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SEXUALLY-DIMORPHIC PATTERNS OF CORTICAL ASYMMETRY, AND THE ROLE FOR SEX STEROID HORMONES IN DETERMINING CORTICAL PATTERNS OF LATERALIZATION

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SUMMARY

Cortical asymmetry varies in degree and direction. Sex differences exist for both dimensions of asymmetry: males tend to exhibit more accentuated asymmetries and stronger right hemisphere dominance compared with females, while females typically exhibit more diffuse lateralization patterns and greater left hemisphere bias compared with males. The following review considers the effects of sex steroid hormones on the sexual dimorphism of cortical lateralization patterns in human and nonhuman animals. Several excellent papers exist which consider sexual dimorphism in cortical asymmetries for morphological, physiological or functional asymmetries alone. This paper attempts to consider influences of sex steroid hormones on cortical lateralization in a framework that includes morphology, physiology and function. Converging evidence from studies that incorporate varying methodologies and theoretical backgrounds indicates that sex steroid hormones are important for influencing cortical asymmetry. Although a mechanism has not yet been identified, testosterone is the most likely candidate to influence cortical dominance. © 1998 Elsevier Science Ltd. All rights reserved.

Keywords—Cortical asymmetry; Sexual dimorphism; Cortical dominance.

INTRODUCTION

Patterns of cortical lateralization can vary along at least two, seemingly independent, axis referred to as the magnitude and the direction of hemispheric specialization (Galaburda, 1995). The magnitude of lateralization is discussed in terms of interhemispheric connectivity and communication (e.g. how much information is shared between the two hemispheres during normal processing), while the direction of lateralization is thought of in terms of intrahemispheric organization (e.g. within which hemisphere is the information processed most efficiently, fastest, or most accurately) (Zaidel et al., 1995). While decades of research with normal and clinical human populations has led to theories that postulate a left hemisphere specialization for language/communicative functioning and a right hemisphere specialization for processing spatial information, individual differences in

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patterns of cerebral lateralization are noted in terms of both the direction and degree of specialization (Hellige, 1990).

This individual variation in hemispheric specialization is currently believed to be influenced by variables such as handedness (Hellige et al., 1994), certain clinical disorders (Bruder, 1995), and sex (for a recent review of sex differences in functional cerebral lateralization see Voyer (1996)). Generally speaking, the magnitude of cerebral lateralization is thought to be sexually dimorphic in the majority of humans studied. The direction of cerebral asymmetry is also sex-biased in people. Males are more likely to be left-handed and to exhibit atypical patterns of functional specialization compared with females; and females are more likely to exhibit extreme degrees of right-handedness compared with males (for a hypothesis that attempts to reconcile observations of increased neural asymmetries in males and stronger right-handedness in females see Galaburda et al. (1990)). The working hypothesis under review in this paper is that males exhibit a greater degree of cortical asymmetry than females for components of cognitive and perceptual processing (Levy, 1973; McGlone, 1980), and that this sex difference may be a consequence of sex steroid hormone action on the cerebral cortex (Geschwind and Galaburda, 1987). For at least a decade, diencephalic structures have been known to be influenced by sex steroid hormones (Gorski, 1984; Swaab and Hofman, 1995), and these hormones appear to affect the asymmetric structural development of diencephalic areas (Holman and Hutchinson, 1991). What is the role then, if any, for sex steroid hormones concerning asymmetries measured in the cerebral cortex? As is the case for the diencephalon, are the sexually-dimorphic neural asymmetries exhibited by the right and left neocortices under the influence of sex steroid hormones?

Levy (1973) first suggested that males exhibit a greater degree of neural asymmetry when it was noted that language functioning is carried out primarily in the left hemisphere of boys and men, while in women these abilities are more evenly distributed throughout both hemispheres. Although theories of laterality were initially focused on the specialization of language processing in humans, this limited framework no longer restricts investigations and theories concerning cortical asymmetries. It is now widely accepted that nonhuman animals also exhibit both magnitude and direction in their patterns of cortical lateralization (Ehret, 1987; Robinson, 1979), and these neural characteristics systematically vary between the sexes (Andrew and Brennan, 1984; Denenberg et al., 1982; Fitch et al., 1993). The inclusion of nonhuman investigations in the study of cortical asymmetries is advantageous because lateralization can be more easily analyzed at the ultimate, or evolutionary, level. However, an evolutionary approach toward studying cortical lateralization in humans is certainly possible, and undoubtedly should be pursued. Additionally, investigations of nonhuman animal cortical asymmetries is beneficial because nonhuman animal models provide experimental opportunities that cannot be obtained with human populations for ethical reasons.

When neural characteristics such as cerebral asymmetries differ between the sexes, several variables including genetic, hormonal, and social factors are likely to contribute to this dimorphism. The present discussion will focus on hormonal (specifically, sex steroid hormone) influences on cerebral lateralization. This focus is for the purpose of simplicity, and is not meant to imply that the influence of other variables are nonexistent or trivial. In fact, much of the nonhuman animal literature considered in this review should emphasize to the reader that it is never possible to truly separate hormonal influences from 'social' variables such as housing conditions and group structure (for a discussion on this point see Breedlove (1994)).

Research findings from a variety of subfields in psychology and neuroscience will be considered in an attempt to ascertain what role sex steroid hormones have on cortical

asymmetries. To accomplish this goal, reports of neuroanatomical, neurophysiological and behavioral sex differences in cerebral lateralization are considered. In addition to nonhuman animal findings, clinical populations are reported in concert with experimental work in healthy human populations in an attempt to illustrate the general phenomenon of sex steroid hormone action on hemispheric specialization across species.

Inter- and intrahemispheric mechanisms thought to underlie cerebral asymmetries are considered in reviewing the human and nonhuman animal studies. For example, the possibility that males exhibit a different pattern of intrahemispheric organization compared with females (Kimura, 1987), as well as the possibility that females possess a different pattern of interhemispheric connectivity via structural differences in the corpus callosum (CC) (de Lacoste and Holloway, 1982; McGlone, 1980) are examined. For intra- and interhemispheric mechanisms, evidence for hormonal influences is provided by: (1) studies in which sex differences in cerebral lateralization of normal human adult populations are observed; (2) studies of cerebral lateralization in humans exposed to abnormal concentrations of sex steroid hormones prenatally; (3) studies of spontaneously cycling women who exhibit fluctuations in neural asymmetry that correspond to their menses; (4) studies attempting to link the timing of human pubescence with lateralization patterns; (5) nonhuman animal studies concerned with sex differences in cortical lateralization observed in normal populations; (6) experimental populations receiving exogenous hormone treatment. Although direct demonstrations of sex steroid hormone action on cortical asymmetries are lacking, when considered as a whole the various lines of research outlined above provide compelling support for the hypothesis that sex steroid hormones do influence cortical asymmetries across a range of vertebrate species.

SEX DIFFERENCES IN HUMAN NEUROANATOMICAL ASYMMETRIES: THE CORPUS CALLOSUM

A structure believed to be associated with functional cortical lateralization at the level of interhemispheric connectivity is the CC, a fiber tract that connects the two cerebral hemispheres in some vertebrates. The CC is of interest in studies of cerebral lateralization because information is thought to be shared between the two cerebral hemispheres via this large bundle of nerves. The current understanding of the functional significance of the CC focuses on diverse components of cognitive processing such as attention (Heilman, 1995), the transfer of language/lexical information (Hines et al., 1992), and the transfer of visual information (Hellige, 1990). Sexually-dimorphic structural asymmetries of the CC have been reported for CC area, shape, and fiber composition. All three of these structural characteristics will be considered in terms of reported sex differences, first among humans and then among nonhuman vertebrates, in the regions of the splenium and isthmus of the CC.

SEX DIFFERENCES IN NEUROANATOMICAL ASYMMETRIES: THE SPLENIUM

The splenium refers to the posterior region of the CC which contains fibers projecting between the main auditory and visual cortical areas of the two cerebral hemispheres. A sex difference was reported for both the shape and area of the splenium of adult and fetal

brains examined postmortem (de Lacoste and Holloway, 1982; de Lacoste et al., 1986; Holloway and de Lacoste, 1986). In a fetal sample, which ranged in development from 26 to 41 weeks of gestation, researchers observed greater splenial width in females compared with males as early as 26 weeks gestation, and this difference persisted throughout week 41 of gestation. In postnatal investigations (chronological age unreported), females again were reported to possess a greater splenial width compared with males, as well as a splenial shape which was described as being more 'bulbous' than that of males. Furthermore, females were reported to exhibit greater total CC area (both when sex differences in brainweight were corrected for as well as when they were not) in the adult sample (Holloway and de Lacoste, 1986). These observations led to the hypothesis that females exhibit a greater amount of connectivity between the auditory and visual cortices of the two cerebral hemispheres, and that this greater structural connectivity might explain why females are less functionally specialized than males on many neuropsychological (McGlone, 1980) and divided-field perceptual tasks (Voyer, 1996).

