vocalizations and are perceived by sight rather than sound, but have the same structural complexity as spoken languages. Sign language processing, as with spoken language processing, localizes to the left hemisphere. Damage to the left hemisphere can have quite specific consequences for signing just as for spoken language, affecting sign comprehension (following damage in Wernicke's area), grammar, or fluency (following damage in Broca's area). These clinical observations are supported by functional neuroimaging. Not surprisingly, production and comprehension of signed and spoken languages do not involve identical brain areas, but the overlap is truly remarkable (Figure 1–8). There is even evidence that processing the constituent parts of signs (eg, handshape used) involves some of the same brain regions involved when making rhyme judgements about speech.

These observations illustrate three points. First, language processing occurs primarily in the left hemisphere, independently of pathways that process the sensory and motor modalities used in language. Second, auditory input is not necessary for the emergence and operation of language capabilities in the left hemisphere. Third, spoken language is only one of a family of language skills mediated by the left hemisphere.

Investigations of other behaviors have provided additional support for the idea that the brain has distinct cognitive systems. These studies demonstrate that complex information processing requires many interconnected cortical and subcortical areas, each concerned with processing particular aspects of sensory stimuli or motor movement and not others. For example, perceptual awareness of an object's location, size, and shape relies on activity in numerous parietal association areas that link vision to potential actions, such as moving the eyes, orienting the head, reaching, and shaping the hand to grasp. The parietal areas do not initiate these actions but evaluate sensory information as evidence bearing on these potentialities. They receive information from the dorsal visual stream—sometimes referred to as the *where pathway*, but more aptly termed a *how pathway*—to construct a state of knowing (gnosia) about the location and other spatial properties of objects. The ventral visual stream, or *what pathway*, is also concerned with possible actions, but these are associated with socializing and foraging. These associations establish *gnosia* about the desirability of objects, faces, foods, and potential mates. In this sense, the *what pathway* might be a *how pathway* too.

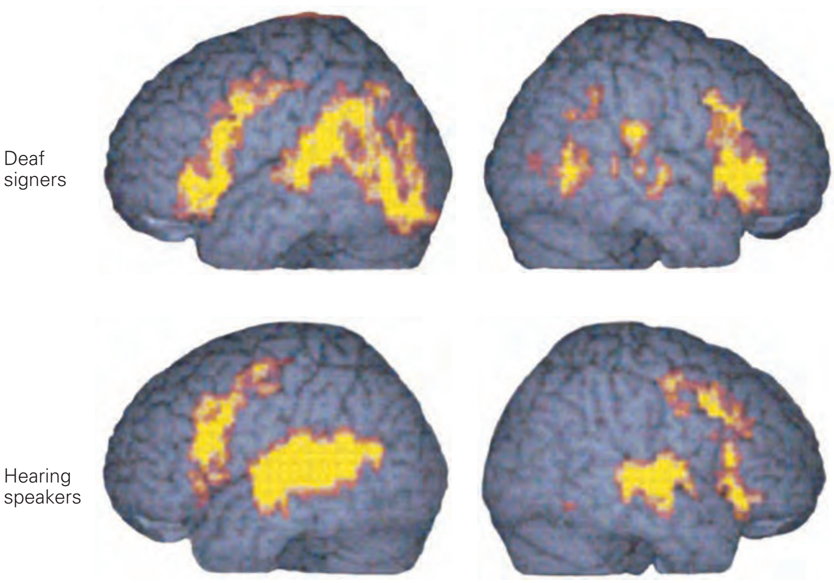

Figure 1–8 Deaf signing and hearing individuals share common language processing areas. Regions of the cortex involved in the recognition of a spoken or signed language, identified by functional magnetic resonance imaging (fMRI). **Yellow** highlight shows the areas of the left and right cerebral hemispheres (*left* and *right columns*, respectively) that were activated more when comprehending language than when performing a perceptual task. For the deaf signers (**top row**), the highlighted regions were more active during comprehension of British Sign Language than during the detection of a visual stimulus superimposed on the same motionless signer. For the hearing speakers (**bottom row**), highlighted regions were more active during comprehension of audio-visual speech than during the detection of a tone while viewing a motionless (silent) speaker. (Adapted, with permission, from MacSweeney et al., 2002. Copyright © 2002 Oxford University Press.)

