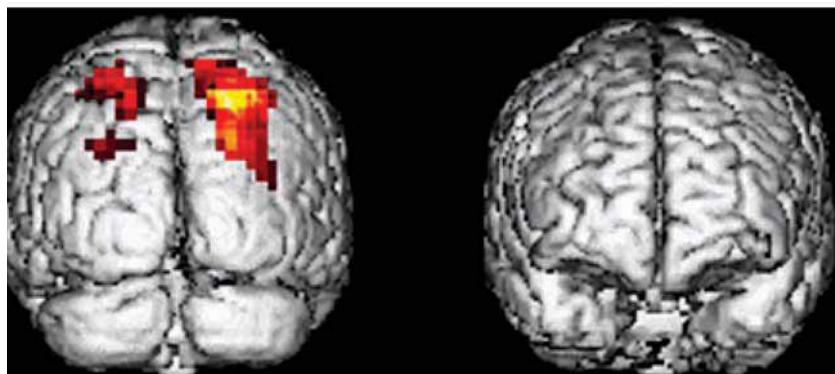
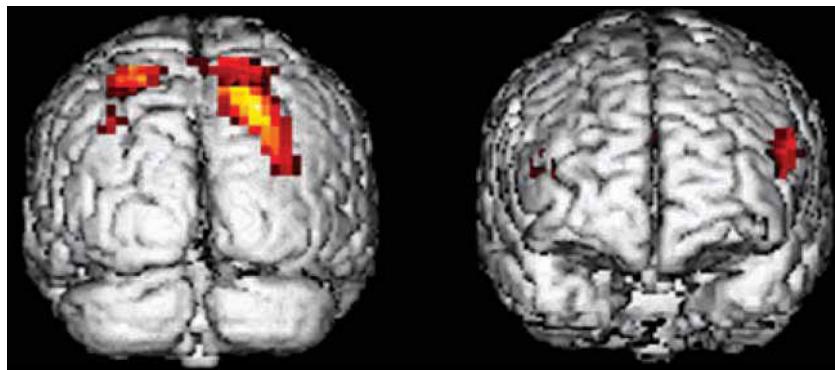
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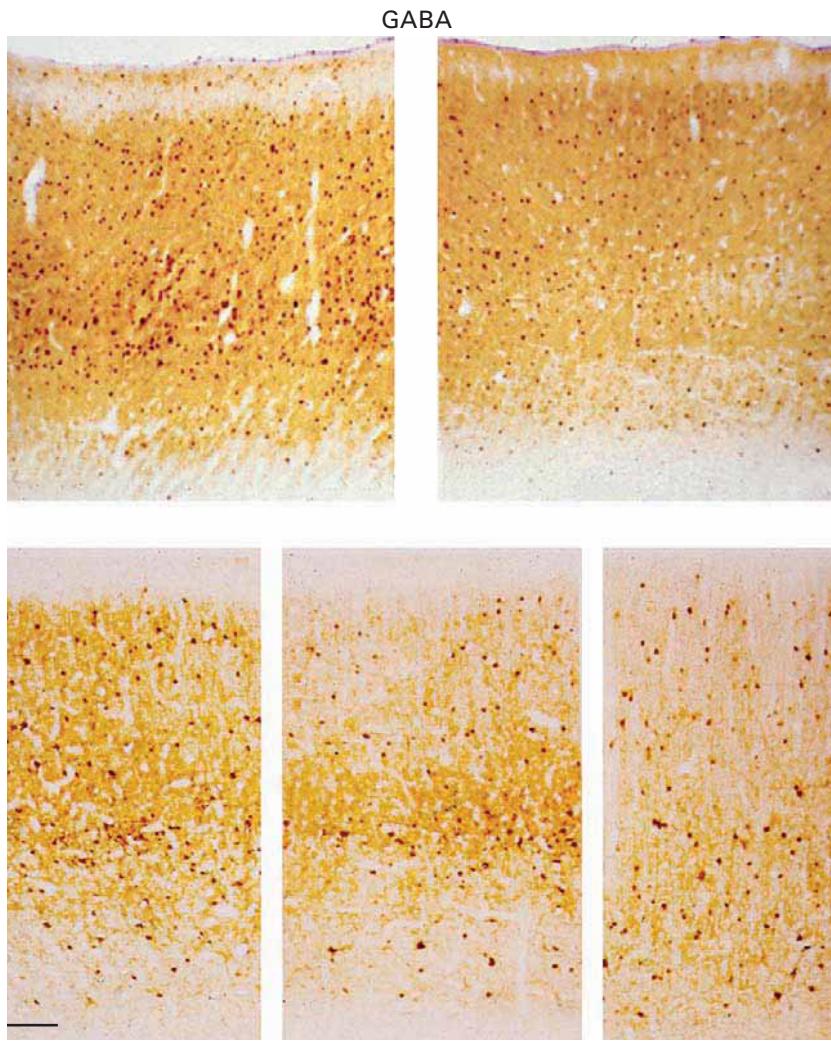
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**Females**