Attempts to replicate observations of the sex difference in human splenium size and area has produced inconsistent findings (Clarke et al., 1989a; Witelson, 1985). For example, in a postmortem fetal sample ranging in development from 20 to 42 weeks gestation, no sex difference was observed in the splenial width of females and males (Clarke et al., 1989a). These researchers also examined postmortem and magnetic resonance imaging (MRI) representations of CC shape and area in children and adults ranging in age from birth to 93 years. Among the postmortem infant sample (birth to 1.2 years of age), males exhibited a larger mean cross-sectional callosal area than females, however this sex difference was not observed in the fetal, child, or adult samples. Additionally, the adult postmortem sample of males exhibited a greater thickness in callosal size than females. Other research teams have also been unsuccessful in replicating the original findings of greater CC width and area in women compared with men, both in overall CC investigations as well as in regional investigation of the splenium (Byrne et al., 1988; Witelson, 1985).

Studies concerning sex differences in splenial shape, unlike area and size, have successfully replicated the initial findings of de Lacoste and Holloway (1982), indicating that measurements of shape may be more robust than area and size assessments when investigating morphological sex differences. For example, Clarke et al. (1989a) noted that the shape of the splenium in their adult postmortem sample was more bulbous in females compared with males, and that this dimorphism in shape was a result of the female brains containing a higher proportion of total CC area in the splenial region of this structure compared with males. A retrospective analysis on data collected from other labs was also carried out in an attempt to assess the reliability of reported sex differences in splenial shape (Clarke et al., 1989a). Several of these studies report the existence of a more bulbous splenium in female brains when the ratio of total CC area:splenial area is accounted for.

Although most research reports concerning sex differences in splenial shape agree that females on average possess a more bulbous splenium than males, the inconsistencies concerning dimorphism of splenial area and size persist in the literature. Why does such disagreement remain for these structural descriptors of the posterior CC?

Potential difficulties in obtaining area measures of the splenium, as discussed by Clarke et al. (1989b), could result from measuring technique (postmortem vs. MRI), small sample sizes, and identification of ventral CC boundaries (Gahr, 1997). Additionally, individual subject variables could influence the outcome of assessing splenial area. For example, individual variation in overall CC shape, chronological age, cranial volume, and handedness appear to act in a complex way with sex to influence splenial area. The following

discussion highlights the investigations of sexually-dimorphic area measures in the posterior CC when these subject variables are considered.

The majority of studies concerning splenial measurements have described the CC in terms of total length and maximal width of the fiber tract, but the quantification of total CC shape is rarely assessed. Davatzikos et al. (1996) recently reported a method that quantifies total CC shape from multiple MRI representations. These investigators noted that when total CC shape was assessed from multiple MRI scans as opposed to a single midsagittal representation, a sex difference in posterior CC cross-sectional area was observed which favored females. One can conclude from this finding that the initial reports of females possessing a larger posterior CC than males may be replicable when total shape of the callosum is determined with a method that accurately reflects the whole topography of this structure.

Another individual variable that appears to be important for detecting sexual dimorphism in splenial area is the age of subjects studied. Allen et al. (1991) measured splenial shape, area and size from MRI scans obtained from age-matched children and adults. Their findings indicate that maximal splenial width was larger in women compared with men, and that the bulbosity of the splenium was greater in women and girls compared with men and boys respectively. Additionally, CC morphology was noted to change with age, where increases in overall callosal size were correlated with advanced age in children of both sexes, and decreases in anterior CC size were correlated with advanced age in adults for both sexes. Interestingly, the rate of CC structural change (both increasing and decreasing) appears to be sexually dimorphic. Additionally, cortical association areas whose projections comprise a large portion of the CC are believed to be affected by structural reduction and atrophy with advanced age (Driesen and Raz, 1995). Finally, the extent of myelinization also decreases with age in adults (Ansari and Loch, 1975; Kirkpatrick and Hyman, 1987), and this reduction has been speculated to have an impact on CC structural dimensions (Driesen and Raz, 1995). Together, these findings suggest that if sex differences exist for CC measurements, then they are likely to be confounded by the complex interactions brought about by aging.

Many investigations of sexually-dimorphic areas comprising human brains take into account the sex difference in overall head size when determining sex differences in size of individual neural structures or nuclei. In postmortem brain samples, this is often accomplished by determining total brain weight, and subsequently making adjustments in measures of neuroanatomical interest according to the difference between male and female brain weights. On the other hand, MRI investigations often estimate head size by extrapolating from a single cross-sectional area measure. Recently, single-slice MRI estimations of head size were suggested to be insufficient to control for individual differences in cranial size, and total cranial volume was proposed necessary for imaging and postmortem investigations (Johnson et al., 1996). These authors suggest that cranial volume better accounts for sex differences in brain size compared with measures such as total body weight or single-slice area estimates of brain size. When overall cranial volume is determined, women are observed to have both a larger overall CC and splenium than men in studies that employ MRI techniques for obtaining this information (Johnson et al., 1996).

Finally, the individual variable of handedness appears to affect the splenium of the CC differently in men and women. In an MRI investigation of elderly men and women greater splenial area was positively correlated with increasing right-handedness in men, but no correlation between handedness and sex was found for women (Burke and Yeo, 1994).

When previous studies had considered handedness, this variable was often assessed only so far as to determine the hand with which a subject preferred to write. A better measure of handedness is to determine both the hand with which a manual activity is carried out, as well as the extent of dependency on the preferred hand for carrying out that activity (Oldfield, 1971). Handedness (when assessed for direction and magnitude) of a population under investigation might conceal sex differences in structural cortical asymmetry (Burke and Yeo, 1994).

The multitude of postmortem and MRI investigations concerning sex differences in the human splenium illustrate two main points. First, the posterior fifth of the CC is consistently reported to exhibit a sex difference in shape, with females possessing a more bulbous splenium compared with males. Second, reported sex differences in area measurements of the splenium indicate that females tend to exhibit greater area in this posterior region of the CC compared with males, but this sex difference can only be measured in a consistent fashion when the subject variables of total CC shape, chronological age, cerebral volume, and handedness are accounted for.

SEX DIFFERENCES IN HUMAN NEUROANATOMICAL ASYMMETRIES: THE ISTHMUS

Unlike investigations of the posterior callosum, study of the isthmal region of the CC has been more likely to reveal uncontested sex differences in measurements of midsagittal area. Functionally, the isthmus is the region of the CC through which fibers connecting the parietal and temporal lobes pass. MRI representations of isthmal cross-sectional area indicate that women exhibit more tissue area in this region of the CC compared with men (Steinmetz et al., 1992). Additionally, an interaction between sex and handedness has been reported for isthmus size in both postmortem (Witelson, 1989; Witelson and Goldsmith, 1991) and MRI investigations (Clarke and Zaidel, 1994; Habib et al., 1991). These studies show that the size of the isthmus is larger in nonconsistent right-handed (NCRH) men compared with consistent right-handed (CRH) men. In contrast, handedness does not appear to interact in any significant way with isthmal area in women. A principle components approach to investigating sex differences in MRI representations of the CC confirms this interaction between sex and handedness for isthmal width (Denenberg et al., 1991). This observation is of importance to the question of hormonal influences on cortical asymmetries because such findings indicate the potential existence for a sexually-dimorphic role of gonadal steroid hormones on the CC and corresponding functional lateralization.

Complementing reports of sex differences in shape and size of the isthmus and splenium of the corpus callosum, are reports of sex differences in fiber composition found within this structure as a whole. The number of fiber types comprising the CC was assessed from postmortem samples taken from adult men and women (Aboitz et al., 1992). No sex difference was reported for either the total number of fibers, or for the midsagittal area of, any region in this structure. A sex difference was observed however, for the callosal fibers measuring > 0.4 and $1.0 \mu\text{m}$ in the isthmus of the CC. These fibers were observed to be negatively correlated with the magnitude of Sylvian fissure asymmetries found in men but not those found in women. Conversely, fibers $> 0.4 \mu\text{m}$ in the anterior splenium were reported to be negatively correlated with Sylvian fissure asymmetries in females but not in males. This sex difference in the correlation between CC fiber type and magnitude of the Sylvian fissure is important because it illustrates the possibility for dimorphic patterns of

interhemispheric connectivity between specific cortical regions believed important for behaviors that demonstrate sex differences such as speech and language comprehension.