Mental Processes Are the Product of Interactions Between Elementary Processing Units in the Brain

There are several reasons why the evidence for the localization of brain functions, which seems so obvious and compelling in retrospect, had been rejected so often in the past. Phrenologists introduced the idea of localization in an exaggerated form and without adequate evidence. They imagined each region of the cerebral cortex as an independent mental organ dedicated to a complete and distinct aspect of personality, much as the pancreas and the liver are independent digestive organs. Flourens's rejection of phrenology and the ensuing debate between proponents of the aggregate-field view (against localization) and the cellular connectionists (for localization) were responses to a theory that was simplistic and without adequate experimental evidence.

In the aftermath of Wernicke's discovery of the modular organization of language in the brain—interconnected nodes with distinctive functions—we now think that all cognitive abilities result from the interaction of many processing mechanisms distributed in several regions of the brain. That is, particular brain regions are not fully responsible for specific mental faculties but instead are *elementary processing units* that together have a role. Perception, movement, language, thought, and memory are all made possible by the interlinkage of serial and parallel processing in discrete brain regions—computational modules—within these regions. As a result, damage to a single area need not result in the complete loss of a cognitive function (or faculty) as many earlier neurologists believed. Even if a behavior initially disappears, it may partially return as undamaged parts of the brain reorganize their linkages. Further, when focal damage adversely affects a mental function it may do so indirectly by disrupting the function of other principal loci (*diaschisis*). Indeed, observations of this nature led Wernicke's student Kurt Goldstein to embrace the more holistic view.

Thus it is not accurate to think of a mental function as being mediated strictly by a chain of nerve cells and brain areas—each connected directly to the next—for in such an arrangement the entire process is disrupted when a single connection is damaged. A more realistic metaphor is that of a process consisting of several parallel pathways in a network of modules that interact and ultimately converge upon a common set of targets. The malfunction of a single pathway within a network may affect the information carried by that pathway without disrupting the entire system. The remaining parts of the network may be able to modify their performance to accommodate the breakdown of one pathway.

Modular processing in the brain was slow to be accepted because, until recently, it was difficult to demonstrate which components of a mental operation were mediated by a particular pathway or brain region. Nor is it easy to define mental operations in a manner that leads to testable hypotheses. Nevertheless, with the evolving convergence of modern cognitive psychology and brain science in recent decades, we have begun to appreciate that mental functions can successfully be broken down into subfunctions.

To illustrate this point, consider how we learn, store, and recall information about objects, people, and events. Simple introspection suggests that we store each piece of our knowledge as a single representation that can be recalled by memory-jogging stimuli or even by the imagination alone. Everything you know about an apple, for example, seems to be stored in one complete representation that is equally accessible whether you see a particular apple, a part of an apple, a red or green apple, the written word apple, or an apocryphal story about the discovery of gravity. Our experience, however, is not a faithful guide to how knowledge is stored in memory.

Knowledge about apples is not stored as a single coherent representation but rather is subdivided into distinct categories and stored separately. One region of the brain stores information about the way you would hold the apple, the way you would feel for softness (bearing on freshness), the color (bearing on preference or freshness), the way you might communicate the presence or taste of the apple to another person, as well as its semantic association with computers, physicists, worms, serpents, and biblical gardens. The concept "apple" entails each of these considerations and many more. A natural assumption is that a coherent concept comprising many details must exist in a single place in the brain; however, an equally valid assumption is that a unified concept like "apple" exists in the mind in the form of multiple links between a variety of neural structures, each with a particular kind of information, coordinated through the action of memory retrieval.

