

## Mini-Review

# Sex on the Brain: Are Gender-Dependent Structural and Functional Differences Associated with Behavior?

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A substantial number of studies provide evidence documenting a variety of sex differences in the brain. It remains unclear whether sexual differentiation at the neural level is related to that observed in daily behavior, cognitive function, and the risk of developing certain psychiatric and neurological disorders. Some investigators have questioned whether the brain is truly sexually differentiated and support this view with several arguments including the following: (1) brain structural or functional differences are not necessarily reflected in appropriate differences at the behavioral level, which might suggest that these two phenomena are not linked to each other; and (2) sex-related differences in the brain are rather small and concern features that significantly overlap between males and females. This review polemizes with those opinions and presents examples of sex-related local neural differences underpinning a variety of sex differences in behaviors, skills, and cognitive/emotional abilities. Although male/female brain differentiation may vary in pattern and scale, nonetheless, in some respects (e.g., relative local gray matter volumes) it can be substantial, taking the form of sexual dimorphism and involving large areas of the brain (the cortex in particular). A significant part of this review is devoted to arguing that some sex differences in the brain may serve to prevent (in the case where they are maladaptive), rather than to produce, differences at the behavioral/skill level. Specifically, some differences might result from compensatory mechanisms aimed at maintaining similar intellectual capacities across the sexes, despite the smaller average volume of the brain in females compared with males. © 2016 Wiley Periodicals, Inc.

**Key words:** brain sexual differentiation; cognition; emotion; intelligence

## SEX DIFFERENCES: THEORETICAL APPROACHES AND MISCONCEPTIONS

As recently as half a decade ago, it was believed that sex-related differences in brain function and architecture

were associated exclusively with sexual behaviors mediated by sex hormones. As a result, studies on the possible sexual differentiation of the brain predominantly focused on the hypothalamus, a region of the brain that is critical for the neural control of hormone secretion and sexual behavior (Levine, 1966; Swaab, 1995). Currently, a rapidly growing body of evidence documents sex differences in various aspects of brain function and structure associated with cognition (learning, memory, language) and emotion (anxiety, stress, empathy)—domains that had previously been assumed to be affected by sex in minor ways or none at all. Moreover, studies indicated that sex is a predictor of relative risk of developing a number of brain

### SIGNIFICANCE

A rapidly growing body of evidence documents sex differences in various aspects of brain function and structure associated with cognition, emotion, and social skills. The studies presented in this review suggest that sex differences in the brain might be considered adaptations, which could either support maintaining equal intellectual abilities despite differences in brain volume or obtaining advantages in some particular skills in order to reach sex-related competencies that match biological/social roles (e.g., emotional/empathic skills in females and mathematical/spatial skills in males). These adaptations may express themselves in many different ways, thus forming a complicated and sometimes difficult-to-capture pattern of results.

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Fig. 1. Examples of a female and a male animal contacting toys. The female animal (left) appears to be conducting an anogenital inspection of the toy doll, similar to inspections of infant vervet monkeys. The male animal (right) appears to be moving the car along the ground in a manner similar to that a child might use. Reprinted from Alexander GM, Hines M. 2002. Sex differences in response to children's toys in nonhuman primates (*Cercopithecus aethiops sabaeus*). *Evol Hum Behav* 23:467–479. © 2002 Elsevier. Used with permission.

disorders of both a neurological and psychiatric character (for reviews, see Cahill, 2006; Cosgrove, 2007; Bao and Swaab, 2010; Lenroot and Giedd, 2010).

The development of advanced imaging methods, such as magnetic resonance imaging (MRI) and positron emission tomography, has contributed tremendously to research on sexual differentiation. These methods have enabled researchers to generate detailed evaluations of brain structures and functions in vivo in order to search for possible associations of the brain characteristics with various behavioral measures, including cognitive, emotional, and social aspects.

Although the field of brain sexual differentiation has received considerable attention from the scientific community (PubMed shows over 17,000 reports on “sex differences in the brain”), the reported studies have failed to resolve basic questions and raise concerns about whether sex is indeed reflected in differences in brain structure and function. Although most studies conducted in this area have revealed differences (for recent meta-analysis or reviews, see Stevens and Hamann, 2012; Sacher et al., 2013; Ruigrok et al., 2014), the picture that emerges from this avalanche of data appears ambiguous (Tan et al., 2016) and allows for contradictory interpretations.

Advocates of one extreme view reject the idea of reliable brain-based sex differentiation, while others argue that the brain presents signs of sexual dimorphism firmly associated with traits held by one sex that are categorically distinct from those of the other sex with little overlap between males and females, if overlap of this kind even exists (for an in-depth discussion on different approaches and common misconceptions, see Cahill, 2006, 2009; McCarthy et al., 2012).

Investigators that are attached to the latter view use the arguments that sexual differences have biological and evolutionary roots and that they are caused by sex hormones shaping the brain during gestational growth (the organizing role) while also modulating the behavior of individuals by exerting an impact on their brains (the activating role) (see for review Cahill, 2006; Cosgrove et al., 2007; McCarthy, 2016). To reinforce their arguments, they point to studies indicating that young males and females of nonhuman primates show sex differences in toy preferences similar to those documented previously in children (Fig. 1), thus providing evidence that those preferences can arise independently of social influences (Alexander and Hines, 2002; Hasset et al., 2008; Hines and Alexander, 2008).

On the other hand, researchers who question the legitimacy of sexual dimorphism in the human brain claim that any such differences are small and do not present sufficient “internal consistency” (sex-differentiated brain features regularly present in individual people). Additionally, they argue that the substantial overlap of those features in males and females “undermines any attempt to distinguish between a male and female form for specific brain features” (Joel et al., 2015, p. 15471). According to this view, individual brains are not male or female but rather “intersex” and comprise a “mosaic” of features (Joel, 2011; Rippon et al., 2014; Joel et al., 2015). Some of these features are more common in females, while others occur more frequently in males.

