Magnetic Resonance Imaging 31 (2013) 366–375

Contents lists available at SciVerse ScienceDirect

Magnetic Resonance Imaging

journal homepage: www.mrijournal.com

Review articles

Sexual dimorphism in the human brain: evidence from neuroimaging

Julia Sacher [a,b,*], Jane Neumann [a,c], Hadas Okon-Singer [a], Sarah Gotowiec [a], Arno Villringer [a,b]

[a] Max-Planck-Institute for Human Cognitive and Brain Sciences, Stephanstr, 1A, Leipzig, Germany
[b] Clinic of Cognitive Neurology, University of Leipzig, Liebigstr, 16, Leipzig, Germany
[c] Leipzig University Medical Center, IFB Adiposity Diseases, Leipzig, Germany

ARTICLE INFO

Article history:
Received 4 December 2011
Accepted 13 June 2012

Keywords:
Sex differences
Neuroimaging
Human brain
Magnetic resonance imaging (MRI)
Positron emission tomography (PET)

ABSTRACT

In recent years, more and more emphasis has been placed on the investigation of sex differences in the human brain. Noninvasive neuroimaging techniques represent an essential tool in the effort to better understand the effects of sex on both brain structure and function. In this review, we provide a comprehensive summary of the findings that were collected in human neuroimaging studies in vivo thus far: we explore sexual dimorphism in the human brain at the level of (1) brain structure, in both gray and white matter, observed by voxel-based morphometry (VBM) and diffusion tensor imaging (DTI), respectively; (2) baseline neural activity, studied using resting-state functional magnetic resonance imaging (rs-fMRI) and positron emission tomography (PET); (3) neurochemistry, visualized by means of neuroreceptor ligand PET; and (4) task-related neural activation, investigated using fMRI. Functional MRI findings from the literature are complemented by our own meta-analysis of fMRI studies on sex-specific differences in human emotional processing. Specifically, we used activation likelihood estimation (ALE) to provide a quantitative approach to mapping the consistency of neural networks involved in emotional processing across studies. The presented evidence for sex-specific differences in neural structure and function highlights the importance of modeling sex as a contributing factor in the analysis of brain-related data.

1. Introduction

Substantial evidence has been gathered from recent neuroimaging studies supporting a sexual dimorphism of the human brain. Given the significant sex-specific differences in the prevalence of a majority of neuropsychiatric disorders, a better understanding of the impact of sex on brain structure and function is of major importance to adequately address the sex differences in the management of risk factors, symptoms, course of disease and treatment. Above all, there is a clear need to integrate neuroimaging findings on brain structure, connectivity, neurochemistry and function in human studies in order to extract the essential comprehensive information on the effects of sex on neural phenotypes.

In this systematic review, we evaluate the literature of the past decade on sex-specific differences in the human brain found in gray matter by voxel-based magnetic resonance (MRI) studies; in white matter by diffusion tensor imaging (DTI); in neural activity and metabolism at baseline by resting-state functional magnetic resonance imaging (rs-fMRI), cerebral blood flow (CBF) and fludeoxyglucose positron emission tomography (FDG-PET); in neurochemistry by receptor-ligand PET and in functional activation in specific brain regions during emotional processing, memory tasks, fear conditioning and visuospatial performance by fMRI. The review of sex differences in neural activation is complemented by a quantitative assessment of functional neural networks that have been observed to differ between males and females during tasks of emotional processing. We applied activation likelihood estimation (ALE) [1–5] to quantitatively model reported brain coordinates in fMRI studies and identify brain regions where individual peak coordinates in standard brain space converge across studies. This facilitates a systematic quantitative review of the evidence for a sexual dimorphism in brain function that is robust across subject populations and consistent among multiple imaging centers.

Overall, this review provides a comprehensive view of structural, functional and neurochemical neural differences between men and women. The evidence calls for integrating sex as a possible contributing factor in neuroimaging studies.