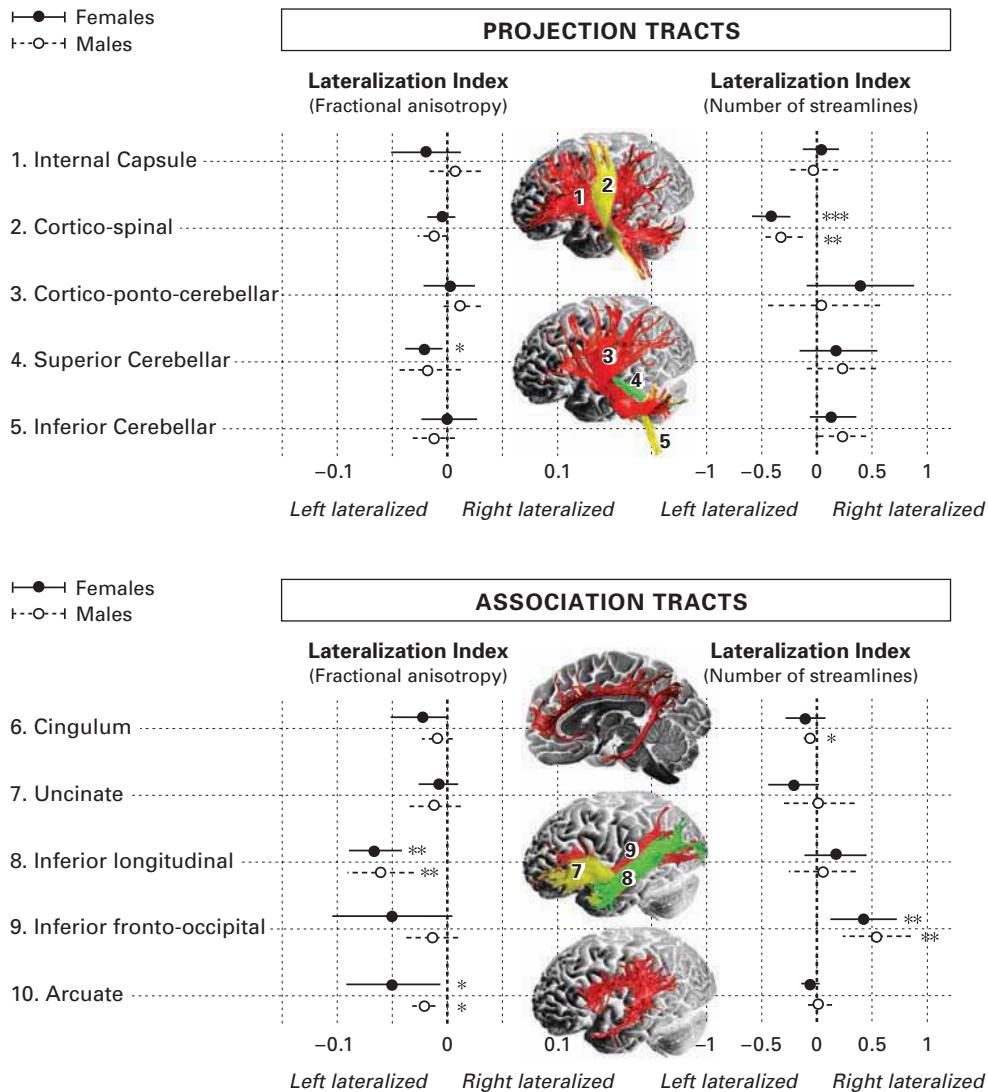
**Plate 1 (figure I.1)**

Functional magnetic resonance imaging/blood-oxygen-level-dependent activations in males and females to a three-dimensional mental rotation task. Note the profound right-over-left parietal asymmetry in both males and females and the unique female left asymmetry in the frontal cortex.