Is there any solution to this interpretation impasse? The best option would naturally be to hold a discussion based on convincing (empirical, if possible) arguments challenging or supporting a particular point of view. A recent publication by Del Giudice et al. (2016) ([www.pnas.org/cgi/doi/10.1073/pnas.1525534113](http://www.pnas.org/cgi/doi/10.1073/pnas.1525534113)) and a reply by Joel et al. (2016) can be seen as a well-guided approach to the problem while also illustrating how important the theoretical approach is, as it often critically influences the methodology and aims of scientific studies. A theoretical approach might also determine the criteria for interpreting the data that are supposed to prove or disprove the existence of sexual differentiation of the brain. Much of the data concerning sex differences in the brain are single “snapshots” and are by-products of studies that never aimed to specifically evaluate male–female disparities. That, of course, does not make them scientifically meaningless, but it does create a large number of unrelated results that are hard to embrace. Even studies focused particularly on male–female comparisons and investigations designed to categorically test for the existence of sex-related differences are often based on inadequate assumptions. One example of a common assumption found among them is the notion that the human brain may be dimorphic in such a way that, as a whole (along with all its regions and subregions), it presents signs of sexual dimorphism regarding many features commonly attributed to males or females. Following this assumption, it thus becomes appropriate to search for common sexually dimorphic features in the entire brain (Joel et al., 2015). Such expectations are not necessarily rational because the human brain is functionally differentiated and sex may separately modify the development of its various components in an evolutionary or socially advantageous way. Obviously, male and female brains can be similar in many aspects, yet still differ in other ways depending on the structures and features in consideration.

Another expectation that underpins some studies is that sexual differentiation of the brain should override individual variations in the features in question to such an extent that they may be regarded as male or female characteristics that do not overlap (or, in the case that overlap exists, it occurs in an insignificant way) (Joel, 2011; Joel et al., 2015). Substantial amounts of literature indicate that personal experiences in life continuously shape the

brain (see Bavelier et al. [2012] and Sale et al. [2014] for recent review) and that the brain plasticity phenomenon extends even to later ages (e.g., Bherer et al., 2013). Obviously, these influences must overlap or interact with the ones related to sex while also determining the structure and function of the brain (Hines, 2005) as a simple consequence of social and biological sex roles providing common experiences to individuals belonging to the same sex. The fact that most papers indeed document some overlap between the distributions of sex-related traits cannot, thus, be considered a sufficient argument against the sex differentiation of the brain under the condition that the average differences are statistically proved.

Another important example of how a false assumption may limit our understanding of potential mechanisms associated with structural and functional changes in the brain in response to life-challenging events is the idea that the only brain sex differences worth considering are those that are directly related to appropriate differences in human behavior. At first glance, this approach seems justified. However, it does not take into account two important yet underappreciated points: (1) that sex differences in the brain could arise to prevent (in case they are maladaptive), rather than to produce, sex differences in behavior (Cahill, 2006; McCarthy et al., 2012); and (2) that the same behavioral effects may potentially be reached via distinct neuronal circuitry (Fine, 2010). As I will show below, there may be no obvious sex differences in a particular behavior or ability despite markedly different structural features between the brains of the two sexes. Nevertheless, a steady and logical image of these differences may indicate that they constitute an expression of some mechanisms working either in the evolutionary or life scale (or both) that serves to achieve some competencies that are biologically or socially profitable. Therefore, studies on this topic should contribute to understanding how sex influences human behavior and the brain.

The present review focuses on various aspects of sex differentiation of the brain and their relation to behavior that has different grounds and results in different outcomes. The review starts with studies showcasing that structural and functional sex differences in the brain may translate into different behaviors. Special attention is given to the existing correlational associations between behavioral performance and the degree of the related changes in brain features as these relationships make for compelling evidence. However, there are other differences in the brain that do not correspond directly with anticipated behavioral outcomes. The next two sections are devoted to studies showing that some sex differences in the brain can be thought of as adaptations serving to prevent, rather than to produce, differences at the behavioral/skill level. Such compensatory effects seem to act at both the global level, supporting the maintenance of equal intellectual abilities despite differences in brain volume between the two sexes, and at more local levels, involving different proportions of gray and white matter, cortical thickness, gyral complexity, and neuronal density.



## THE SEXUAL DIFFERENTIATION OF THE BRAIN IN RELATION TO COGNITIVE, EMOTIONAL, AND SOCIAL ABILITIES IN THE TWO SEXES

The brain consists of many structures specialized for various functions, including those that are considered sexually differentiated. Therefore, it is interesting to examine whether the size and function of particular brain structures in males and females correlate with behavioral differences between the sexes. This subject is also important because some authors (e.g., De Vries and Södersten, 2009) question the reliability of the sexual differentiation of the brain unless it can be proven that it affects human behavior and thus has its counterparts in various skills and abilities that have been documented as being sex dependent. On the other hand, there is much discussion as to the effect size of sex differences in behavior (some authors claim the differences are negligible or small, e.g., Hyde, 2014) and about their nature (whether they are categorical or just dimensional, e.g., Carothers and Reis, 2013). Interestingly, it has been argued that because of differences between measures, some individual tests focusing on specific abilities may show bigger effects than meta-analyses or reviews that consider more general behavioral/skill constructs (Hines, 2010). In addition, it has been found that these differences may change over a lifetime (De Vries, 2004; Hines, 2010). For this reason, the present review concentrates mainly on particular skills and behaviors that are commonly regarded as sexually differentiated in adult subjects, and (if possible) on those showing correlational associations with the degree of the related brain features.

Before addressing the studies that appear to be the most relevant to the present topic, it is worth mentioning that, in line with numerous observations indicating that females have an advantage in many linguistic tasks and males in tasks that require visual-spatial abilities (for review, see Sommer et al., 2004; Baron-Cohen et al., 2005), it has been demonstrated that the volume of the temporal and parietal regions (surroundings of the Sylvian fissure) engaged in language processing is comparatively larger in females, whereas males have larger parietal cortices associated with visual-spatial function.

Hemispheric specialization underlies important aspects of sensory and cognitive integration and is known to differ between the sexes (males brains are more asymmetric, whereas female brains show more bilateral organization). A number of studies have focused specifically on sex-related differences in the corpus callosum—the band of commissural fibers connecting the hemispheres, and thus essential for interhemispheric communication and functional integration. Findings pointing to sex-dependent differences in size of the corpus callosum and its relationship to gender differences in cognitive function have been highly disputed in the literature. Early observations (e.g., DeLacoste-Utamsing and Holloway, 1982) as well as more recent studies (e.g., Dubb et al., 2003) have pointed toward sex-related differences in the shape and/

or cross-sectional surface area of the human corpus callosum, particularly in the splenium/isthmus, the posterior portion of the corpus callosum. In females this region was found to be more bulbous and larger than in male counterparts. Because peristriate, parietal, and superior temporal fibers course through the splenium, these findings have been associated with possible gender differences in the degree of lateralization for visuospatial functions, in line with behavioral studies indicating greater hemispheric symmetry in females. It has been argued that a larger corpus callosum may provide better communication between the two hemispheres and thus lead to diminution of hemispheric asymmetry/specialization. The size of this region also has been found to correlate positively with performance on verbal fluency tasks and negatively with language lateralization in female subjects (Hines et al., 1992)—a finding in keeping with the observation that females tend to perform better in verbal fluency tasks and have greater bilateral brain organization. However, several recent studies have indicated that absolute callosal size is larger in males, and sex differences may disappear when statistically correcting for brain size (see Luders et al., 2006, 2014; Gupta et al., 2011).