2. Sexual dimorphism in structure

2.1. Gray matter

Sexual dimorphism in human brain anatomy has been investigated by a wealth of studies, primarily addressing overall brain size,

* Corresponding author. Max Planck Institute for Human Cognitive and Brain Sciences, Cognitive Neurology, Stephanstrasse 1A, Leipzig, Germany.
E-mail address: sacher@cbs.mpg.de (J. Sacher).

0730-725X/$ – see front matter © 2013 Elsevier Inc. All rights reserved.
http://dx.doi.org/10.1016/j.mri.2012.06.007

the ratio between gray and white matter, and regional brain volume, as well as neural microstructure.

The most agreed-upon difference between men's and women's brains is that men have larger brain volumes than women [6]. Considering the general sex difference in body weight, it is important to note that sex differences in absolute brain size were observed and consistently replicated even after correcting for body size differences [7–11].

In addition, it is also established that women — compared to men — have proportionally greater gray matter volume compared to white matter volume [7,12–14]. Early studies initially found sex differences in white matter but not gray matter volumes [15,16]. However, Gur et al. [13] observed, based on larger samples, that while both gray and white matter volumes are smaller in women than men, the white matter difference is more pronounced. Additionally, cortical thickness has been mapped by neuroimaging techniques, and increased cortical depth in women versus men has been found [17–19].

As a corollary to studies of gray-to-white matter ratios, recent findings have shown that there may be a connection between gray matter volume and hormone levels of testosterone, estrogen or progesterone [20]. Van Amelsvoort et al. [21] suggest that sex steroids and chromosomal makeup might explain the sexual dimorphism exhibited in the human brain. However, it is not yet fully understood how sex hormones affect brain anatomy. Sex hormones having an effect on brain structure correspond to an emerging area of interest that is growing in neuroimaging research. Among the immediate next steps in the process of elucidating these mechanisms is to further investigate the potential neuroplastic changes that occur in the female brain across the lifespan.

Recent findings have narrowed the focus to specific areas of interest that show consistent sex based difference in regional brain volume. Chen et al. [6] observed increased regional brain volume for men compared to women in midbrain, left inferior temporal gyrus, right occipital lingual gyrus, right middle temporal gyrus and both cerebellar hemispheres. Women showed more gray matter volume in dorsal anterior, posterior and ventral cingulated cortices and right inferior parietal lobule. Brun et al. [22] reported increased gray matter volume in women's left hemisphere auditory and language-related regions as well as expanded primary visual and visuospatial association areas in men. Keller and Menon [23] showed that, compared to males, females had greater regional density and volume on dorsal and ventral stream regions.

Overall, the evidence for sex differences in total brain size, the gray matter–white matter ratio and regional brain volume reinforces the need to account for sexual dimorphism when conducting structural brain imaging studies. Differences in regional gray matter volume in particular further suggest specific functional alterations between men and women as will be discussed in detail in Section 3, as well as a sexual dimorphism in hemispheric lateralization.

2.2. White matter

Sex differences in white matter, as can be investigated noninvasively by DTI, could suggest potential differences in neural information transfer and connectivity. Based on the measurement of water molecule motion, DTI facilitates the visualization and characterization of white matter in the brain in vivo in both health and disease [24]. This way, DTI could substantially increase our understanding of the brain's structure and function [25] and thus of learning, cognition and psychiatric diseases [26], fields that continue to report sex-specific differences in behavior and pathology prevalence rates.

DTI data collected over the past few years have revealed substantial sex differences in white-matter-based anatomical connectivity [27]. Areas of note include the thalamus, cingulum and corpus callosum (CC), regions that play a role in emotion and motor function as well as in the mediation of higher-level cognitive processes such as attention and conflict monitoring, along with visuospatial and memory functions. Subsequent studies replicated those results and extended the findings to frontooccipital fasciculus, white matter underlying the parahippocampal gyrus, the bilateral internal capsule, white matter underlying the medial frontal gyrus, fusiform gyrus, hippocampus, insula, postcentral gyrus, as well as frontal and temporal lobes [28–32]. A very recent study critically reevaluated the sexual dimorphism previously described in the CC by controlling for partial volume effects and could only unequivocally detect a sex difference for the genu and the truncus of the CC [33].