**Plate 2 (figure 2.5)**

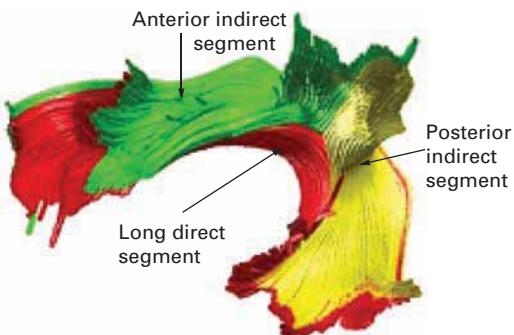
(Top) Immunocytochemical labeling of GABA in area Tpt of left (a) and right (b) hemispheres of a macaque brain shows a striking asymmetrical distribution across cortical layers. In particular, a dense population of GABA immunoreactive cells is present on the left side. (Bottom) Immunocytochemical labeling of parvalbumin in area Tpt of left and right hemispheres of macaque shows a distinct asymmetrical distribution across cortical layers. In particular, a dense population of parvalbumin immunoreactive cells and processes were present on the left side layer II and layer V similar to GABA. Area Tpt on both sides is distinct from a random control on the inferior wall of the right superior temporal gyrus (R-iSTG). WM, white matter.



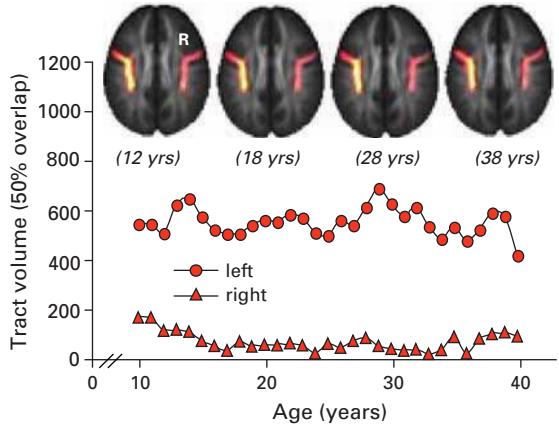
#### Plate 3 (figure 7.5)

Asymmetry of the projection and association tracts. The images are based on tractography indices derived from the analysis of 40 healthy subjects . \* $p < .05$ ; \*\* $p < .01$ ; \*\*\* $p < .001$ . Intervals are 95% confidence intervals.

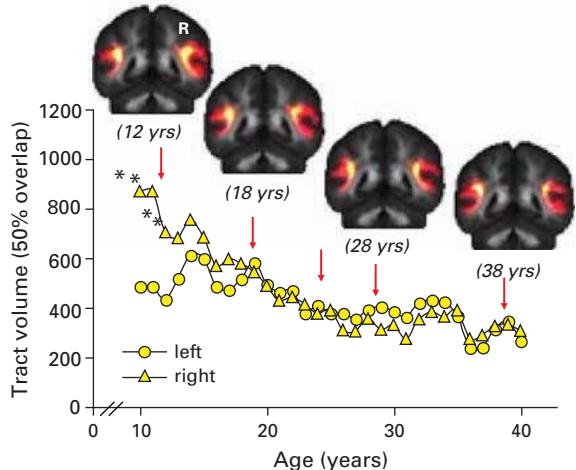
### A Virtual in vivo dissection of the arcuate