In addition, at a structural level, an MRI analysis of 380 adult subjects indicated that males show more asymmetry at the majority of brain regions (Kovalev et al., 2003), including those involved in spatial and motion-related visual processing—functions that are more dependent on the right hemisphere than the left one and that show advantages among male subjects (e.g., Johnson et al., 2002). Interestingly, right-hemispheric dominance in a mental rotation task was observed in males but not females; this finding was considered to reflect a more bilateral organization of visuospatial processing in females than males (Johnson et al., 2002).

Below, we present data that directly focus on the relationship between performance on a specific tasks that exhibit sexual differentiation and the brain structures that are believed to subserve those particular behaviors.

Considering that many studies have consistently shown marked sex-related differences in emotional responses and perceptions as well as in social abilities (with females being generally more adept than males), investigators have examined whether these differences are associated with regional brain activation and/or structure.

In a functional magnetic resonance imaging (fMRI) study by Hofer et al. (2006), various pictures that carried a positive or negative emotional charge (selected from the IAPS base) were presented to young male and female volunteers. The subjects were asked to use the pictures to help them feel happy or sad while their brain activity was recorded. The authors reported that both positive and negative stimuli evoked more activation in the brains of the female participants (Fig. 2). Notably, these differences were more pronounced for negative emotions. However, a different picture emerges from a meta-analysis of imaging studies carried out by Stevens and Hamann (2012). Their study revealed that for negative emotions, females exhibited greater activation in left amygdala and other

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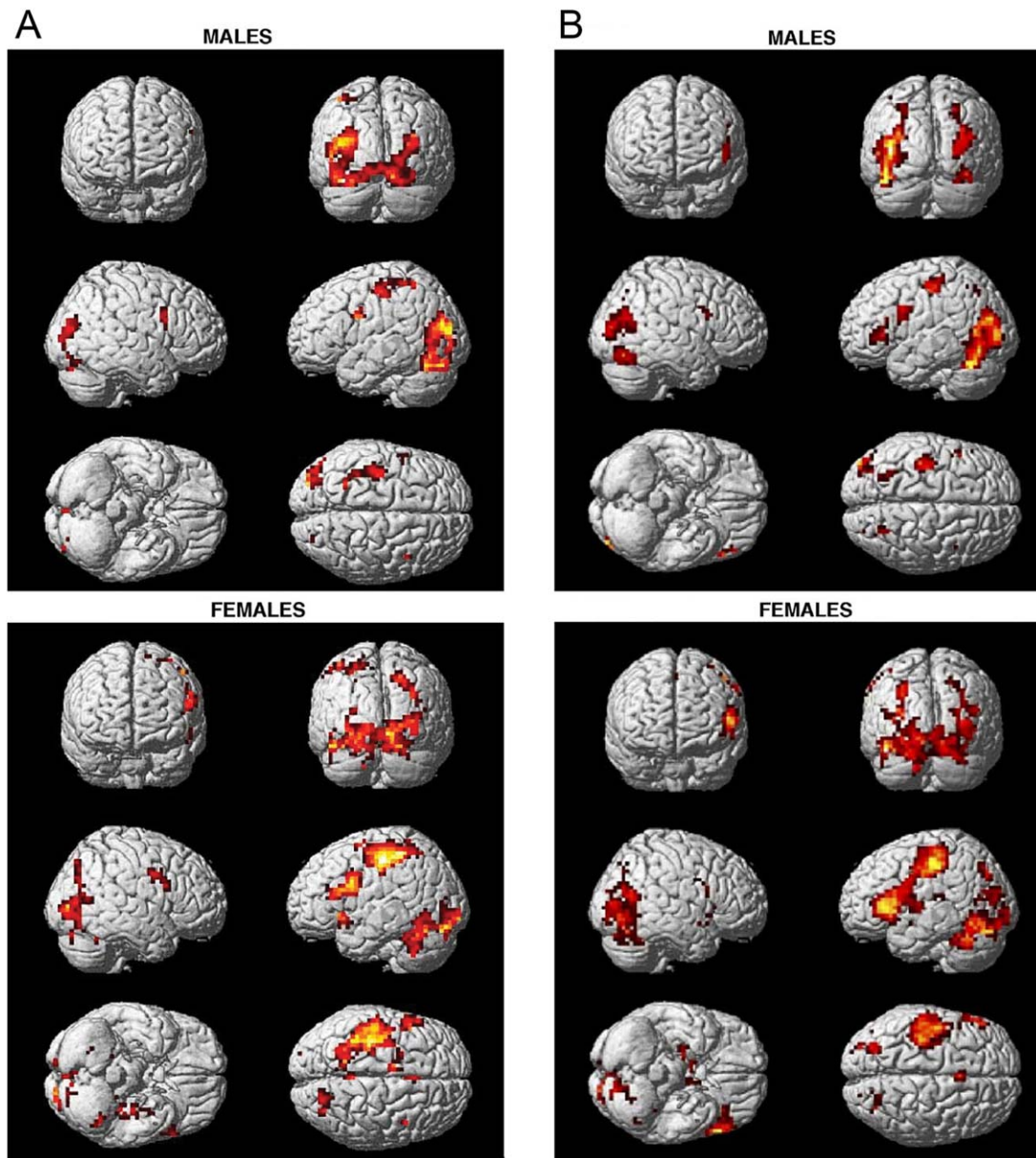


Fig. 2. Activation map of the differential contrast positive (A) and negative (B) mood induction minus reference condition (threshold at  $P < 0.05$ , corrected at cluster level). Reprinted from Hofer A, Siedentopf CM, Ischebeck A, Rettenbacher MA, Verius M, Felber S, Fleischhacker WW. 2006. Gender differences in regional cerebral activity during the perception of emotion: a functional MRI study. *Neuroimage* 32:854–862. © 2006 Elsevier. Used with permission.

brain regions compared with males, whereas for positive emotions, males exhibited greater activation than females in left amygdala and other brain regions. The authors suggested that this sex-related pattern of neural responses may be associated with previous reports that females respond more strongly to negative emotional stimuli and exhibit a higher prevalence of depression and anxiety disorders.