SEX DIFFERENCES IN NEUROANATOMICAL ASYMMETRIES: THE NEOCORTEX

In addition to the CC, cortical structures are sexually-dimorphic and may therefore be differentially affected by concentrations of sex steroid hormones. Such sex differences are indicative of the direction, or intrahemispheric pattern, of cerebral lateralization. For example, the planum temporale (PT), a brain area involved in higher-order language processing (Galaburda et al., 1978) and included in Wernicke's Area, has been shown through MRI investigation to be sexually dimorphic (Kulynych et al., 1994) in age-matched men and women considered to be right-handed. Specifically, the left PT is significantly larger than the right in men, while women do not exhibit this asymmetry in cortical organization. Furthermore, this imaging data is in agreement with an earlier postmortem study in which it was reported that women were more likely than men to possess a reverse pattern of PT asymmetry, where the right PT measured larger than the left (Wada et al., 1975). It has been speculated that this sex difference in structural asymmetry of the PT is correlated with observations of increased functional language lateralization in males compared with females (McGlone, 1980).

Postmortem studies indicate that the Sylvian fissure is also sexually dimorphic in structural dimensions. The horizontal segment of the Sylvian fissure (HSF) for the left hemisphere was reported to be larger in a consistently-right-handed (CRH) male post-mortem sample (handedness was measured prior to death) compared with other men and all women (Witelson and Kigar, 1992), while no association was observed between HSF anatomy and handedness in women. This sex difference remained significant when HSF was measured relative to brain weight. When asymmetry was assessed for the Sylvian fissure as a whole, and not limited to certain portions of this structure, men possessed greater absolute asymmetry than women in favor of the left hemisphere (Witelson and Kigar, 1992). Finally, an MRI investigation of 53 females (27 right-handed, 26 left-handed) and 51 males (25 right-handed, 26 left-handed) ranging in age from 18 to 49 years revealed that right-handed males and left-handed females possess greater parietal area in the left hemisphere compared with the right (Kertesz et al., 1990). Conversely, these researchers reported left-handed males and right-handed females exhibit structural symmetry of the parietal lobe.

In summary, structural differences of the CC and the neocortex are reported to exist between the sexes when subject variables such as age, handedness, and cranial volume are taken into account. Therefore, it is reasonable to speculate that sex steroid hormones may be influential in determining these morphological differences. When sex differences are reported for the CC, women tend to possess a larger splenium and isthmus than men. Interestingly, language lateralization, assessed by a consonant-vowel dichotic listening task, was found to be negatively correlated to splenial MRI measures (Hines et al., 1992). A negative correlation between language lateralization and splenial MRI measure is consistent with predictions based upon the hypothesis of de Lacoste and Holloway (1982) that a decrease in functional neural asymmetry is due to increased interhemispheric exchange via the CC.

Men possess a larger left planum temporale (PT) than women. CRH men possess a larger left HSF and parietal area than women, and men show greater absolute Sylvian fissure asymmetry in favor of the left hemisphere compared with women. Perhaps the greater morphological asymmetries for language areas observed in males contribute to their increased functional lateralization? Although neuroanatomical asymmetries provide substrates upon which gonadal hormones might act to result in sexually-dimorphic expressions of functional lateralization, it is not yet clear how this could happen.

SEX DIFFERENCES IN STRUCTURAL CORTICAL ASYMMETRIES IN NONHUMAN ANIMALS, AND CORRESPONDING EVIDENCE FOR THE INFLUENCE OF SEX STEROID HORMONES ON THESE ASYMMETRIES

Due to the correlational nature that is inherent to studies of sex differences in human structural brain lateralization, it is essential to look to the nonhuman animal literature for more direct evidence of hormonal influences underlying cortical asymmetries. Hemispheric specialization in nonhuman animals has been demonstrated across a variety of vertebrate species (Nottebohm, 1977; Sherman et al., 1980; Yeni-Komishan and Benson, 1976), and like human cortical asymmetries, these patterns of specialization appear to be sexually-dimorphic (Denenberg and Yutzy, 1985; Glick and Ross, 1981). As mentioned earlier, the nonhuman animal models presented here are valuable for two reasons. First, the presence of sex differences in cortical asymmetries across multiple vertebrate species indicates that a dimorphic pattern of hemispheric specialization might be advantageous to animals. Furthermore, because neural asymmetries are sexually-dimorphic, it is reasonable to postulate that the differences between males and females concerning hemispheric specialization could relay a reproductive advantage to individuals possessing these sexually-dimorphic traits (Andersson, 1994; Darwin, 1871). Second, nonhuman animal models have the increased ability to demonstrate a more direct role for sex steroid hormones in cortical asymmetries. The following section reviews findings of sex differences in both the fiber tracts connecting the cerebral cortices, as well as in neocortical structures in nonhuman animals.

EXAMPLES OF SEX DIFFERENCES IN NEUROANATOMICAL ASYMMETRIES IN NONHUMAN ANIMALS: THE CORPUS CALLOSUM

In a study by Berrebi et al. (1988), the influence of sex and experience on CC size in mice was investigated. The genu, body, and splenium of the CC were studied in both a region-specific manner, as well as in the entire CC structure. Young mice (110 days of age) exhibited a sex difference with males possessing greater total CC area compared with females both when differences in brain weight were, and were not, taken into account. For older mice (215 days of age), this sex difference disappeared after corrections regarding brain weight were carried out. The same pattern of results (male measurements exceeding female measurements in younger but not older animals when sex differences in brain weight were accounted for) was reported for CC regional width. An interaction between sex and handling was noted in the younger animals such that CC area and regional width were greatest for the males handled during infancy, and smallest for the young females who received the same treatment. This interaction of sex and handling during infancy was

not observed in the older animals studied, again indicating the dynamic role of chronological age in CC morphology (although body weight cannot be eliminated as an important factor because older animals are also heavier). These findings have led the authors to suggest that “early experience differentially affected the growth rate of the callosal width dimension in the two sexes” (Berrebi et al., 1988).

Complementing the above-mentioned gross measures of sex differences in callosal width and area are observations of sex differences in the ultrastructure of the rat CC (Juraska and Kopcik, 1988). Young (55 days of age) and old (113 days of age) male and female rats reared in either enriched or isolated environments were investigated for sex differences in both gross and ultrastructural investigations of the splenium. No gross morphological differences were observed between males and females reared in similar environments for either age group, however ultrastructural composition of the CC did differ significantly between the sexes. Electron microscopy revealed that in young rats, females possessed more unmyelinated fibers in the splenium compared with males, and environmental conditions affected the number of myelinated fibers found in females (enriched females > impoverished females), but this was not the case for males. Greater axon number can indicate, among other things, a larger distribution of projection neurons crossing the CC. In an attempt to determine if this greater number of fibers found in the female rat splenium is indeed the result of greater distributions of projection neurons, horseradish peroxidase (HRP) was injected into the primary visual cortex of young male and female rats raised in enriched environments (Kopcik et al., 1992). No sex differences were detected in the number of splenial projection neurons originating from visual areas 17 and 18a/b. It was noted, however, that male rats exhibit greater axonal diameter of their unmyelinated splenial fibers compared with females, and environmental condition of rearing influenced this characteristic of the splenium in males, but not in females (enriched males > impoverished males) (Juraska and Kopcik, 1988).

Fiber number, type, and commissural area were quantified in an axon electron microscopic ($n = 9$; three females and six males) investigation and a glial immunocytochemical investigation ($n = 6$; two females and four males) in female and male adult rhesus monkeys (Lamantia and Rakic, 1990). It was noted that females showed greater overall cross-sectional area of the CC compared with males, while males possessed on average 10 million more callosal axons than females. These authors note, however, that in addition to having a small sample size the individual variables such as body size and chronological age were not controlled for. The human literature illustrates the importance of such variables on CC structure, thereby making interpretations of reported sex differences measured in the rhesus CC difficult.