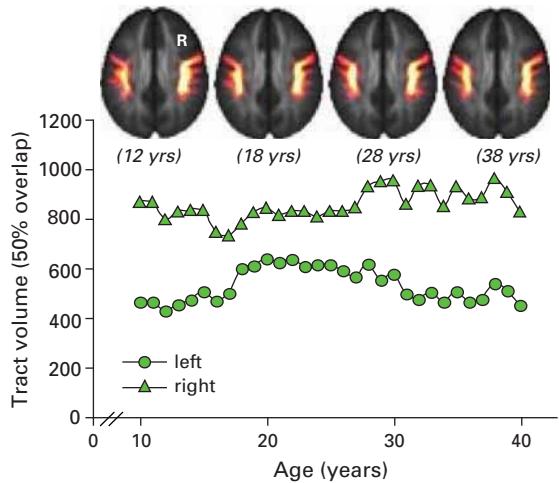
### B Long direct segment



### C Posterior indirect segment

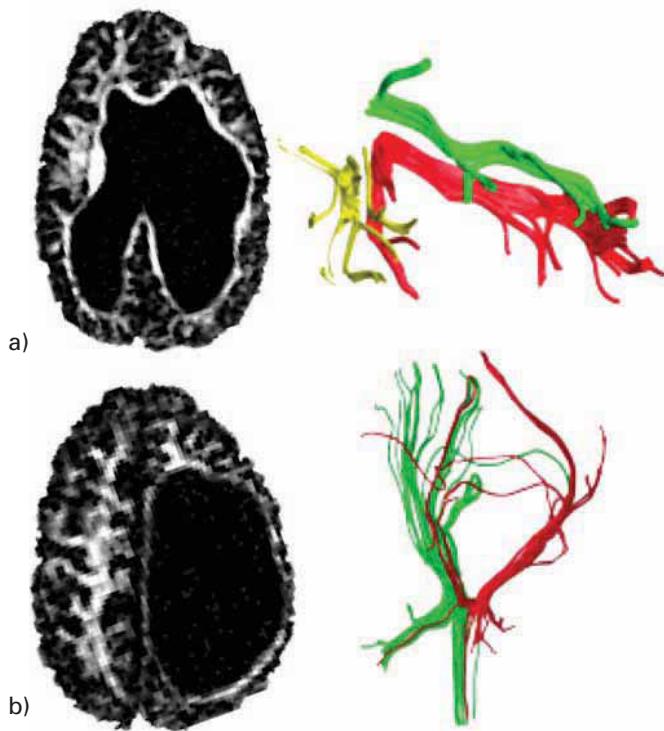


### D Anterior indirect segment



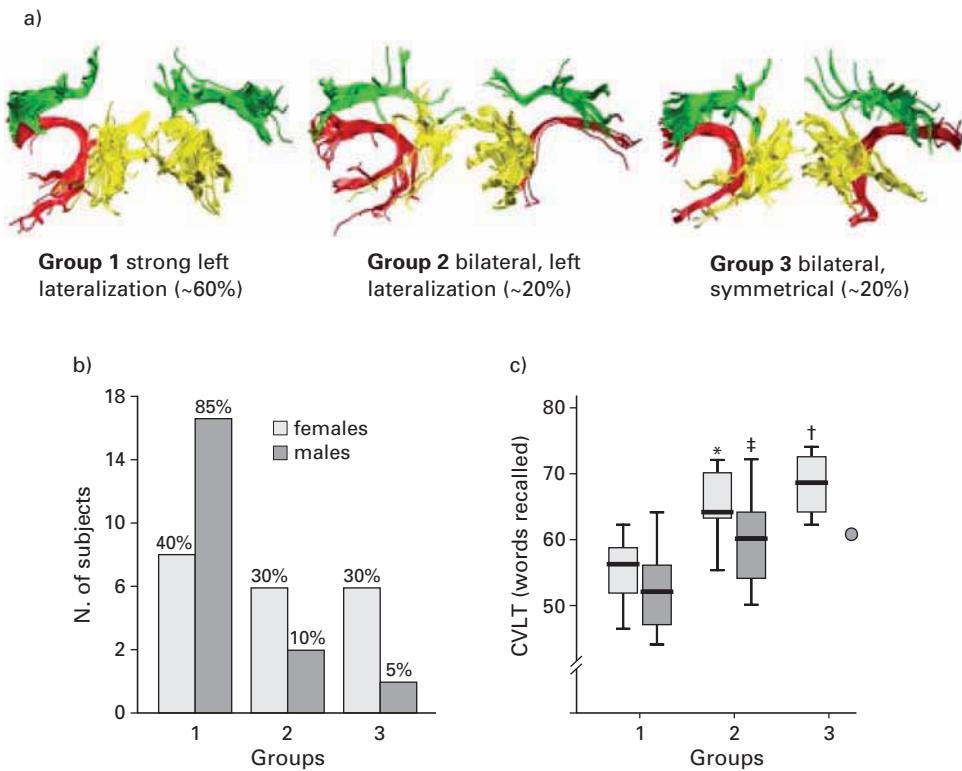
### Plate 4 (figure 7.6)

(A) Tractography reconstruction of the direct (long segment) and indirect pathway (anterior and posterior segment) of the arcuate fasciculus (reprinted from Catani et al., 2005). (B–D) The lateralization of the three segments of the perisylvian network from childhood to adulthood. The lateralization remains stable for the long and anterior segment, while the posterior segment becomes progressively symmetrical. \*Indicates statistical significant difference.



**Plate 5 (figure 7.7)**

Diffusion-tensor imaging of an 18-year-old male born very preterm at 26 weeks of gestation. (a, b) The axial fractional anisotropy images show marked dilatation of the lateral ventricles, particularly in the left hemisphere. (c) Tractography reconstruction of the perisylvian language pathways was only possible for the right hemisphere. (d) The asymmetry of the corticospinal tract is also evident with a rightward lateralization, which is usually observed in less than 15% of the male population (red streamlines indicate the left CST). Considering the normal IQ of this subject and the left-handedness, a compensatory reorganization of the lateralization of language and motor tracts may have followed the white matter damage at birth.



**Plate 6 (figure 7.8)**

(a) Distribution of the lateralization pattern of the direct long segment (red) and (b) gender differences. (c) Performances on the California Verbal Learning Test (CVLT) according to the lateralization pattern and gender \* $p < .05$  vs. group 1; † $p < .01$  vs. group 1; ‡ $p < .05$  vs. group 1).