The most astonishing example of the modular organization of mental processes is the finding that our very sense of self—a self-aware being, the sum of what we mean when we say "I"—is achieved through the connection of independent circuits in our two cerebral hemispheres, each mediating its own sense of awareness. The remarkable discovery that even consciousness is not a unitary process was made by Roger Sperry, Michael Gazzaniga, and Joseph Bogen in the course of studying patients in whom the corpus callosum—the major tract connecting the two cerebral hemispheres—was severed as a treatment for epilepsy. They found that each hemisphere had a consciousness that functioned independently of the other.

Thus while one patient was reading a favorite book held in his left hand, the right hemisphere, which controls the left hand but plays only a minor role in language comprehension, found that the raw visual information it received from simply looking at the book was boring. The right hemisphere commanded the left hand to put the book down. Another patient would put on his clothes with the left hand while at the same time taking them off with the other. Each hemisphere has a mind of its own! In addition, the dominant hemisphere sometimes commented on the performance of the nondominant hemisphere, frequently manifesting a false sense of confidence regarding problems to which it could not know the solution, which was provided exclusively to the nondominant hemisphere.

Such findings have brought the study of consciousness, once the domain of philosophy and psychoanalysis, into the fold of neural science. As we shall see in later chapters, many of the issues described in this chapter reemerge in neural theories of consciousness. No one questions the idea that much information processing—perhaps the lion's share—does not reach conscious awareness. When sensory information, a plan of action, or an idea does become conscious, neural science seeks to explain the mechanisms that mediate this transition. While there is as yet no satisfactory explanation, some brain scientists would liken the process to a shift in the focus of attention, mediated by distinct groups of neurons, whereas others believe that awareness requires a qualitative change in the functional interaction between widely separated areas of the brain.

The main reason it has taken so long to understand which mental activities are mediated by which regions of the brain is that we are dealing with biology's deepest riddle: the neural mechanisms that account for consciousness and self-awareness. There is at present no satisfactory theory that explains why only some information that reaches our eyes leads to a state of subjective awareness of an item, person, or scene. We know that we are consciously aware of only a small fraction of our mental deliberations, and those thoughts that do pierce conscious awareness must arise from steps carried out by the brain unconsciously. As we propose in Chapter 56, some answers to the riddles of consciousness may be closer than imagined.

Meanwhile, the current gap in our understanding also poses practical, epistemological challenges for neural science. We cannot help but rely on our conscious experiences of the world, body, and ideation in our characterization of perception, behavior, and cognition. In doing so, however, we risk mischaracterizing many mental processes that do not pierce conscious awareness. For example, we tend to characterize the problem of perception in terms consistent with the subjective experience of sensory information, whereas even sophisticated but nonconscious knowledge of the content of perception may have greater resemblance to a behavioral utility (affordance), in effect an answer to whether this is something I might choose to eat, sit upon, or engage further. Similarly, cognitive processes, such as reasoning, strategizing, and decision making, are likely to be carried out by the brain in ways that only loosely resemble the steps we infer from conscious deliberation.

These cautionary notes have a bright corollary. The insight that many cognitive functions transpire without conscious awareness raises the possibility that principles of neural science revealed in the study of more rudimentary behaviors can furnish insight into more complex cognitive processes. Neural recordings from the brains of animals trained to perform complex tasks have led to an understanding of cognitive processes such as decision making, reasoning, planning, and allocating attention. These experimental models often extrapolate to human functions, and where they fall short, they inspire new hypotheses. For more often than not, there is inspiration if not insight to be gleaned from the gaps in our understanding.