Because females tend to present higher social awareness and social skills in addition to emotional sensitivity compared with males, investigators have also examined whether brain structures known to be associated with social skills are sexually differentiated (Wood et al., 2008). Much research has implicated the ventral frontal cortex (VFC), as well as other areas, in social cognition and

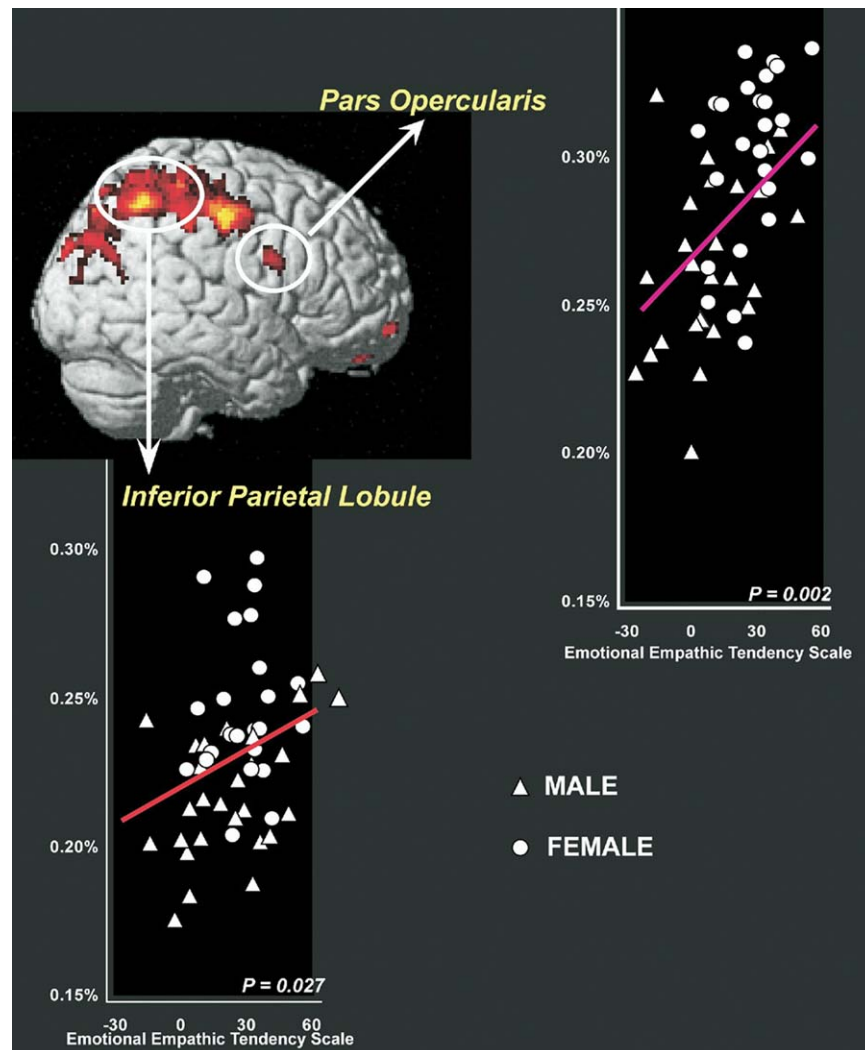


Fig. 3. Neuroanatomical correlates of the human Mirror neuron structures and an empathy questionnaire (EETS). The horizontal axis depicts the scoring of the EETS, and the vertical axis represents the ratio of the regional gray matter volume over the TIV. **A:** Pars opercularis. **B:** Inferior parietal lobule of the right hemisphere. Reprinted from Cheng Y, Chou KH, Decety J, Chen IY, Hung D, Tzeng OJ, Lin CP. 2009. Sex differences in the neuroanatomy of human mirror-neuron system: a voxel-based morphometric investigation. *Neuroscience* 158:713–720. © 2009 Elsevier. Used with permission.

behavior. Interestingly, a proportionally larger VFC, relative to total cerebral or intracranial volume, has been reported in females (Goldstein et al., 2001; Gur et al., 2002). The study by Wood et al. (2008) used MRI to measure the volume and surface of two medial regions of the prefrontal cortex known for their role in social interactions. These regions included the orbitofrontal cortex (OFC) and the straight gyrus (SG). In addition, the authors evaluated the relationship between the size of those regions and performance on psychological tests of social cognition and femininity/masculinity. The authors did not find any sex-related differences in OFC, or a

relationship of this structure to performance on psychological tests. The SG was found to have a 10% larger volume and surface area in females, and most important, its size correlated positively with performance on a social cognition test and with greater identification with feminine characteristics. The authors speculated that because women traditionally were child-rearers, their brains developed a larger SG, to prepare them to be sensitive nurturers.

Research and everyday experiences indicate that women are more empathic (e.g., Rueckert and Naybar, 2008). This poses the question of whether or not this



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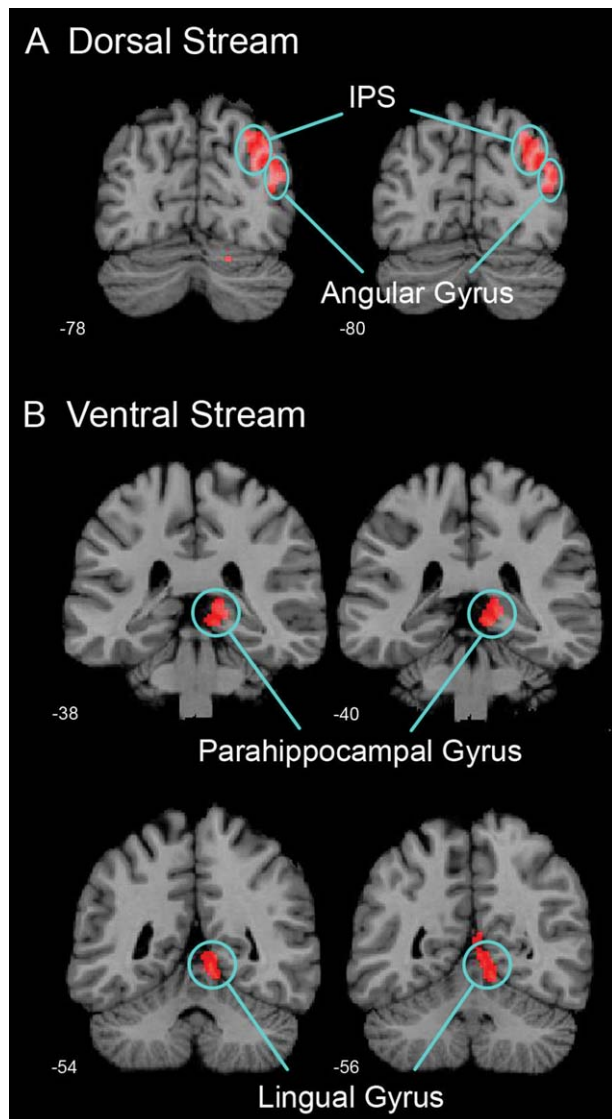