In a previous study, Gong and colleagues [34] examined aging and gender effects on the topology of anatomical brain networks and found that females showed greater overall cortical connectivity including brain areas in the left Heschl's gyrus, superior temporal gyrus, superior parietal gyrus, inferior parietal gyrus, insula and right fusiform gyrus, most regions in the left hemispheric regions, whereas men had higher connectivity in two right hemispheric regions. Yan and colleagues [35] replicated sex differences in regional white matter using DTI, concluding that the anatomical organization of the human brain is associated with both sex and brain size.

In summary, DTI methods have been utilized to find robust sexual differences in the white matter of the human brain. Several studies have reinforced the need to systematically account for sex when establishing DTI study designs.

3. Sexual dimorphism in function

3.1. Resting states in fMRI and in PET

Rs-fMRI measurements provide an estimate for the functional connectivity in the brain at rest. They are based on coordinated and intrinsic spontaneous fluctuations in brain activity at baseline without performing a task [36]. Rs-fMRI provides insight into the unprompted activity that is naturally produced within the brain, which subsequently promotes communication across regions.

Comparisons of male and female brains during rs-fMRI studies have revealed that both sexes have robust functional asymmetry in several brain areas that have also been implicated in vision, attention and language [37]. Biswal and colleagues [38] examined sex effects in a large-scale rs-fMRI cohort ($n=1414$, across 35 imaging centers): women exhibited stronger connectivity than men in the posterior cingulate cortex, medial prefrontal cortex and the inferior parietal lobe, but weaker connectivity in the dorsal anterior cingulate cortex (dACC), insula, superior temporal gyrus, superior marginal gyrus and occipital regions. Those findings were largely replicated by a subsequent study aiming to disentangle regional and sex differences in resting-state activity throughout the lifespan. This study also reported sex-related differences in the developmental trajectory of functional homotopy in the amygdala and within the dorsolateral prefrontal cortex (DLPFC), both key areas in the corticolimbic circuit involved in emotional processing [39].

Kong and colleagues [40] studied a sample of 100 healthy subjects and focused on the periaqueductal gray (PAG), known to play a vital role in pain modulation but also mood and emotional regulation: They reported women to show stronger connectivity from the PAG to the dACC, but weaker connectivity from PAG to the left medial orbital prefrontal cortex, right insula/operculum and prefrontal cortex.

Rs-fMRI research has also been employed to examine sex-related differences in the way that functional networks are organized in the

human brain [41]: In their study, the researchers measured network efficiency from rs-fMRI data within each hemisphere in healthy adults and found a sex-by-hemisphere interaction: Males and females showed strikingly asymmetric patterns in the efficiencies in their networks. Specifically, males tended to exhibit more local efficiency in their right hemispheric networks. Conversely, females tended to be more locally efficient in their left hemispheric networks. Tian and colleagues also noted that many of the regions that they found to demonstrate significant hemisphere-related differences in their study have been previously observed as structurally or functionally asymmetric between both sexes [41].

The differences in functional connectivity that have been studied by using rs-fMRI are not without controversy. Aside from the studies discussed above, several studies found no effect of sex in rs-fMRI data. One example is a study by Weissman-Fogel and colleagues [42] that reported no sex differences in three resting-state functional networks. They concluded that there is a comparable resting-state connectivity pattern between the sexes and even suggested that sex differences do not need to be controlled for in rs-fMRI studies. This discrepancy between findings shows a clear need for further research in order to determine the existence and nature of the sex differences in connectivity.