To analyze how the brain gives rise to a specific mental process, we must determine not only which aspects of the process depend on which regions of the brain but also how the relevant information is represented, routed, and transformed. Modern neural science seeks to integrate such understanding across many scales. For example, studies at the level of both the single nerve cell and its molecular constituents elucidate the mechanisms underlying electrical excitability and synaptic connections. Studies of cells and simple circuits lend insights into neural computations, ranging from basic operations, like controlling net excitation, to more masterful feats of computation, such as the derivation of meaningful information from raw sensory data. Studies of the interactions between circuits and brain areas can explain how we coordinate widely separated muscle groups or express a belief in a proposition. Knowledge at all these levels is knit together by mathematical formalizations, computer simulation, and psychological theory. These conceptual tools can now be combined with modern physiological techniques and brain imaging methods, making it possible to track mental processes as they evolve in real time in living animals and humans. Indeed, the excitement evident in neural science today stems from the conviction that the biological principles that underlie human thought and behavior are within our grasp and may soon be harnessed to elucidate and improve the human condition.

Highlights

1. The neural sciences seek to understand the brain at multiple levels of organization, ranging from the cell and its constituents to the operations of the mind.
2. The fundamental principles of neural science bridge levels of time, complexity, and state—from cell to action and ideation, from development through learning to expertise and forgetting, from normal function to neurological deficits and recovery. As a first step, one must understand the building blocks—the electrical properties of the nerve cell and its connections to other nerve cells—and the organization of the nervous system from supporting cells to pathways.
3. The neuron doctrine states that individual nerve cells (neurons) are the elementary building blocks and signaling elements of the nervous system.
4. Neurons are organized into circuits with specialized functions. The simplest circuits mediate reflexes; more complex cognitive functions require more sophisticated circuits. This organizational principle extends the neuron doctrine to cellular connectionism.
5. Even within complex circuits, critical nodes can be identified as areas associated with a specific function. The first clear evidence for localization of brain function came from the study of a specific impairment of language production.
6. The two cerebral hemispheres receive information from the opposite side of the body and control the actions of the opposite side.
7. While the principle of localization of function in the brain is superior to its main historical alternatives—aggregate-field and the theory of mass action—it is constantly being refined. No area of the cerebral cortex functions independently of other cortical and subcortical structures.
8. A major refinement of localization is the principle of modular functional organization. The brain contains many representations of information organized by both the relevance of certain features for particular computations and by the variety of uses to which such information may be put. This is a form of redundancy with respect to purpose or potential action.
9. The future of brain science will require integration of ideas that cross the boundaries of traditional disciplines. We must open our minds to a wide variety of sources to guide our intuitions and strategies for research, from the sublime—the nature of consciousness—to the seemingly mundane—what general anesthesia does to a calcium sensor in the ring of cells around the thalamus.

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Michael N. Shadlen

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2

Genes and Behavior

All behaviors are shaped by the interplay of genes and the environment. The most stereotypic behaviors of simple animals are influenced by the environment, while the highly evolved behaviors of humans are constrained by innate properties specified by genes. Genes do not control behavior directly, but the RNAs and proteins encoded by genes act at different times and at many levels to affect the brain. Genes specify the developmental programs that assemble the brain and are essential to the properties of neurons, glia, and synapses that allow neuronal circuits to function. Genes that are stably inherited over generations create the machinery by which new experiences can change the brain during learning.

In this chapter, we ask how genes contribute to behavior. We begin with an overview of the evidence that genes do influence behavior, and then review basic principles of molecular biology and genetic transmission. We then provide examples of the way that genetic influences on behavior have been documented. A deep understanding of the ways that genes regulate behavior has emerged from studies of worms, flies, and mice, animals whose genomes are accessible to experimental manipulation. Many persuasive links between genes and human behavior have emerged from the analysis of human brain development and function. Despite the formidable challenges inherent in studying complex traits in humans, recent progress has begun to reveal the genetic risk factors in neurodevelopmental and psychiatric syndromes such as autism, schizophrenia, and bipolar disorder, offering another important avenue to clarify the relationship between genes, brain, and behavior.