Fig. 4. Gender differences in brain activation during mental arithmetic. Significant gender differences in activation were observed in two clusters encompassing (A) the dorsal visual stream and (B) the ventral visual stream during the Calculation, compared with the Identification, condition ( $P < 0.01$ , corrected for multiple spatial comparisons). In the dorsal stream, males showed greater activation in the right intraparietal sulcus (IPS) and the right angular gyrus. In the ventral stream, males showed greater activation in the right parahippocampal gyrus and right lingual gyrus. All gender differences were lateralized to the right hemisphere. No brain areas showed greater activation in females compared with males. Reprinted from Keller K, Menon V. 2009. Gender differences in the functional and structural neuroanatomy of mathematical cognition. *Neuroimage* 47:342–352. © 2009 Elsevier. Used with permission.

common belief is reflected in the brain. It is believed that so-called mirror neurons play an important role in empathic responses and in the reception of social signals in general. To assess whether the neuroanatomy underlying the

human mirror neuron system exhibits sex differences, Cheng et al. (2009) used voxel-based morphometry (VBM) analyses and found that females have significantly larger volumes of gray matter in the pars opercularis and inferior parietal lobule—brain regions where networks of mirror neurons are located. It should also be mentioned that the volume of gray matter in the pars opercularis correlated with empathy competence assessed by the participants via a questionnaire (see Fig. 3). fMRI has been used to show many other complex and intriguing aspects of sexual dimorphism in empathy. Research carried out by Singer et al. (2006) is one of the best known examples of this. The authors studied brain responses during empathy-evoking situations with an MRI scanner and reported that females experienced empathy when somebody suffered pain even when this person had behaved unfairly towards them in the past. This was concluded based on activations of brain structures associated with experiencing empathy. In contrast, the brains of males tended to be more “self-interested”: the empathy-related neural responses were significantly reduced in males when observing an unfair person receiving pain. This effect was accompanied by increased activations in reward-related areas (nucleus accumbens) and correlated with an expressed desire for revenge. In females, the nucleus accumbens did not show increased activity.

Regarding skills showing an advantage for males, there have been attempts to analyze why males perform better than females in some mathematical tasks (Benbow, 1988), especially those that require a high level of mathematical reasoning. Investigations have been carried out to determine whether differences between males and females in brain architecture can account for differences in mathematical skills. Seeking sex similarities and differences at the neural level with MRI, Keller and Menon (2009) found that during a mental arithmetic task, males exhibited significant advantages through brain activation in the right dorsal and ventral visuospatial information processing streams (Fig. 4). Interestingly, VBM analyses revealed greater regional density in females in the same areas that were found to be more active in males. These included the intraparietal sulcus area and angular gyrus—regions that belong to the dorsal stream as well as the lingual and parahippocampal gyri that belong to the ventral stream. There were no brain areas where females showed greater functional activation than males, and no brain areas where males showed greater structural density or volume than females. According to the authors’ view, the finding that females perform comparably well, despite lower activation levels, points to more efficient use of neural processing resources. This might be due to increased gray matter density in the same regions that present higher activity in males.

As mentioned earlier, males consistently outperform females on spatial tasks. This specifically concerns mental rotation, which is the ability to identify how 3D objects would appear if rotated in space. As the parietal lobe is thought to play an important role in spatial processing in general and mental rotation specifically (Jagaroo, 2004),

Koscik and colleagues (2009) examined whether sex-related differences in the structure of the parietal lobe were associated with performance on the mental rotation test. The authors found that males, compared with females, had proportionately greater parietal lobe surface area, and this morphological difference was associated with a performance advantage in males on the mental rotation test. On the other hand, females had proportionately greater gray matter volume in relation to white matter volume in the parietal lobe, compared with males, and this morphological difference appeared to be disadvantageous for females on mental rotation test performance.

In summary, research focusing on particular, specialized brain structures involved in specific behaviors (dependent on cognitive, emotional, and social functions) indicates a relationship between sex-dependent differences in various forms of behavior and sexual differentiation of brain regions underpinning that behavior. However, the neuronal mechanisms involved in sexual differentiation are complex and cannot be unambiguously attributed to size or the activity of particular regions. Further, more systematic studies on how brain structure and function translate to sexual differences in behavior are required.

#### **SEX DIFFERENCES IN TOTAL BRAIN VOLUME VS. INTELLIGENCE**

The most pervasive and commonly cited difference between male and female brains is that the mean brain size (weight or volume) among males is 9% to 13% larger than in females (postmortem: Dekaban and Sadowsky, 1978; Witelson et al., 2006; MRI: Gur et al., 2002). Meta-analyses and reviews provide similar data (Lenroot and Giedd, 2010; Sacher et al., 2013; Ruigrok et al., 2014). Considering brain volume with respect to body size, these differences are usually negligible. However, there are also studies suggesting that even after adjustments, male brains have certain advantages over female brains (Cosgrove et al., 2007). It is worth noting, however, that these data center on average values, and the individual variability of brain size is relatively significant. Consequently, some female brains may be larger than male brains, and vice versa. In other words, not every man has a larger brain than the typical woman.

Despite differences in brain volume, studies clearly show that females and males do not differ in levels of general intelligence (Gur et al., 1999; Witelson et al., 2006). This raises the question of how smaller female brains can be as effective as their larger male counterparts. A larger brain requires more energy, leading to poor energy management. Unless the larger brain functions better than the smaller one, no clear evolutionary need for it exists. Perhaps the very assumption that larger brains within the same species have greater intellectual capabilities is inherently wrong? Studies attempting to determine whether there is a relationship between general brain volume and intelligence found a positive yet weak correlation between these two variables (Gur et al., 1999; Witelson

et al., 2006). In this context, it is important to mention that a positive correlation was found in both males and females. Interestingly, intelligence per unit of brain volume was proportionally greater in females (Gur et al., 1999), which might suggest that females “use” their relatively smaller brains more effectively. This result suggests that the female brains may take advantage of mechanisms that compensate for their generally lower brain volume and that this compensation is somehow related to the structure and size of the brain. Perhaps “the devil lies in the details,” where “details” refers to the different proportions of particular sections of the brain between sexes. In line with this belief, investigators have attempted to determine whether differences exist in brain architecture (considered from a structural and functional perspective), which may underpin abilities and behavior.