Global CBF or cerebral metabolic rates of glucose utilization have been used to visualize brain regional activity at rest by means of PET. Evidence from a majority of those studies points towards higher global CBF [43,44] and a higher cerebral rate of glucose utilization during rest in women [45], particularly in the orbital frontal area [46], though the latter has not been demonstrated as consistently [47,48]. This metabolic indicator for glucose has also been shown to change significantly within different phases of the menstrual cycle [49], thus revealing potential acute hormonal changes to impact brain activity. The increased CBF rates observed in the female brain could be suggestive of a more rapid distribution of pharmaceuticals that bind to central target sites and thus be an important aspect to consider in the design of psychotropic drug studies.

3.2. Evidence for sexual dimorphism in neuroreceptor ligand imaging PET and single photon emission tomography

The brain neurotransmitter serotonin is the monoamine that has been discussed most extensively for its involvement in the complex regulation of mood. However, in vivo findings for brain serotonin transporter binding are mixed: lower serotonin transporter binding in women was observed using the radioligand [^{11}C]MADAM [50], while several other studies found higher serotonin transporter availability in women compared to men [51]. It has been argued [8] that baseline function of the serotonergic transporter in females may be higher, and this interpretation has been linked to a better response rate to selective serotonin reuptake inhibitors (SSRIs) in women compared to men. Data to support this claim stem from observations in studies comparing the remission rates of men and women to different classes of antidepressants [52], as well as from SSRI studies in female populations in phases of hormonal transition [53,54]. For the serotonergic receptors, sex differences have been discussed based on reports of increased binding for the serotonin-1A receptor in female subjects [55] and lower serotonin-2A receptor-binding capacity in women [56]. While those findings could not be unequivocally replicated in further studies [57–62], more consistent results were obtained on sex hormone states having a significant impact on the regulation of serotonin receptor availability [63–66]. For the dopaminergic system, reports of sex differences thus far seem inconsistent [67–70]. Overall, it appears that more evidence could be gathered on a tendency of an increased dopaminergic tone in striatum [51,71–73] and higher extrastriatal dopamine receptor density in women compared to men [74]. The monoaminergic systems continue to be a field of high interest to further explore sex-specific changes in the human brain: Recently, rapid increase of monoamine oxidase A (MAO-A), an enzyme that breaks down serotonin, dopamine and norepinephrine, was demonstrated in the immediate postpartum period in healthy women [75], providing a neurobiological model for postpartum blues.

Other neurotransmitter systems have not been studied this extensively so far, but a few reports point towards interesting angles of future studies: For the opioid system, a major player in the management of pain and reward, sex differences were detected in mu-opioid binding revealing higher binding capacity across a number of cortical and subcortical areas [76]. In an additional study, mu-opioid receptor binding in the amygdala and hypothalamus has been demonstrated to be influenced by fluctuating estradiol levels [77]. The cholinergic system, associated with memory and cognition, has also been implicated to be influenced by sudden changes in female steroid hormones [78,79].

In summary, the neurochemical findings on sexual dimorphism in the human brain support the overall request for a more systematic approach to the design of neuroimaging studies and a call for a better standardization of hormonal aspects.

3.3. Overview on sex differences in fMRI findings

In line with the anatomical, functional and neurochemical evidence at rest, fMRI methods have been employed to reveal sex differences in neural activation during tasks targeting various perceptual, cognitive and emotional functions. Although there is wide evidence for sex differences in neural activation, to date, there is no 'default' systematic use of sex as a covariate in fMRI studies (see Ref. [80] for a similar discussion regarding the use of sex in anatomical studies). Many fMRI studies so far did not include sex in the analysis, and thus, it is impossible to know whether sex may have influenced the findings. Studies considering the possible impact of sex can further be divided into studies using sex as a covariate of interest, studies that use sex as a nuisance covariate and studies that included only men or women participants in the sample.