Researchers examining the structure–function relationship between CC morphology and behavioral lateralization investigated the relationship between lines of mice selectively bred for varying degrees of functional asymmetry (assessed by paw preference), size of forebrain commissures (anterior commissure and CC), and extent of myelination of the callosum (Cassells et al., 1990). Although no sex difference was observed for paw preference, area of commissures, or myelination of the CC in this particular study, an interesting observation was noted for the highly lateralized line of mice (HI). The HI animals exhibited greater behavioral lateralization, greater brain size, and greater cross-sectional area of both the CC and anterior commissure in both sexes compared with the weakly-lateralized mice (LO). When the larger brain measure in the HI line of animals was accounted for, however, the proportional CC area was actually less than that observed in the weakly lateralized (LO) lines of mice, a finding that is in agreement with de Lacoste

and Holloway's theory for humans which states that increased interhemispheric transfer is associated with decreased functional asymmetry of the cortex. A similar study also reported both strongly and weakly-lateralized strains of mice to possess a smaller CC, as assessed by cross-sectional area, compared with control mice (Ward and Collins, 1985). This finding introduces the possibility that a larger CC does not necessarily correspond with greater or lesser functional asymmetry.

SEX DIFFERENCES IN NEUROANATOMICAL ASYMMETRIES IN NONHUMAN ANIMALS: EVIDENCE FOR THE INFLUENCE OF SEX STEROID HORMONES ON THE CORTEX

The cerebral cortex in male Long-Evans rats is thicker in the right hemisphere compared with the left (Diamond et al., 1975), and the reverse pattern of structural lateralization occurs more often in females. Asymmetric patterns of cortical thickness can be measured at birth in Long-Evans rats and in aged rats this characteristic disappears (Diamond et al., 1983). Asymmetry, as it pertains to cortical thickness, is not specific to Long-Evans rats, but can be generalized to other rat strains (Sherman and Galaburda, 1985; Stewart and Kolb, 1988), as well as to other species (Kolb et al., 1982).

A great deal of evidence has accumulated that indicates gonadal hormones are important factors that influence asymmetric patterns of cortical thickness (Lewis and Diamond, 1995). For example, female Long-Evans rats ovariectomized at birth results in a masculine pattern of cortical asymmetry in individuals, so that the right hemisphere is significantly thicker than the left (Diamond et al., 1981). Furthermore, males of this strain exhibit a shift in structural asymmetry that is female-typical when rat pups are castrated at birth (Diamond et al., 1979). The remaining question then, is which sex steroid hormones (if any) are responsible for sexual dimorphism of cortical thickness, and through what mechanisms do these chemicals act?

Prenatal stress lowers circulating testosterone levels in male rat pups (Ward and Weisz, 1980), and also alters cortical asymmetry (Fleming et al., 1986). This evidence, in conjunction with the finding that early castration of males leads to female-typical patterns of cortical thickness, implies that testosterone is a likely factor for influencing structural cortical asymmetries in rats. Androgen receptors have not been detected in the prenatal brains of rats however, making it difficult to propose a mechanism for the direct action of testosterone for affecting cortical lateralization (Lewis and Diamond, 1995).

Estrogen, like testosterone, is a sex steroid hormone that may potentially influence the structural asymmetry of the cortex in a sexually-dimorphic manner. In adult, female Long-Evans rats, ovariectomy leads to increased cortical thickness in Brodman's Area 4 while exogenous administration of estrogen to gonadectomized females results in decreased cortical thickness in this region (Pappas et al., 1978, 1979). Importantly, estrogen receptors have been shown to exist in the cortex of a variety of vertebrates species both pre- and post-natally (McEwen, 1981), indicating that this hormone-receptor system is capable of functioning early in development. However, alpha-fetoprotein (AFP) is also detected in the rat neocortex perinatally, which suggests that AFP probably binds to, and thus inactivates, the majority of estrogen found in the neonatal brain of rats (Soloff et al., 1972). In summary, testosterone and estrogen are both present in prenatal rat cortex. While estrogen is believed to be inactivated by AFP, the androgen receptors needed for the direct action of testosterone are not present in the cortex at points in development when cortical asymmetry is already known to exist.

The above-mentioned dilemma has led Diamond and her colleagues to implicate the process of aromatization (for a discussion of both aromatization and AFP protection refer to MacLusky and Naftolin (1981)) as the underlying hormonal mechanism associated with sexually-dimorphic patterns of cortical thickness in rats. The enzyme aromatase, which is necessary to convert testosterone to estrogen, has not been detected in the neocortex of rats (MacLusky et al., 1985), but has been detected in the diencephalon (Roselli et al., 1997). This enzyme has been detected, however, in the cortex of other mammalian species (Negri-Cesi et al., 1989; Roselli and Resko, 1986) using more sensitive measures than those carried out in experiments with rats (Lewis and Diamond, 1995).

Studies of sexually-dimorphic neonatal tail bias support Diamond's hypothesis that testosterone is an influential factor in determining neural asymmetries. Analogous to handedness in humans, neonatal tail posture appears to be a stable postural characteristic within populations of animals, and it appears to be sexually-dimorphic just as left-handedness is more typical in boys and men in human populations. Specifically, female newborn rats were noted to be right-ward biased, while male neonatal tail posture was left-ward biased (Ross et al., 1981). In a follow-up investigation, pregnant rats were injected with testosterone propionate (TP) which can be aromatized to estrogen, dihydrotestosterone propionate (DHTP) which cannot be aromatized to estrogen, or oil control (Rosen et al., 1984). Both the DHTP and oil treatments did not significantly affect tail posture in female pups, however the TP treatment significantly shifted the female bias toward a male-typical, right-ward tail position. Similarly, paw preference for food reaching is right-ward biased in cats (Tan and Kutlu, 1991). This paw preference can be reduced in female cats with intramuscular injections of TP (Tan et al., 1991). These results illustrate that Diamond's hypothesis for the importance of testosterone in influencing neural asymmetries is not limited to morphological lateralized, but can be extended to behavioral asymmetries as well.

In primates, unlike rodents, it is believed that aromatization may not be necessary for masculinization of sexually-dimorphic brain areas such as the hypothalamus. Instead, it is possible that testosterone acts directly upon androgen receptors for neural masculinization to occur (Wallen, 1997). Androgen receptors have been noted to exist in prenatal rhesus monkey cortex, and perhaps more importantly, the expression of these receptors is asymmetric between the two hemispheres in males but not females (Sholl and Kim, 1990). If androgen does influence sex differences in cortical thickness in primates, the asymmetric expression of receptors upon which this hormone acts could partially explain how this dimorphism occurs.

In summary, the work of Diamond and colleagues indicates that a great deal of indirect evidence exists for the proposal that sex steroids influence structural cerebral asymmetry in rodents, and that the mechanisms underlying these influences likely include the conversion of testosterone to estrogen via the biochemical process of aromatization. Although a direct demonstration of these processes has not been carried out, investigations of asymmetries in cortical thickness and neonatal tail posture offers some of the most compelling evidence in favor of a theory that includes sex steroid hormone influences, particularly testosterone, on structural cortical asymmetries and corresponding behavioral traits.

Measurements of sexually-dimorphic neuroanatomical asymmetries discussed here, though consistently obtained when appropriate controls are initiated, do not provide a

simplistic description of how the sexes differ in terms of lateralized cortical morphology. On the one hand, the primate data fit well with the hypothesis of Levy (1974) that males exhibit an increased magnitude of neural asymmetries (Levy was specifically referring to functional cerebral lateralization) compared with females. The commissural and neocortical findings in primate studies provide a working anatomical framework upon which to apply Levy's behavioral theory; because the larger CC exhibited by females and the greater discrepancy between left and right cortical language areas in males have been interpreted as providing an anatomical substrate for greater interhemispheric transfer of information and increased intrahemispheric specialization respectively (Zaidel et al., 1995). However, studies of rodent species do not correspond as well with Levy's theory of increased neural asymmetries in males compared with females. Although male rodents exhibit a greater discrepancy in cortical thickness between the two hemispheres than females (an analogous situation to the planum temporale and Sylvian fissure asymmetries found in humans), the pattern of sex differences observed in the commissures of various rodent species contradicts Levy's predictions. For example, male mice actually exhibit larger regional and total callosal measures than females. If Levy is correct in her theory, then either: (a) Levy's hypothesis only applies to the primate species of animals investigated thus far; (b) neural substrates other than the CC underlie the interhemispheric transfer of information; (c) other mechanisms such as the increased intrahemispheric specialization in males, as evidenced by the male-typical asymmetry of cortical thickness, are responsible for sexually-dimorphic patterns of hemispheric specialization in rodents.