#### **SEX DIFFERENCES IN LOCAL BRAIN ARCHITECTURE (PROPORTION OF GRAY/WHITE MATTER, CORTICAL THICKNESS AND COMPLEXITY, NEURONAL DENSITY)**

A study by Gur et al. (1999) was one of the first to raise the above-mentioned issue. Gur and colleagues identified sex-dependent differences in the proportion of gray and white matter. They found that females tended to have proportionally more gray matter, whereas males were found to have greater amounts of white matter and cerebrospinal fluid. Gray matter consists of somatodendritic tissues of neurons, while white matter is made up of myelinated connecting axons. Because of this, these authors suggest that a higher percentage of gray matter in females indicates the engagement of more brain tissue in computation relative to that used for information transfer across distant regions relative. This may compensate for the “losses” related to smaller intracranial spaces in women. Interestingly, the authors found that the amount of gray matter increased more rapidly with cerebral volume in women than in men, providing more convincing evidence that proportional increases in gray matter volume may constitute a compensatory mechanism initiated to a higher extent as brain size decreases. This effect, however, has not been found by others (Luders et al., 2002; Leonard et al., 2008).

Using segmentation into separate gray matter, white matter, and cerebrospinal fluid volumes, a higher proportion of gray matter relative to white matter in females was documented by many other MRI studies including the one by Leonard et al. (2008) performed on a large group of 200 individuals. The observation that female brains have a proportionally greater percentage of gray matter was also validated through the use of VBM (Cheng et al., 2009). This study demonstrated that many cortical regions of female brains contain significantly more gray matter in comparison with males. Interestingly, no single region of the male cortex was found where the volume of gray matter was greater than in females. On the other hand, male brains presented higher volumes of gray matter in



some subcortical nuclei (amygdala, hypothalamus, hippocampus, and basal ganglia regions).

This data stays in line with measurements of cortex thickness. Im et al. (2006) compared cortical thickness using 3D surface-based methods, which enabled more accurate cortical measurements in deep sulci and localized regional mapping compared with volumetric analysis. The authors found that in stereotaxic space (i.e., after individual differences in brain size had been accounted for), the mean cortical thickness across the entire cortex of both hemispheres was significantly larger in females compared with males (see Fig. 5A). As shown in Figure 5B, mapping the statistically significant differences in cortical thickness between the two sexes revealed a localized cortical thickening in females in many cortical regions, most noticeably the left hemisphere. Interestingly, in native space (i.e., when brain sizes in males and females were preserved), a statistical analysis demonstrated some local increases in cortical thickness in females compared with males despite smaller average brain sizes in females. No significant local increases in cortical thickness were observed in males relative to females in either stereotaxic or native spaces.

The sexual dimorphism in cortical thickness favoring females was also reported by Luders et al. (2006). Based on the analysis of a relatively large sample of 60 subjects, Luders and colleagues' study revealed significantly greater cortical thicknesses among females compared with males once individual differences in brain size had been accounted for (Fig. 6, on the left). No significant increase in regional thickness was observed in males. Similarly, less pronounced effects were observed when no brain size corrections were applied (Fig. 6, on the right). The authors suggest that "increased cortical thickness in female brains might accompany similar or approximately equal numbers of cortical neurons in larger male and smaller female brains. Thus, it is also probable that there is no clear functional correlate to the increased regional thickness of the cortex in the female brain other than neuronal compensation" (Luders et al., 2006, p. 322). Additionally, this study revealed an interesting correspondence between regional increases in the thickness of the female cortex and regions that previous animal studies have shown to be dense in sex steroid receptors (Goldstein et al., 2001). This may suggest modulatory effects of sex steroids on gender-specific brain morphology.

Regional sex differences in gray matter thickness have also been mapped in a large sample ( $N = 176$ ) of subjects spanning an age range from early childhood to old age (7–87 years). The study (Sowell et al., 2007) revealed thicker (by 0.45 mm on average) cortices in females. These differences (especially pronounced in temporal and parietal regions) were both present when the comparisons were done with and without correction for total brain volume or body size and were maintained from late childhood throughout life. Differences of 0.45 mm may seem negligible; however, since cortical thickness ranges from 1.5 to 3.4 mm (on average), these differences can be profoundly important (Luders et al., 2006).

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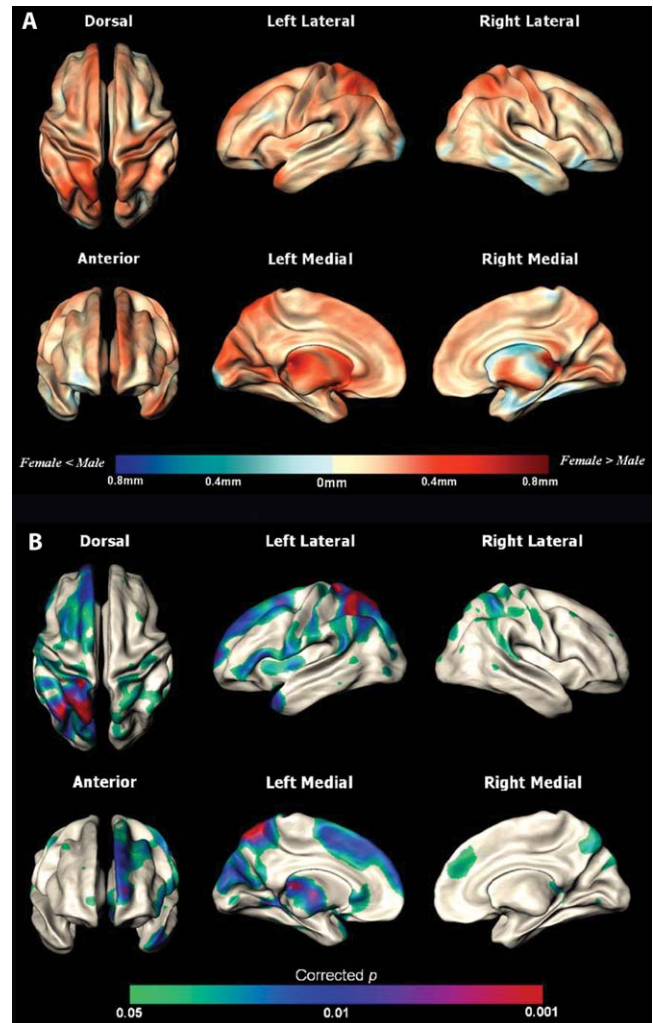


Fig. 5. **A:** Gender difference maps of cortical thickness in millimeters in stereotaxic space. The color scale at the bottom represents the difference of the mean cortical thickness in each voxel, with red and yellow indicating regions of greater cortical thickness in women. **B:** Corrected statistical maps showing greater cortical thickness in women in stereotaxic space. Significantly greater cortical thickness in women was found in several cortical regions. Reprinted from Im K, Lee JM, Lee J, Shin YW, Kim IY, Kwon JS, Kim SI. 2006. Gender difference analysis of cortical thickness in healthy young adults with surface-based methods. *Neuroimage* 31:31–38. © 2006 Elsevier. Used with permission.