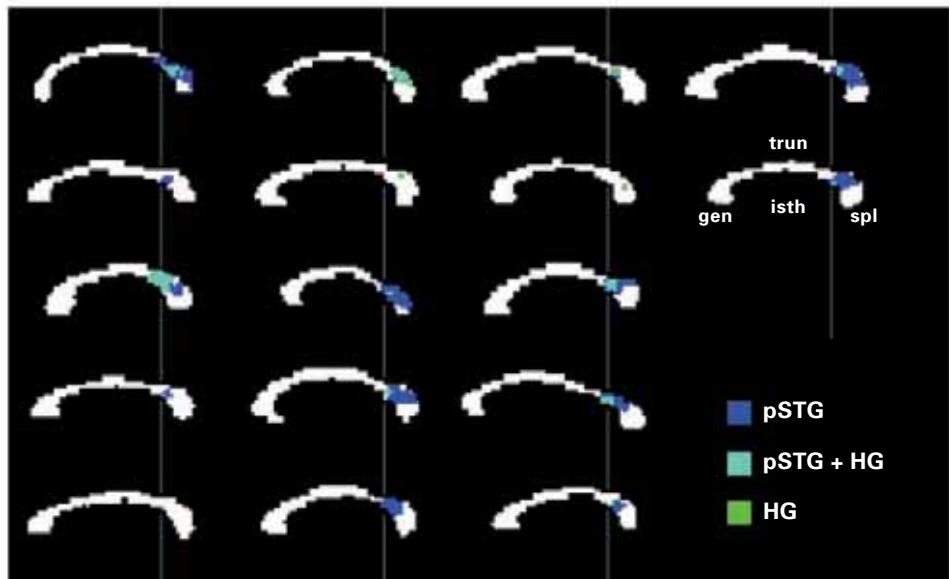
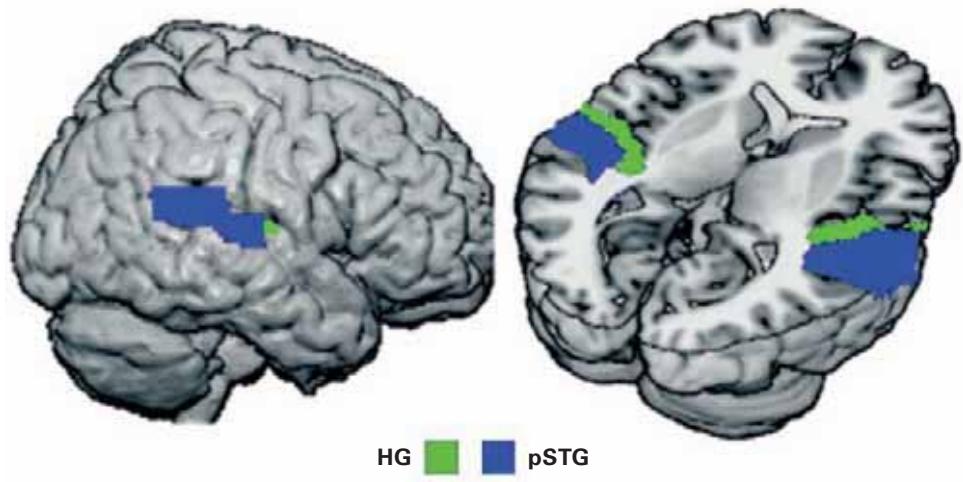
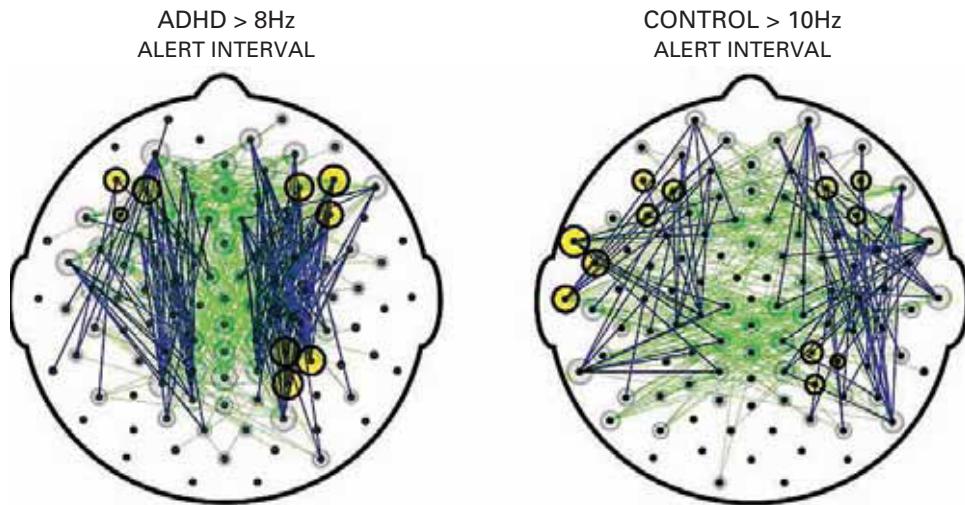


Plate 7 (figure 15.5)

Individual midsagittal fiber tracking (bottom) for Heschl's gyrus (HG, green) and posterior superior temporal gyrus (pSTG, blue; areas shown in top half of figure). (Reprinted with permission from Westerhausen et al., 2009.)