SEX DIFFERENCES IN NEUROPHYSIOLOGICAL ASYMMETRIES OBSERVED IN HUMANS

Complementing the findings of morphological sex differences in neocortical and commissural structures that comprise male and female brains, are reports of sex differences in neurophysiological measures of asymmetries including electroencephalography (EEG), positron emission tomography (PET), and functional magnetic resonance imaging (fMRI). Unlike the previous section of this paper that emphasized brain structure and the relationship between neuroanatomical structures and brain functions; the second section focuses on neurophysiology to understand how these neuroanatomical structures work (Cacioppo and Tassinari, 1990). The neurophysiological level of analysis is important because it can potentially uncover asymmetries that are not obvious at the gross anatomical level. "Asymmetry may not come about by either induction or selection, but rather symmetry and asymmetry may result simply from differences in allocation or storage of an anatomical substrate that does not vary in size (at least not with respect to asymmetry), whereby in asymmetrical cases the allocation is unequal and in symmetrical cases equal between the hemispheres" (Galaburda et al., 1990).

The technology for visualizing information processing abilities of brains at the level of neurophysiology is extremely important for understanding how sex differences in brain morphology lead to sexual dimorphism in neural function. "Rapid technical advances in brain-imaging devices such as positron emission tomography (PET), functional magnetic resonance imaging, EEG and EMG have increased the capabilities for visualizing the working brain, and uncovering the cerebral areas participating in the realization of cognitive tasks" (Sergent, 1994).

SEX DIFFERENCES IN NEUROPHYSIOLOGICAL ASYMMETRIES: EEG MEASURES

The activation of a cerebral hemisphere during cognitive processing can be assessed through EEG patterns by determining which alpha rhythm is suppressed during specific types of information processing (Galin and Ornstein, 1972; Morrell and Salamy, 1971). Of interest here is that suppression of the alpha rhythm during both baseline activity and tasks correlated with functional cortical lateralization in humans appears to differ between men and women (Butler, 1984).

Sex differences have been observed for baseline patterns of alpha activation in humans (Ray et al., 1976; Rebert and Mahoney, 1978). In these studies, men and women were instructed not to carry out any specific cognitive functioning. Resulting baseline EEG activation was expressed in these subjects with females exhibiting increased alpha activity in the left hemisphere compared with males during a relaxed state. These findings indicate that different patterns of electrophysiological cerebral activation occurs, during relaxation at least, between women and men. Resting state measures can be problematic, however, because experimenters cannot easily control for cognitive functioning in subjects during this type of test session. It is likely that these subjects are carrying out some type of mental activity, but it is impossible to know what specifically is occurring. Therefore, it may be more informative to investigate cortical EEG asymmetries under circumstances in which subjects are given more explicit instructions concerning their mental activity.

In an effort to extend the findings of sex differences in cortical alpha activation during resting state, EEG measures are often obtained during verbal (left hemisphere) and visuospatial (right hemisphere) perceptual and cognitive tasks. For instance, alpha rhythm from the temporal regions of both hemispheres was assessed during tasks which were right- or left hemisphere biased in six right-handed female and male subjects (Ray et al., 1976). A significant difference was observed between the left and right EEG pattern in men during verbal mathematical tasks (left hemisphere) compared with right hemisphere tasks such as listening to music or visualizing scenes. No difference in alpha asymmetry was observed for female subjects during these same left- and right-biased tasks. Additionally, greater alpha suppression was observed in the right hemispheres of males compared with females during visualization and music information processing tasks, and in the left hemisphere during verbal and arithmetic processing.

An investigation of EEG asymmetry during spatial information processing in both high-spatial-ability and low-spatial-ability males and females illustrates that lateralization of alpha deactivation during object visualization tasks interacts with the subject variables of sex and ability level (Trotman and Hammond, 1979). Fourteen female and 14 male subjects (handedness not reported) were divided into two groups (high and low spatial ability) based upon performance on an object visualization survey. Alpha asymmetry was computed for these subjects by computing $(\text{right} - \text{left})/(\text{right} + \text{left})$ scores. Better performance on the object visualization survey was simultaneously correlated with increased right and decreased left hemisphere activation in males but not females. Furthermore, low-spatial-ability males and all females exhibited less right hemisphere and more left hemisphere activation (alpha deactivation) compared with high-spatial-ability males during object visualization.

In addition to indicating which hemisphere is actively participating in various types of mental functioning, EEG recordings can indicate when multiple processing strategies are employed by subjects (Galin et al., 1978). For example, Earle and Pickus (1982) investi-

gated alpha power over left and right parietal regions when subjects were either at rest, or during performance on mental arithmetic tasks that spanned various levels of difficulty. Alpha asymmetry between the right- and left hemispheres occurred in men when task difficulty was high and in women when task difficulty was low, illustrating a sexually-dimorphic interaction of cognitive load and alpha wave lateralization.

In common with the neuroanatomical asymmetries described previously, EEG asymmetries appear to be influenced by the interaction between sex and handedness (Butler, 1984). For example, right-handed individuals exhibited EEG asymmetries (greater left hemisphere activation) during writing and block design in parietal and central regions (Galin et al., 1982). This effect was not obtained in left-handed subjects. Sexual dimorphism was noted in that there was an interaction between sex and handedness. Specifically, left hemisphere alpha suppression was predominantly measured in left-handed women during a writing (left hemisphere) task.

For cortical lateralization, sinistrality (having left-handed relatives) also clearly interacts with sex. Patterns of lateralization appear to differ between right-handed subjects who do and do not report sinistrality in their families (Butler et al., 1982). Males reporting no family sinistrality expressed the greatest left hemisphere activation during arithmetic (left hemisphere) processing, while increased right hemisphere activity was observed in males with left-handed relatives on a face recognition task (right hemisphere processing). In contrast, women with no left-handed family members showed increased left hemisphere activation for both arithmetic and face processing.

Like the neuroanatomical findings, the EEG studies reported here indicate that sexual dimorphism exists for cortical asymmetry in humans. Typically, males exhibit a greater discrepancy between alpha wave suppression of the two cerebral hemispheres during cognitive tasks that require greater participation of either the left or right cortex. This pattern of sexual dimorphism is not simple, however. Variables such as ability level, cognitive strategy, and handedness interact in significant ways with sex to determine patterns of electrophysiological lateralization.

SEX DIFFERENCES IN NEUROPHYSIOLOGICAL ASYMMETRIES: PET MEASURES

Positron emission tomography (PET) is a technique used for measuring cerebral blood flow through the method of injecting a radioactive tracer into subjects, and subsequently observing metabolic emission patterns of positrons from this tracer at various neuroanatomical locations. PET has proven to be a successful technique for measuring cerebral blood flow patterns associated with hemispheric specialization when the processing of visual and verbal information is required. Consequently, a consideration of PET findings regarding sex differences in cerebral lateralization is appropriate.

Correlational analysis of PET data collected during a resting, wakeful state suggests that men and women differ on a metabolic brain asymmetry index (Azari et al., 1992). An asymmetry index was defined as the difference between a subject's absolute metabolic rate in both hemispheres, divided by the average metabolic rate in either the left- or right hemisphere. No sexual dimorphism was observed for brain metabolism of both hemispheres when considered in combination, but correlational analyses revealed that the pattern of metabolic correlations observed in the brains of women differed from those of men. Specifically, women had more inter-hemispheric than intra-hemispheric metabolic

correlations, and women also displayed more left- than right hemisphere intra-hemispheric correlations. Conversely, men had more intra-hemispheric than inter-hemispheric metabolic correlations, and men exhibited more right- than left hemisphere intra-hemispheric correlations. These findings are in agreement with observations obtained from other physiological, anatomical and behavioral measurements in which females show a lesser degree of cortical asymmetry between the two cerebral hemispheres, and males are typically right hemisphere dominant while the female pattern of dominance is characterized by the left hemisphere.

A second PET study that assessed sex differences in resting state cerebral blood flow patterns (Gur et al., 1995) also found no dimorphism for overall brain metabolism. Inspection of specific brain regions resulted in men and women expressing different laterality indices in the orbito-frontal areas, the posterior cingulate, and posterior CC. In all of these regions women had greater left hemisphere metabolism than men. Again, this finding is consistent with the sexually-dimorphic model for cortical asymmetry first noted in early clinical and behavioral studies (McGlone, 1980).