It was also noted that differences exist in cortical complexity, a measure that quantifies the spatial frequency of gyrification and fissuration of the cortex. Luders et al. (2004) reported greater gyrification in females in the frontal and parietal regions using a 3D analytic technique with MRI (Fig. 7). The authors concluded that increased structural complexity in females indicates greater cortical surface area, which, in turn, may offset discrepancies in brain volume between males and females.

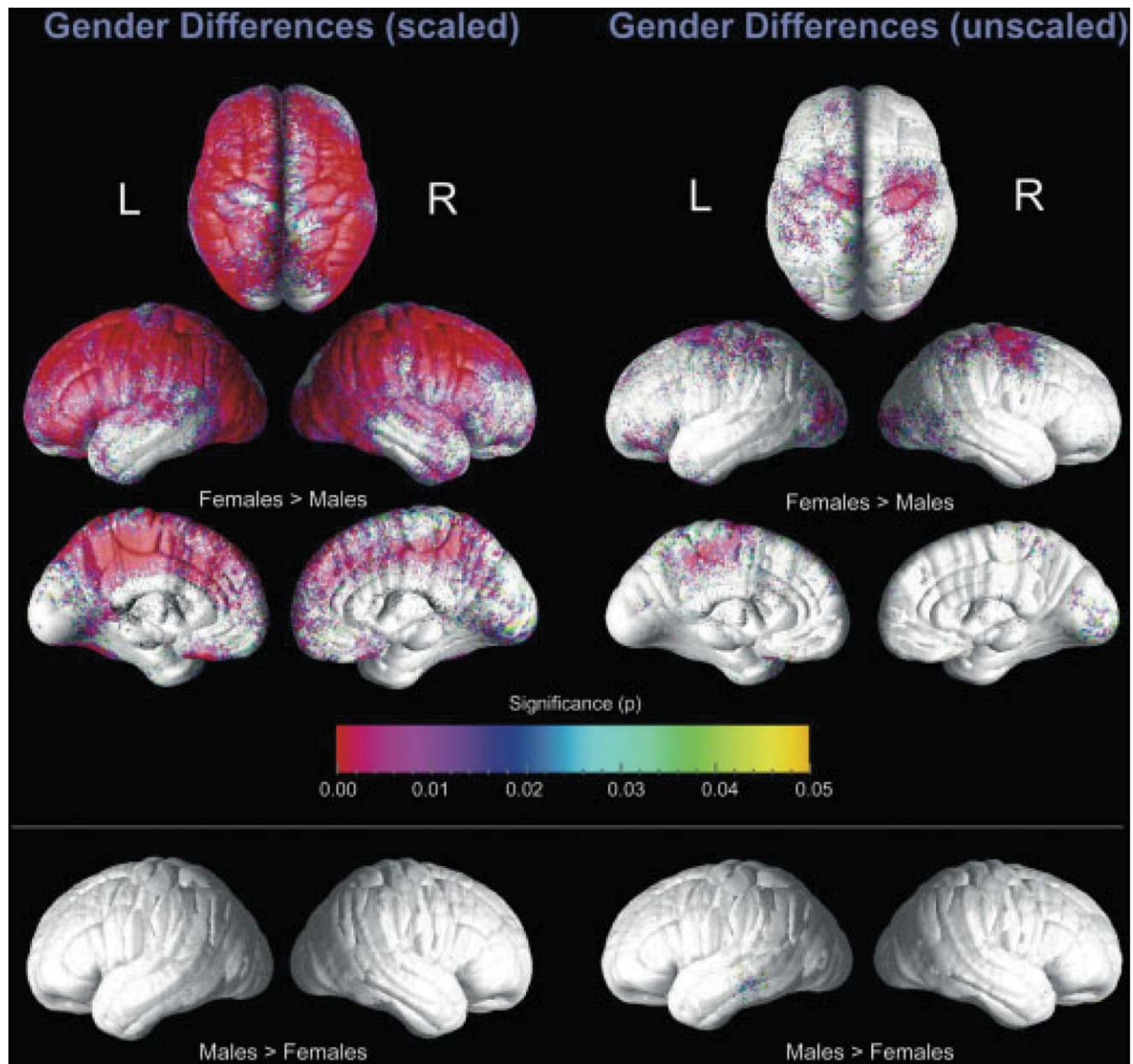


Fig. 6. Uncorrected statistical maps of gender differences in cortical thickness for scaled (after controlling for cerebral volume—upper left panel) and unscaled (when the actual brain sizes of men and women were preserved—upper right panel) data. No significant increases were observed in males (lower panels). Reprinted from Luders E, Narr KL, Thompson PM, Rex DE, Woods RP, DeLuca H, Jancke L, Toga AW. 2006. Gender effects on cortical thickness and the influence of scaling. *Hum Brain Mapp* 27:314–324. © 2006 John Wiley and Sons. Used with permission.

Although results concerning gray matter volume are clear, the interpretation of these findings is not straightforward. A thicker cortex may indicate a greater number of neurons, more densely packed neurons, larger cell bodies, or more neuropils. Although there are only a few studies addressing this particular issue, to date, findings support at least two of the aforementioned possibilities—i.e., increased neuronal density (Witelson 1995) and

increased number of neuropils (Rabinowicz et al., 1999, 2002).

Postmortem anatomical microscopic examination of the brain is the best method to obtain reliable data concerning differences between male and female brains at the cellular level. MRI does not enable study at this resolution. Studies conducted by Witelson et al. (1995) on nine brains revealed surprising differences between male and



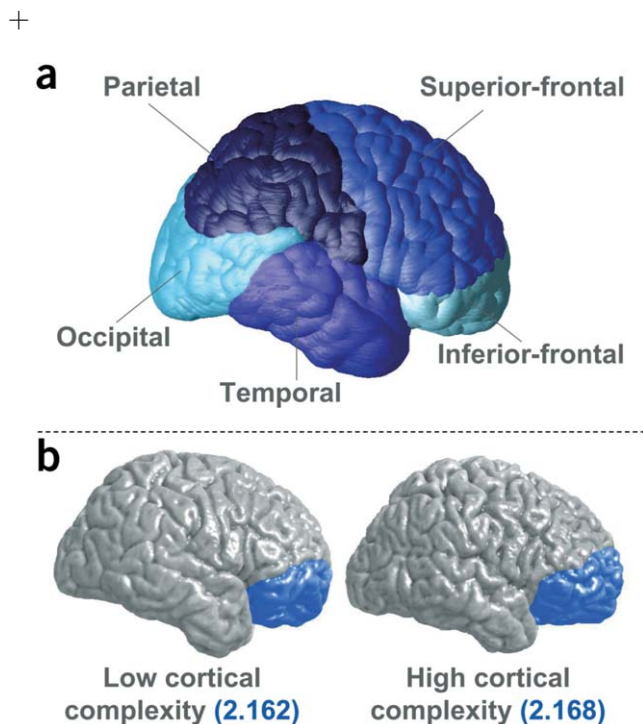


Fig. 7. The cerebral cortex. **a**: The parcellation of the cortical surface into five lobar regions in each hemisphere. **b**: Examples show low (2.162) and high (2.168) cortical complexity indices as measured from the right inferior frontal lobe region of two different individuals. Reprinted from Luders E, Narr KL, Thompson PM, Rex DE, Jancke L, Steinmetz H, Toga AW. 2004. Gender differences in cortical complexity. *Nat Neurosci* 7:799–800. © 2004 Nature Publishing Group. Used with permission.