**Plate 8 (figure 19.2)**

(Left) Topography of attention-deficit/hyperactivity disorder (ADHD) group coherence elevation at 8 Hz in the alert interval. (Right) Control group coherence elevations at 10 Hz. Within-hemisphere electrode pairs are plotted in blue and between hemisphere pairs in green. (Opposite) Example spectra for both groups in the alert and stimulus intervals. Spectra are averages of the labeled electrode clusters, each representing averages across nine electrode pairs. The left frontal cluster of electrodes "A" includes AF7 (Geodesic Sensor Net electrode No. 27), AF3 (24), and F5 (28). The right frontal cluster "B" includes AF8 (2), AF4 (3), and F6 (123). The right posterior cluster "C" includes P4 (87), P6 (93), and P04 (86). The left anterior temporal cluster "D" includes F9 (39), FT7 (40), and T9 (45).

(Geodesic Sensor Net 10-10 electrode equivalents from Luu and Ferree, 2000. Reprinted with permission from Murias et al., 2007.)

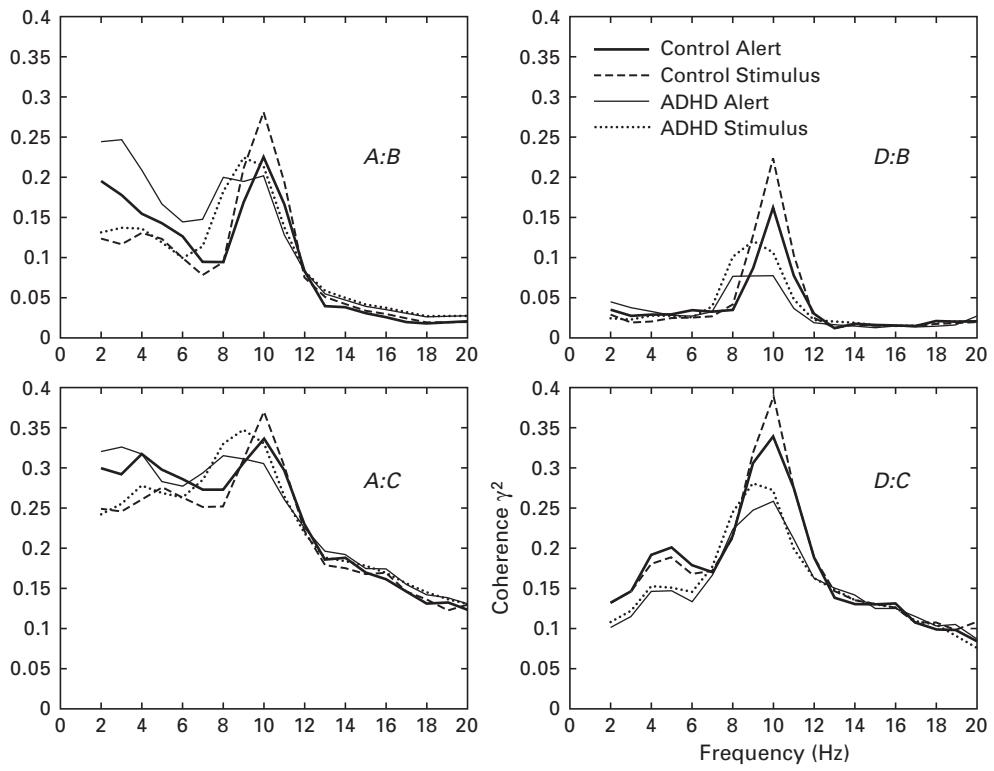
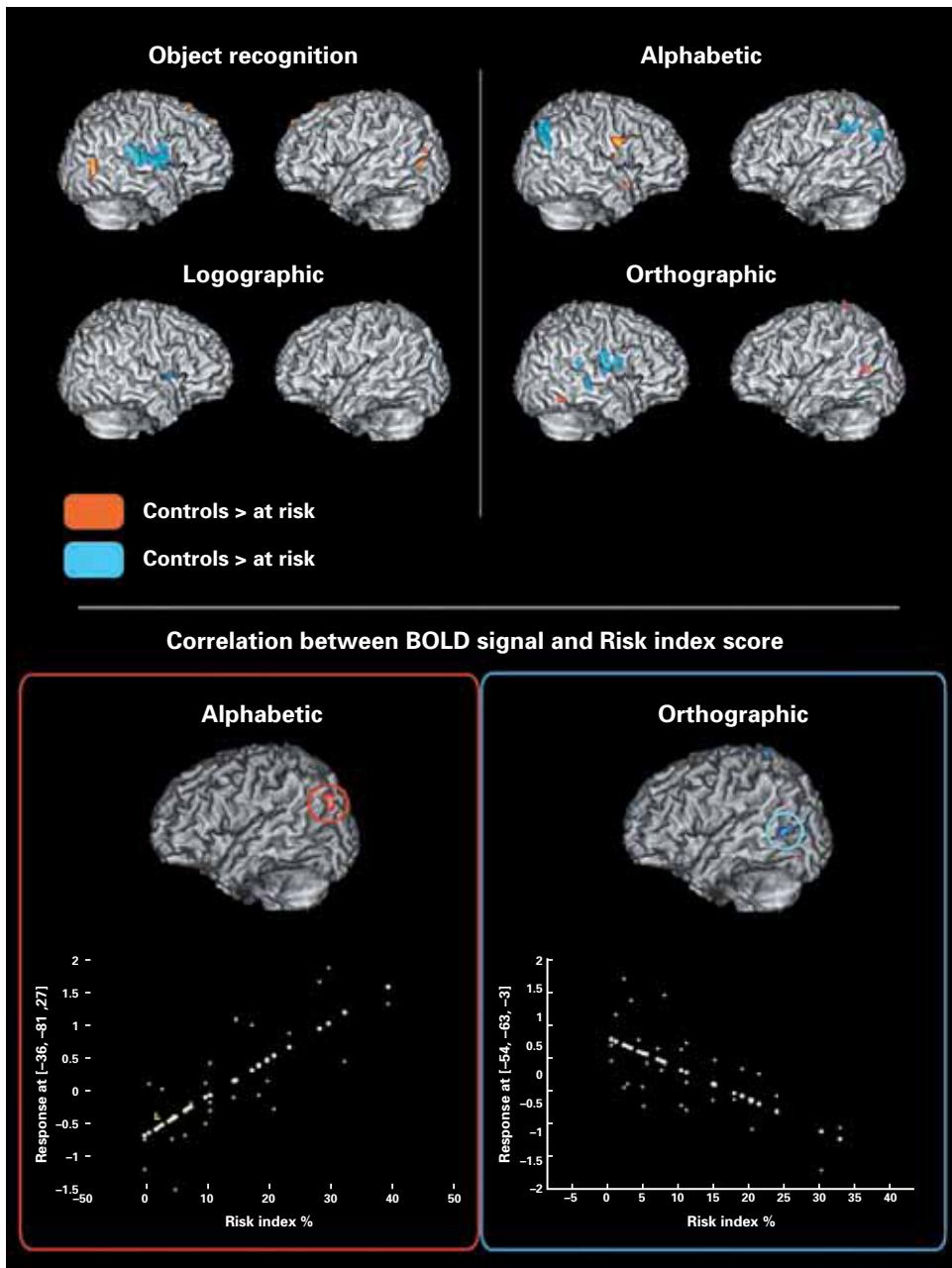
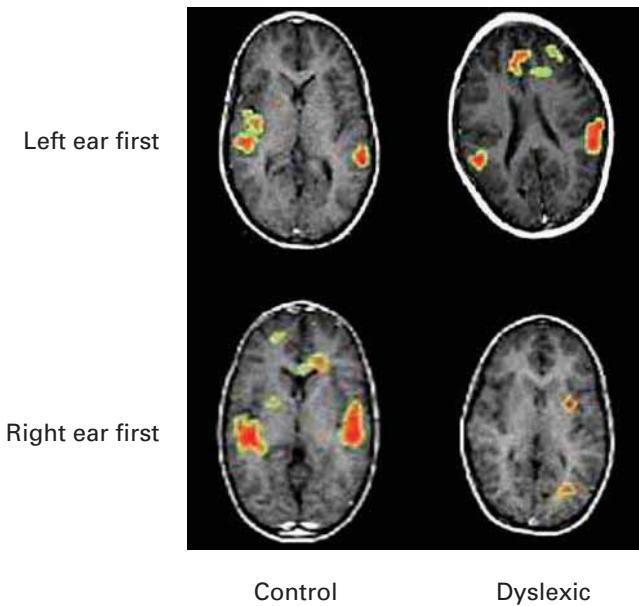


Plate 8 (figure 19.2)

(continued)