SEX DIFFERENCES IN NEUROPHYSIOLOGICAL ASYMMETRIES: FUNCTIONAL MAGNETIC RESONANCE IMAGING

MRI is a brain imaging technique that clearly provides an observer the ability to distinguish between gray and white cortical tissue. A number of MRI findings were considered earlier when the literature on morphological sex differences in cortical asymmetries was reviewed. fMRI is similar to MRI, except that fMRI has the advantage of imaging neural tissue during cognitive processing. This technique of visualizing the working brain is extremely valuable because it provides the possibility for better understanding the structure–function relationships in a complex, dynamic neural system. Shaywitz et al. (1995) employed the method of fMRI in their investigation of sex differences in cortical asymmetries. In this study, subjects were instructed to complete three verbal processing tasks (orthographic, phonologic and semantic processing), each analyzed for distinct component processes comprising verbal ability. During phonological processing, brain activation was observed to be lateralized to the left inferior frontal gyrus in males, while in females the activation occurred in this region in both hemispheres. Overall, EEG, PET and fMRI studies reveal a similar pattern of findings despite their different procedures for exploring human brain functioning at the physiological level. As in the anatomical investigations, women tend to show more diffuse patterns of physiological activation in both hemispheres for a variety of information processing tasks, and men typically show more physiological asymmetry between the left and right cortices when completing cognitive tasks. Specifically, women tend to express a decreased magnitude of inter-hemispheric cortical lateralization compared with men. Furthermore, intra-hemispheric differences in cortical lateralization exist between the sexes, with females exhibiting greater left hemisphere dominance and males increased right hemisphere reliance.

EVIDENCE FOR SEX STEROID INFLUENCES ON FUNCTIONAL ASYMMETRIES IN HUMANS

When reviewing the human functional literature with the intent of identifying pre-

dictable patterns between hormone exposure and cortical asymmetries, it becomes obvious that some studies are interested in organizational influences of sex steroid hormones while others focus on the activational effects of these substances. Briefly, organizational actions of hormones are those that influence the neural development that underlies a behavior, and the activational actions of hormones are those that influence the pre-existing neural circuits (Phoenix et al., 1959). The human literature presented here considers both organizational and activational actions of sex steroid hormones on behavioral asymmetries. In general, investigations of prenatal hormone exposure address the issue of organizing principles, and studies concerning fluctuations in sex steroid hormone levels later in development (usually beginning at puberty and extending to older age) focus on activational effects.

ORGANIZATIONAL ACTIONS OF SEX STEROID HORMONES ON FUNCTIONAL ASYMMETRIES

In an investigation concerning prenatal androgen exposure in girls and boys, and their subsequent behavioral asymmetry at age 10, a correlation was identified between blood testosterone concentration and functional lateralization (Grimshaw et al., 1995). Fetal testosterone exposure was measured from amniotic fluid sampled during the second trimester of gestation (measures ranged from 14 to 20 gestational weeks), and behavioral asymmetries were assessed with a handedness questionnaire, a left hemisphere biased dichotic listening task for pairs of rhyming words, and a right hemisphere biased Emotional Words Test. Prenatal testosterone concentrations were related to both handedness and performance on the dichotic rhyming words task. Higher testosterone concentrations correlated with stronger measures of right handedness and left hemisphere dominance for processing dichotically-presented rhyme pairs. For boys, prenatal testosterone concentrations related to their performance on the Emotional Words Test, such that boys with higher testosterone concentrations were more strongly lateralized for performance on this task (greater right hemisphere performance). These authors note that for their populations of boys and girls studied, increased testosterone concentrations were associated with greater degrees of functional lateralization in the direction of the pre-established sex bias associated with the tasks employed.

Diethylstilbesterol (DES) is a synthetic form of estrogen that was once commonly prescribed to pregnant women for the purpose of pregnancy maintenance in situations where potential miscarriages were a concern. DES has masculinizing and/or defeminizing effects on neural and subsequent behavioral development in nonhuman species (Hines and Gorski, 1985). For this reason, DES-exposed males and females provide a valuable opportunity for investigating possible influences of a synthetic estrogen on hemispheric specialization.

In a study of cognitive abilities and functional asymmetry in DES-exposed women and their unexposed sisters, the influence of DES on verbal, visuospatial and dichotic listening tasks was investigated (Hines and Shipley, 1984). Subjects for this study included 25 right-handed women exposed to DES for at least 5 months prenatally (with 3 of those months occurring during the second trimester when human sexual differentiation is believed to occur), and their unexposed sisters who served as controls. Five months exposure to DES in utero was chosen as a criterion by these authors to ensure that DES

could act during critical periods of human neural development. No differences were detected between the DES women and the control women on either the Word Fluency or Spatial Relations sections of the Primary Mental Abilities Tests. A difference between DES and control groups was detected in performance on a dichotic listening procedure that employed consonant–vowel syllables as stimuli. Specifically, DES-exposed women exhibited a stronger negative correlation between left-ear (right hemisphere) performance and right ear (left hemisphere) performance compared with controls. Additionally, DES-exposed women produced increased right-ear (left hemisphere) scores compared with controls, but the two groups did not differ for their left-ear (right hemisphere) scores. These results suggest that like men, DES-exposed women exhibit an increased degree of functional asymmetry for processing verbal information compared with normal unexposed women.

A second investigation of DES effects on neural asymmetries studied DES-exposed males and their unexposed brothers (Reinisch and Sanders, 1992). Ten boys exposed to DES in utero for at least 1 month during the first or second trimester of pregnancy comprised the experimental group for this study. Age of testing for both DES-exposed boys and controls ranged from preadolescence to young adulthood. All subjects were tested with the Witelson Dichhaptic Shapes Test (Witelson, 1976) to assess functional lateralization for spatial information processing, and the Wechsler Intelligence Scales. All ten of the DES-exposed boys were considered to be right-handed based on the Harris Test of Lateral Dominance, compared with the unexposed controls that included three left-handers and seven right-handers. Although limited by the small sample size, the increased occurrence of right-handedness in the DES-exposed boys is female-typical for human populations. Performance on the Witelson Dichhaptic Shapes Test resulted in DES boys exhibiting decreased functional lateralization compared with their control brothers. Twenty per cent of the DES boys could be classified as showing lateralized responses on this task compared with 80% of the controls. Therefore, these results indicate that prenatal DES exposure results in decreased functional lateralization in boys compared with their unexposed brothers.

The results from these two DES investigations seem at first to be contradictory. For females, prenatal DES exposure appears to influence neural asymmetry by increasing functional lateralization, while the same treatment appears to result in decreased functional lateralization in males. What then is the role of DES, if any, for influencing functional asymmetry in humans? First, it is important to realize the methodological differences between these two studies when attempting to understand the different outcomes of the female and male experimental groups. In the Hines and Shipley (1984) study, functional lateralization was assessed for verbal information processing, while Reinisch and Sanders (1992) measured functional specialization for spatial information processing. It is possible that DES could influence hemispheric specialization of the left and right hemispheres independently, so that behavioral measures from each are qualitatively different despite similar estrogenic treatment. Second, it is not clear that the two experimental groups for these studies are actually as similar as they may first appear. For example, the DES-exposed women may have been exposed to other hormonal treatments in utero in addition to the DES treatment, while the men exposed to DES were specifically chosen because it was documented that they were not exposed to any other hormones prenatally (Reinisch and Sanders, 1992). Third, both the time and extent of gestational exposure to DES differed between the DES females and DES males. The DES women were exposed to the synthetic estrogen for at least 5 months which included the second

trimester, while the DES men were exposed during either the first or second trimester in utero, and the extent of exposure in this group ranged from 5 to 14 weeks. Fourth, the average dosage prescribed to the mothers of the DES women was not reported. This could have differed significantly from Reinsch and Sanders' study in which the average total dosage prescribed was 2440 mg. Finally, despite the methodological differences between these two investigations, the opposite patterns of functional lateralization observed is actually in agreement with studies of nonhuman animals in which sex steroid treatment both masculinizes females and demasculinizes males (Diamond et al., 1973).