An Understanding of Molecular Genetics and Heritability Is Essential to the Study of Human Behavior

Many human psychiatric disorders and neurological diseases have a genetic component. The relatives of a patient are more likely than the general population to have the disease. The extent to which genetic factors account for traits in a population is called *heritability*. The strongest case for heritability is based on twin studies, first used by Francis Galton in 1883. Identical twins develop from a single fertilized egg that splits into two soon after fertilization; such monozygotic twins share all genes. In contrast, fraternal twins develop from two different fertilized eggs; these dizygotic twins, like normal siblings, share on average half their genetic information. Systematic comparisons over many years have shown that identical twins tend to be more similar (concordant) for neurological and psychiatric traits than fraternal twins, providing evidence of a heritable component of these traits (Figure 2–1A).

In a variation of the twin study model, the Minnesota Twin Study examined identical twins that were separated early in life and raised in different households. Despite sometimes great differences in their environment, twins shared predispositions for the same psychiatric disorders and even tended to share personality traits, like extraversion. This study provides considerable evidence that genetic variation contributes to normal human differences, not just to disease states.

Heritability for human diseases and behavioral traits is usually substantially less than 100%, demonstrating that the environment is an important factor in acquiring diseases or traits. Estimates of heritability for many neurological, psychiatric, and behavioral traits from twin studies are around 50%, but heritability can be higher or lower for particular traits (Figure 2–1B). Although studies of identical twins and other kinships provide support for the idea that human behavior has a hereditary component, they do not tell us which genes are important, let alone how specific genes influence behavior. These questions are addressed by studies in experimental animals in which genetic and environmental factors are strictly controlled and by modern methods of gene discovery that are now leading to the systematic, reliable identification of specific variations in DNA sequence and structure that contribute to human psychiatric and neurological phenotypes.

The Understanding of the Structure and Function of the Genome Is Evolving

The related fields of molecular biology and transmission genetics are central to our modern understanding of genes. Here we summarize some key ideas in these fields; a glossary at the end of the chapter defines commonly used terms.

Genes are made of DNA, and it is DNA that is passed on from one generation to the next. In most circumstances, exact copies of each gene are provided to all cells in an organism as well as to succeeding generations through DNA replication. The rare exceptions to this general rule—new (de novo) mutations that are introduced into the DNA of either germline or somatic cells and that play an important role in disease risk—are discussed later. DNA is made of two strands, each of which has a deoxyribose-phosphate backbone attached to a series of four subunits: the nucleotides adenine (A), guanine (G), thymine (T), and cytosine (C). The two strands are paired so that an A on one strand is always paired with a T on the complementary strand, and a G with a C (Figure 2–2). This complementarity ensures accurate copying of DNA during DNA replication and drives *transcription* of DNA into lengths of RNA called transcripts. Given that nearly all of the genome is double-stranded, bases or base pairs are used interchangeably as a unit of measurement. A segment of the genome encompassing a thousand base pairs is referred to as 1 kilobase (1 kb) or 1 kilobase pair (1 kbp), whereas a million base pairs are referred to as 1 megabase (1 Mb) or 1 megabase pairs (1 Mbp). RNA differs from DNA in that it is single-stranded, has a ribose rather than a deoxyribose backbone, and uses the nucleoside base uridine (U) in the place of thymine.

In the human genome, approximately 20,000 genes encode protein products, which are generated by *translation* of the linear messenger RNA (mRNA) sequence into a linear polypeptide (protein) sequence composed of amino acids. A typical protein-coding gene consists of a coding region, which is translated into the protein, and noncoding regions (Figure 2–3). The coding region is usually arranged in small coding segments called *exons*, which are separated by noncoding stretches called *introns*. The introns are deleted from the mRNA before its translation into protein.