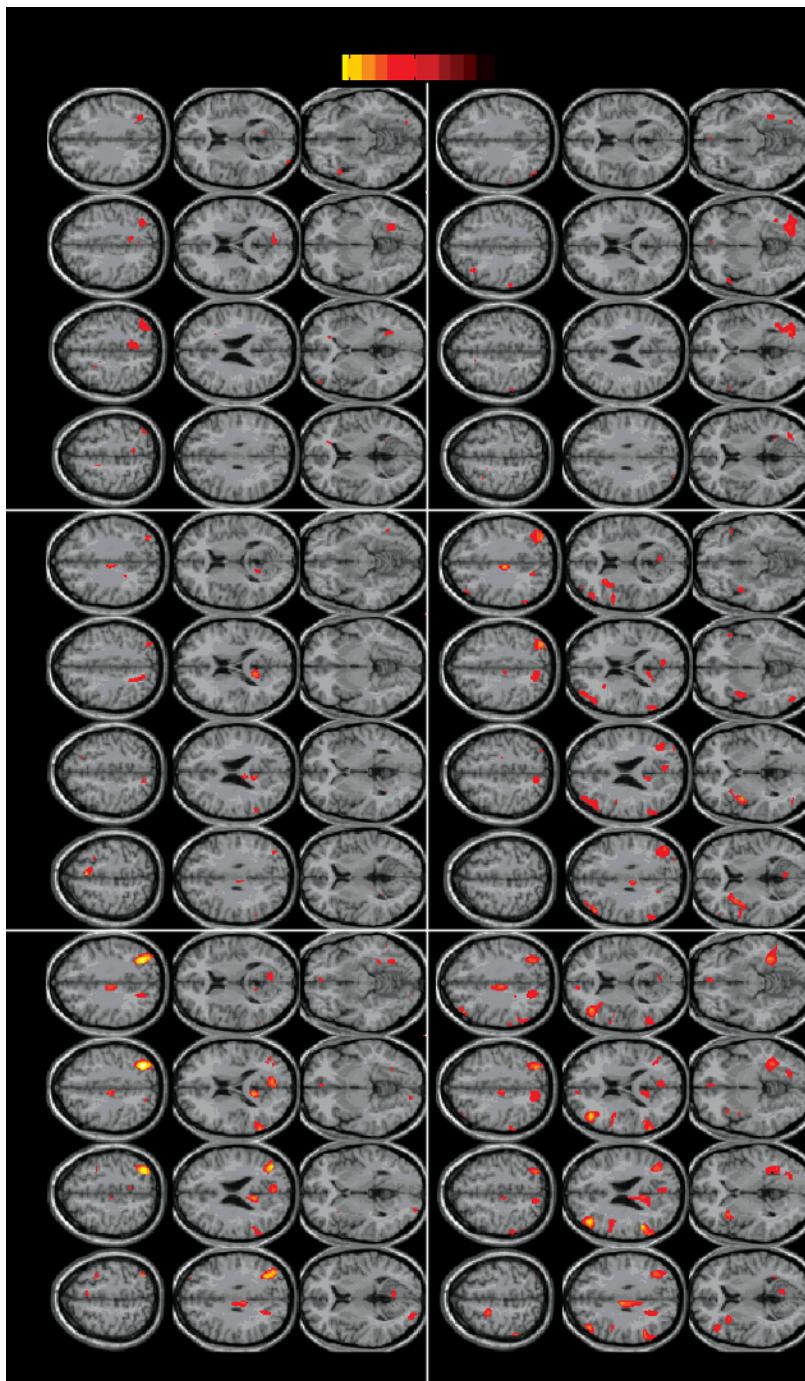


**Plate 10 (Figure 19.6)**

Activation observed during the binaural separation task for a representative child in each monitoring condition. Left hemisphere is on the right and right hemisphere is on the left in the images.

◀ **Plate 9 (Figure 19.4)**

The upper panel displays the significant differences between the groups, rendered onto the lateral view of a child's brain (nonparametric SnPM analysis, alpha level = .005, cluster threshold = 10). The lower panel displays the correlation with the risk index score for the two literacy conditions (threshold  $p(\text{FDR-corrected}) < .05$ , cluster threshold = 10, left: whole brain threshold, right: small volume correction for the occipitotemporal area). BOLD, blood oxygen level dependent; SnPM, SPM2 software package; FDR, false discovery rate. (Reprinted with permission from Specht et al., 2009.)



**Plate 11 (figure 20.1)**

Control, patient, and control versus patient laterality maps for the default mode network at rest and during an auditory oddball (AOD) task. The left side shows the R > L significant activations, while the right side shows the L > R significant activations. The maps are sorted according to group and task.