Clinical conditions in which humans are exposed pre- and perinatally to endogenous sex steroid hormones provide additional opportunities to evaluate hormonal influences on neural asymmetries aside from laboratory observations. Traditionally, three such conditions have been studied in terms of functional lateralization. These are congenital adrenal hyperplasia (CAH), Turner Syndrome (TS), and Klinefelter Syndrome. CAH is a condition that occurs in both males and females, and it can be characterized by abnormal concentrations of circulating adrenocorticotrophic hormones and sex steroid hormones. Due to abnormal production of adrenal and gonadal products in CAH babies, afflicted boys and girls are exposed to an atypical hormonal milieu prenatally and postnatally, or until treatment with cortisol is initiated. Turner Syndrome is a genetic condition that affects females only. TS women possess only one normal X chromosome as opposed to the normal female occurrence of two, and these individuals are thus karyotyped as 45,X females (as opposed to normal women who are characterized as 46,XX). TS women are unable to produce sufficient amounts of gonadal hormones because fully-functioning ovaries are usually replaced by gonadal streaks in these individuals. As a result, TS girls are exposed to an atypical hormonal milieu (in this case an almost complete absence of ovarian steroid exposure) until they receive estrogens and/or progestins at late adolescence to induce pubertal maturation. Paralleling TS is Klinefelter Syndrome, which is a genetic condition found exclusively in males. Klinefelter males are karyotyped as 46,XXY, and this condition is characterized in part by small testes, gynaecomastia, and low levels of testicular hormone production compared with normal 46,XY males. Klinefelter males, due to their lowered testicular androgen production, are also subject to an abnormal hormonal environment pre- and postnatally (for an excellent overview of CAH, Turner Syndrome, and Klinefelter Syndrome see Migeon et al. (1994)).

Functional cerebral lateralization was assessed with a handedness questionnaire, a finger tapping test, and a dichotic consonant–vowel listening task in 22 CAH adult women and 22 age-matched controls (Helleday et al., 1994). The CAH subjects were chosen for this study through medical charts which confirmed prenatal virilization in these women by either an enlarged clitoris noted at birth or labial fusion. Contrary to the authors' hypothesis that prenatal virilization of genitalia would be correlated with masculinized patterns of functional asymmetry; neither handedness, motor-speed, manual dexterity, nor functional lateralization for consonant–vowel processing differed between the CAH women and control women. Perhaps the sample size may have been too small to detect a difference in functional lateralization between the experimental and control groups in this study (Helleday et al., 1994). Furthermore, the tasks used to determine individual patterns of asymmetry may not have been the most appropriate. For instance, prenatal androgen exposure may influence functional lateralization for spatial but not for verbal information processing. Additionally, the consonant–vowel dichotic listening task employed by these researchers does not always detect the sex difference for language lateralization that

typically exists between females and males (Bryden, 1988), and may therefore be an inappropriate measure for sex steroid influences on functional asymmetry in CAH women.

A handful of studies concerning functional lateralization in TS girls and women illustrate that these individuals possess a pattern of cortical asymmetry that deviates from that which is typically associated with females (Netley, 1977; Waber, 1977). For example, a dichotic listening investigation of 35 age-matched TS girls and normal 46,XX females of comparable verbal IQ, revealed that lateralization differed significantly between these two populations. Normal 46,XX subjects presented with a dichotic test involving the identification of digit triads showed the expected right ear (left hemisphere) advantage, while TS females were both less likely to exhibit a right ear advantage, and more likely to exhibit the reverse pattern of specialization, independent of overall accuracy rate. Netley and Rovet (1982) measured functional hemispheric specialization in 35 TS girls and women as well as in 35 46,XX females matched for age and verbal IQ. Again, a dichotic listening procedure was employed in this study to determine functional lateralization of the cerebral cortex. TS subjects were more likely than controls to exhibit a strong left ear/right hemisphere advantage for digit triads. Finally, a study that incorporated dichotic listening tasks for both digit triads and words illustrates that TS females performed differently than normal women on a measure of behavioral lateralization (Gordon and Galatzer, 1980). Specifically, TS subjects failed to show a right ear/left hemisphere advantage for processing dichotically-presented words, while control females exhibited a strong left hemisphere specialization on this task.

Klinefelter boys were tested with a battery of lateralization tasks composed of both auditory and visual information believed to be preferentially processed by either the left or right hemispheres (Netley, 1988; Netley and Rovet, 1984). Compared with age-matched normal controls, Klinefelter subjects exhibited a stronger right hemisphere involvement for processing visually-presented verbal information (a predominantly left hemisphere task). Klinefelter boys also exhibited a greater right hemisphere bias for processing auditorally-presented melodies and visually-presented dot displays (both right hemisphere tasks) compared with controls. These results indicate that Klinefelter males exhibit decreased functional lateralization for some forms of verbal processing, and increased functional asymmetry for some forms of right hemisphere information processing.

What information then, if any, do the existing clinical studies offer in terms of sex steroid hormone effects on patterns of functional cortical lateralization? There is no evidence at this point that CAH girls and women possess a masculinized pattern of cortical asymmetry to coincide with their genital virilization. In addition to the methodological flaws of the CAH study mentioned above, it is interesting to wonder if adrenal androgens are not sufficient for masculinizing the cortex, and perhaps such an effect can only result from androgens of testicular origin. And the TS and Klinefelter studies? Again, they are limited in number and by methodological errors, as well as by the fact that individuals with abnormal genotypes often possess lowered intelligence which makes it difficult to compare them with normals on behavioral abilities. However, TS and Klinefelter patients do tend to exhibit atypical patterns of performance on dichotic listening tasks and tachistoscopic tasks. It is difficult to assess if the TS and Klinefelter results indicate masculinized/defeminized and feminized/demasculinized performance respectively. What can be said is that TS and Klinefelter populations exhibit atypical functional lateralization when compared with same sex, chromosomally-intact controls. Hypotheses pertaining to the role that lowered sex steroid hormone concentrations associated with these syndromes may have can and should be developed, but much testing and theoretical conceptualization is needed.

ACTIVATIONAL ACTIONS OF SEX STEROID HORMONES ON FUNCTIONAL ASYMMETRIES

An investigation of right- and left hemisphere functional lateralization in boys and girls ranging in age from 6 to 13 years, indicates that boys are more functionally asymmetric than girls when carrying out the Witelson dichaptic shapes task (a predominantly right hemisphere task), but no sex difference is evident for performance on a verbal (left hemisphere) dichotic listening task (Witelson, 1976). Waber (1977) hypothesized that this pattern of sexually-dimorphic behavioral lateralization is influenced not so much by the sex of the individual, but by the rate of physical maturation leading to pubertal development in boys and girls.

Waber's hypothesis is dependent upon the belief that early- and late-maturing adolescents exhibit different profiles of endogenous sex steroid hormones. According to Waber, the fact that females typically undergo pubertal development earlier than males might be part of the reason for sex differences in neural asymmetries. Specifically, she suggests that early pubertal maturation is correlated with symmetrical patterns of cortical asymmetry (the female-typical pattern), while late pubertal maturers exhibit patterns of greater asymmetry (the male-typical pattern) regardless of sex. In the Waber (1977) study a verbal dichotic listening task was employed to measure hemispheric specialization. Late maturing males and females (assessed by height/weight increases and the development of secondary sex characteristics) exhibited a greater degree of lateralization on the dichotic listening procedure than early pubertal maturers in favor of the right ear/left hemisphere confirming Waber's prediction.

A second study concerned with pubertal maturation rate and functional lateralization (Waber et al., 1985) longitudinally followed extremely early- and late-maturing adolescents, and assessed the performance of these individuals on a phoneme and word dichotic listening task. Results indicated that performance for phoneme dichotic listening was improved in the early-maturing group of boys and girls compared with late-maturers. Additionally, early-maturers were more likely to make fusion errors when mistakes were made in phoneme processing, suggesting that this group was superior at lateralized verbal information processing.

Another examination of maturational effects on both left- and right hemisphere dominant tasks was carried out on a group of early- and late-maturing children both before and after puberty (Vrbancic and Mosley, 1988). A consonant-vowel dichotic task, a simple square-wave tone dichotic task, and a complex square-wave tone dichotic task were used because previous work had focused primarily on left hemisphere processing by employing verbal lateralization tasks only. Contrary to the prediction of Waber (1977), these results indicate that late maturers were not more lateralized regarding consonant-vowel processing. However, late-maturers exhibited an increase in their magnitude of right hemisphere preference for tones when examined prepubertally, and early-maturers exhibited increased right hemisphere performance for tone processing after the onset of puberty (but for an opposite pattern of results with a different behavioral measure see Newcombe and Bandura (1983)). The inability of Vrbancic and Mosley (1988) to replicate Waber's result of increased lateralization in late-maturing adolescents complements the finding of Meyer-Bahlburg et al. (1985) that females who had undergone idiopathic precocious puberty (a condition in which individuals undergo pubertal maturation at extremely young ages, for unknown etiological reasons) did not differ in their pattern of lateralization from normal females. Perhaps individuals with idiopathic precocious puberty should not be

compared with normals due to undetected/undiagnosed endocrine complications in these children. At present, it is unclear if early and late maturing adolescents differ in performance on dichotic listening tasks as a result of their sex, their timing of puberty, or some other variable working alone or in concert with sex and maturation rate.