female brains in the *planum temporale*—an area localized in the lateral and posterior surfaces of the Sylvian fissure. In humans, this region contains the associative auditory cortex and is responsible for language processing. The number and density of neurons per unit volume in this region were compared using sections from all cortex layers and individual sections of particular layers (the cortex normally consists of six layers that contain different cell types). The differences between neuronal density in males and females were significant. In females, the density was approximately 11% greater with no overlap of scores between the sexes. Interestingly, this difference was especially pronounced in the layers containing granular cells (second and fourth layer), which, according to the authors, may indicate sex differences in input and output components in the cortical functional units. This could have implications for sex differences in behavior and cognition. The overall number of neurons did not significantly differ between males and females in any layer, although cell count was marginally greater in the second and fourth layer in females.

In contrast, Rabinowicz et al. (1999, 2002) provided evidence in support of significantly higher neuronal densities in males but significantly larger neuropil volumes in females based on anatomical studies conducted on

11 brains. It is possible, however, that numerous disparities in methodology between Witelson's and Rabinowicz's studies may account for these differences. Importantly, Rabinowicz et al. did not find any sex differences in cortical thickness, which contrasts with the numerous aforementioned MRI reports. An increased number of neurons in a particular unit volume and increased neuropil volume might suggest that neuronal processing is more significant in women (Rabinowicz et al., 1999), which conforms to the views of Gur et al. (1999), which assert that more brain tissue is engaged in computation relative to the tissue responsible for long-distance data transmission in females compared with males.

At present, there is an increasing number of reports addressing the issues highlighted in the aforementioned papers. Many of them use MRI and well-validated computational cortical pattern-matching methods. This enables the estimation of the number of gray matter voxels relative to the total number of voxels within a given sphere on the cortical surface. Based on cortical matching MRI methodology, gray matter concentration is assessed in particular regions of the cortex. The term “gray matter concentration” is used to contrast it with the anatomical examinations, which assess the number of neurons per brain tissue volume. The advantage of this methodological approach is that it allows for the highly accurate alignment of surface anatomy in each subject so that local measures of gray matter can be related to other cortical surface locations across the entire cortex. MRI enables the examination of numerous healthy subjects in contrast to postmortem anatomic examinations, which may only be possible in a limited number of cases. It should be mentioned, however, that a disadvantage of the MRI method is its lower resolution, in comparison with the traditional anatomical (microscopic) methods. As the resolution is not sufficient to see neurons, establishing their number/density with MRI methodology is not feasible. As such, the MRI-based estimates can only be considered to be indirect measures of cortical density.

Using this technique, Luders et al. (2005) reported that female brains have greater gray matter concentrations in many regions of the cortex than male brains. This finding is even more meaningful because gray matter concentrations were not found to be higher in any regions of the male cortex (after correcting to individual brain size). Thus, the results not only confirm general findings that gray matter is more concentrated (or its amount is greater) in the female brain but additionally show that this phenomenon is exceptionally profound in some particular locations. This gave ground for the authors' claim that sex “is a major contributor to regional and global [gray matter] differences between individuals” (Luders et al., 2005, p. 493).

Importantly, the data presented above provide strong arguments against the recently proposed notions that imply that sex differences can be fully explained by size differences between male and female brains (Giedd et al., 2012; Luders et al., 2014). First, sex differences in



gray matter volumes are present not only after correction for individual brain size (i.e., when the male–female comparisons are done after covarying for total brain volume) but also when comparisons are done in native space (i.e., when brain sizes in males and females are preserved). Second, as indicated by some studies presented in this review, after corrections for brain size, greater gray matter volumes were found in several regions of the cortex among females. Meanwhile, greater volumes in males were exceptional or were not found at the cortical level. Third, similar effects were found when other measures, such as cortical thicknesses or gray matter concentration, were applied. Perhaps the strongest argument comes from a study by Luders et al. (2009), where analyses of brain sex differences were performed on brains chosen from a large databank of imaging data on the basis of having identical total intracranial volumes. This study also revealed bigger amounts of gray matter in several regions (caudate, left superior temporal gyrus, and left superior frontal gyrus) in female brains compared with male brains.

Generally, the data indicate several differences between male and female brains that make up a coherent picture pointing to the presence of compensatory mechanisms in females that enable their smaller brains to work as effectively as male brains. Similar “compensation” arguments have been made elsewhere by De Vries (2004). The differences between the two sexes are relatively significant and, in numerous cases, are dimorphic—i.e., particular features, such as regional increases in volume or density of gray matter, concern only one sex (in this case, females).

## CONCLUSION

This review discusses recent studies that have investigated the sexual differentiation of the brain as a whole as well as with regard to particular structures. In both cases, these differences can be regarded as adaptations that serve some particular evolutionarily/socially justified aims. Many of the sex-related neural differences (regarding both the structure and the function of the brain) are reflected in behavior, thus supporting the possibility that they might form a neural base for particular sex-differentiated skills or preferences (e.g., related to visual-spatial or mathematical skills in males vs. social, emotional, and empathic skills in females) that are helpful in fulfilling sex-differentiated roles. However, there are other differences in the brain that do not correspond with anticipated behavioral outcomes. This does not necessarily mean that they are accidental or that there is no correlation between brain structure, activity, and behavior. On the contrary, it seems that these differences may have served to equalize the sexes in some respects (e.g., intellectual) rather than to differentiate them.

Consequently, the differences may not necessarily form a coherent picture, as they may have arisen to fulfill different goals, thus leading to the elimination of differences if they are maladaptive (e.g., lower intellectual ability in females) or strengthening the differences when they are profitable (adaptation to sexually differentiated biological and social roles). The complicated and sometimes

difficult-to-capture patterns of results could also be due to the incidental character of many findings. A more systematic and hypothesis-driven approach may help to better evaluate and explain the effects of sex on brain functions and structure.

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