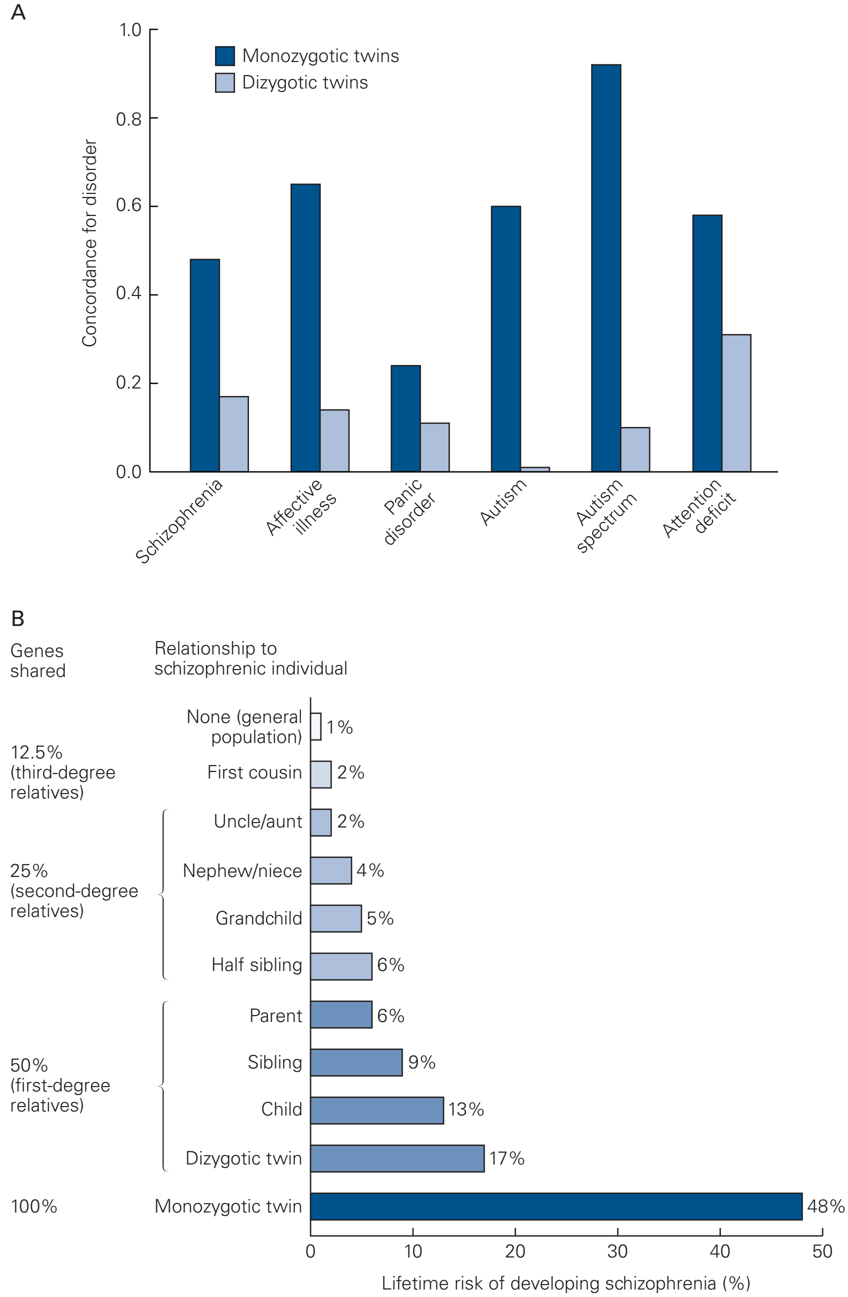

Figure 2–1 Familial risk of psychiatric disorders provides evidence of heritability.

A. Correlations between monozygotic twins for psychiatric disorders are considerably greater than those between dizygotic twins. Monozygotic twins share nearly all genes and have a high (but not 100%) risk of sharing the disease state. Dizygotic twins share 50% of their genetic material. A score of zero represents no correlation (the average result for two random people), whereas a score of 1.0 represents a perfect correlation. (Adapted from McGue and Bouchard 1998.)

B. The risk of developing schizophrenia is greater in close relatives of a schizophrenic patient. Like dizygotic twins, parents and children, as well as brothers and sisters, share 50% of their genetic material. If only a single gene accounted for schizophrenia, the risk should be the same for parents, siblings, children, and dizygotic twins of patients. The variation between family members shows that more complex genetic and environmental factors are in play. (Adapted, with permission, from Gottesman II. 1991.)