For the last section of this review, activational influences of sex steroid hormones on cortical asymmetry will be assessed through studies that take advantage of the cyclic fluctuations of estrogens and progesterone associated with menstruation. Briefly, pituitary and gonadal steroid concentrations are low during menstruation, with an increase in estrogens, leutenizing hormone, and follicular stimulating hormone during the follicular phase of the cycle. The luteal phase of the cycle follows next, which is characterized by high levels of both estrogens and progesterone. Finally, the premenstrual phase occurs when progesterone begins to decrease, while estrogens have already plummeted.

Studies that attempt to link menstrual phase with cortical asymmetry inferred from measures of cognitive ability will not be included here because it is impossible to know that a person is relying on one hemisphere or the other when completing a test of cognitive achievement or ability. Therefore, the focus here will be those studies that directly measure functional lateralization via tachistoscopic tasks. It is curious that dichotic and dichaptic tasks have not been employed when studying the menstrual phases, but perhaps these procedures will further investigations in this area soon.

A tachistoscopically-presented lexical decision task (left hemisphere biased) was administered to 24 young women who experienced predictable, spontaneous menstrual cycles (Chiarello et al., 1989). All subjects were right-handed, and reported to not have taken exogenous steroids for at least 3 months prior to testing. Subjects were observed in a counterbalanced manner once during the menstrual, follicular, and luteal phases respectively. Accuracy for lexical performance was observed to be unvarying throughout the menstrual cycle in the women tested. Interestingly, response criterion appeared to be influenced by menstrual phase, and thus potentially by the fluctuating sex steroid concentrations associated with menstrual phase. Specifically, a stronger response criteria was observed for the right hemisphere compared with the left (the usual finding) during both follicular and luteal phases of these women, but this pattern was replaced by a left hemisphere dominance during menses.

Right-handed young women ($n = 12$) not taking birth control pills and experiencing normal menstrual periods were recruited for an experiment that again consisted of a lexical decision task (left hemisphere dominant) and a face decision task (right hemisphere dominant) (Heister et al., 1989) at the following test times: (1) day 1, 2, or 3 of bleeding (menses); (2) day 8 to 14 proceeding menses (follicular); (3) day 15 to 22 following menses (luteal); (4) day 23 to 28 proceeding menses (premenstrual). Neither response time nor accuracy measures varied with menstrual phase for the lexical decision task. For the face decision task, however, a phase by hemisphere interaction was observed such that during the premenstrual phase the left hemisphere exhibited faster response times while the right hemisphere was fastest (the typical pattern) during all other points observed in a cycle.

Bibawi et al. (1995) investigated functional cortical asymmetries across the menstrual cycle with a right hemisphere dominant face chimera task and a chair identification task believed to elicit no particular pattern of lateralization. Women in this study were tested on these tasks three times each, twice during menstruation (days 3–5 of bleeding) and once during the presumed midluteal phase. Women's performance on the chimeric face processing task did not differ between menses and the midluteal phase, but performance on the chair identification task did fluctuate between these points in the cycle. Women's perfor-

mance improved for left hemisphere processing during the chair task during their midluteal phase, while both hemispheres performed equivalently during menses. This finding is in disagreement with the idea that during menses sex steroid hormone concentrations are low (a woman's hormonal milieu is most similar to that of a man's), and a woman's performance on a lateralization measure is most masculinized (Kimura and Hampson, 1993).

Limitations to the menstrual cycle literature can be summarized by the following points. First, sex steroid hormone concentrations are not directly measured, and are only inferred from calendar dating methods. This is problematic not only because it is very difficult to correctly predict menstrual phase from calendar methods alone, but also because these studies tend to consist of young college women who are prime candidates for being anovulatory due to their age, dietary intake, and sleep schedules. Additionally, due to the repeated measures design inherent to much menstrual cycle research, subjects may be able to guess quite accurately the hypothesis being tested. Another problem in comparing the results of these studies is that different parts of a menstrual cycle were investigated, and phases were not always determined by the same calendar procedure. Finally, as in the human clinical investigations, more studies employing a variety of behavioral measures are needed.

Despite all of these procedural difficulties, the menstrual cycle provides many benefits for investigating activational effects of gonadal steroids on functional cortical asymmetry. Subjects for study are abundant and easily recruited, and women on birth control pills, Depo Provera, and Norplant can serve as obvious controls. Additionally, of the few studies that have actually measured cortical lateralization directly via behavioral tasks, interesting interactions are obtained between menstrual phase and hemispheric activation/processing. Precisely what these interactions mean is unclear at this time.

SUMMARY OF EVIDENCE: DO SEX STEROID HORMONES INFLUENCE CORTICAL ASYMMETRIES?

At the beginning of this article, it was noted that hemispheric lateralization varies among individuals in both degree and direction. Systematic sex differences in magnitude of lateralization are often noted such that females express a decreased magnitude of asymmetry and males exhibit increased asymmetry of hemispheric specialization. Furthermore, females tend to be left hemisphere biased while males are usually right hemisphere dominant. What is the evidence then, that these sex differences in degree and direction of cortical lateralization are influenced by sex steroid hormones?

First, neuroanatomical sex differences believed to be associated with functional cortical asymmetry are reviewed. An emphasis is placed on human CC investigations as well as on nonhuman animal studies which focus on cortical thickness. In general, it appears that females possess a larger, more bulbous, medial and posterior CC compared with males when relevant variables are accounted for. This is consistent with the idea that a larger CC is associated with greater interhemispheric exchange of information and thus decreased magnitude of asymmetry. It is not clear from these studies, however, which sex steroid hormones are important for influencing these functional and morphological sex differences.

The nonhuman animal literature is a bit more successful than human studies in demonstrating the importance of gonadal hormones for influencing neuroanatomical

asymmetries. The ability to reverse asymmetric patterns of right- and left hemisphere thickness through gonadectomy of male and female rodents, as well as the ability to reinstate original hemispheric patterns with hormone replacement indicates that sex differences in lateralization are influenced by gonadal steroids. The most likely candidate appears to be aromatizable testosterone, at least in the rodent models studied most extensively thus far.

Second, findings from the neurophysiological studies reviewed converge nicely with the behavioral and anatomical work indicating that females exhibit a more diffuse pattern of hemispheric activation than males, as well as a predominantly left hemisphere dominance pattern compared with the right hemisphere bias observed in boys and men. Although some physiological signals are less than perfect for establishing localization of brain activity, PET and fMRI procedures seem well-suited to demonstrate sexual dimorphism in patterns of hemispheric lateralization.

Across a wide range of species, hemispheric asymmetries have been shown to vary not only in accordance with sex, but also in accordance with gonadectomy, hormone replacement, and natural fluctuations of endogenous sex steroid hormones. It is reasonable to assert from the converging findings of morphological, physiological and functional studies that sex differences in lateralization must be due, at least in part, to the actions of sex steroid hormones. Furthermore, it seems probable that for many vertebrate species testosterone is an important influence on cortical asymmetry.

Although specific modes of action of testosterone have not been elucidated concerning cortical asymmetry, nonhuman animal work seems near the point of uncovering these mechanisms. Equally promising to attempts at understanding gonadal steroid effects on hemispheric specialization is the increasingly widespread use of hormone replacement therapy in both men and women. Clinical situations such as HRT will allow for the assessment of varying hormonal treatments and doses on human hemispheric specialization. Imaging studies carried out in concert with behavioral measures of lateralization in men and women receiving hormone replacement offers an extremely valuable avenue to follow in the attempt to understand hormonal influences of behavior in humans. Although PET and fMRI studies exist which report sex differences in brain activation, to my knowledge none have included hormonal manipulations.

In conclusion, the direct actions of sex steroid hormones on cortical hemispheric lateralization are not yet understood, yet seem undeniable when the vast amount of converging evidence is considered. With increased testing, the sex steroid hormones responsible for influencing lateralization and their mechanisms of action will surely be detected. Importantly, vastly different areas of neuroscience and psychology will need to consolidate findings on this issue to understand not only how gonadal steroids affect cortical lateralization, but to also tackle the virtually untouched question of why these sex differences in cortical lateralization exist in so many species.

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