Emotional processing is known to differ between men and women. Accordingly, in a meta-analysis of functional studies examining *emotional face processing*, men showed greater neural reactions to emotional faces compared to women in limbic and prefrontal regions, while women showed greater activation compared to men in the right subcallosal gyrus [81] (but see Ref. [82] for no evidence for sex differences in response to surprised faces; see also the qualitative meta-analysis of emotional processing at the end of this section). Sex differences may depend on the specific emotional expression. It was shown that both males and females respond with bilateral frontal and left parietal activation to happy faces. However, females showed enhanced activation in additional regions. Viewing of sad faces also resulted in sex differences in neural activation [83]. Aleman and Swart [84] compared neural responses to contempt, disgusted or neutral faces. Sex differences were revealed in response to facial expression of contempt and disgust in a diffused network [85]. These differences may be related to other differences in the processing of specific emotions between male and female. Sex differences in neural reactions may further depend on the sex of the face stimulus. It was shown that men and women respond differently to angry and fearful male or female faces [86]: men respond with higher activation than women in the visual cortex and the anterior cingulate gyrus to presentation of male as opposed to female faces, possibly reflecting enhanced vigilance in potentially dangerous situations in men.

Are sex differences in emotional recognition confined to faces? Lee and colleagues [87] presented subjects with facial expressions, scenes and words portraying happy or sad emotions. Male

participants responded with activation of the right insula and left thalamus to both happy and sad emotions in all three forms of stimuli. In contrast, such consistent neural activation was not observed in female subjects. Sex differences were also found in response to emotional speech [88]. Women, compared to men, showed larger activity in the inferior frontal gyrus in response to incongruent emotional prosody, possibly reflecting larger influence of emotional prosody on semantic processing in women than men. Women showed higher activation in the left orbitofrontal cortex (OFC) than men in response to pleasant and unpleasant odors [89]. This difference may be related to the advantage of women in odor identification. However, evidence for sex differences in perception is mixed, and thus, the difference may be due to the emotional value of the odors. No sex differences in neural activation were found during perception and imagery of complex sounds [90], as well as passive viewing of neutral pictures of faces and buildings [91]. In contrast, during passive viewing of words, women showed higher activation for words presented in the right visual field, while there was no such difference for men. Sex differences were repeatedly shown for sexual material. For example, during passive viewing of pictures with sexual or neutral content, while controlling for arousal differences between men and women, men responded with larger activation bilaterally in the amygdala and hypothalamus and the right cerebellum, while women did not show higher activation than men in any neural region [92]. Takahashi and colleagues [93] showed subjects sentences depicting sexual and emotional infidelity. Men reacted to jealousy-evoking sentences with higher activation in the amygdala and hypothalamus, while women responded with increased activation in the posterior superior temporal sulcus. It was suggested that this neural pathway may underlie aggressive reactions to sexual jealousy in men.

In a series of studies focusing on emotional memory, Cahill and colleagues reported that men activate the right hemisphere, while women activate the left hemisphere [94–96]. Mackiewicz and colleagues suggested that sex differences in lateralization are confined to the ventral amygdala [97]. Koscik et al. observed similar right lateralization for men and left lateralization in women for executive functions [98]. Lesion studies show that lesions in the right ventromedial prefrontal cortex and amygdala resulted in a major loss of everyday functioning in men, while similar lesions in the right hemisphere resulted in severe losses in women [98].

Several studies focused on visuospatial abilities, showing greater right hemisphere activation in men than women during a visual–spatial perception test [99]. Mental rotation was shown to activate different regions in men and women: while men activate the superior parietal lobule, women activate the inferior frontal cortex [100]. It was suggested that, during mental rotation, men rely on coordinate processing, while women rely on a serial categorical approach.

In summary, there is substantial evidence for sex differences in emotional perception and memory, fear conditioning and visuospatial abilities in fMRI studies. Evidence for sex differences in early perception, pain and empathy is mixed.

3.4. Towards quantification of sexual dimorphism in functional activity patterns during processing of emotional stimuli: a quantitative meta-analysis

To test the consistency of findings on sexual dimorphism during functional activation patterns in emotional processing circuits, we focused on a subfield of the above-described fMRI findings shown to differ between male and female. We set out to take a quantitative

Table 1
QUORUM diagram: Database PubMed 2000–2011

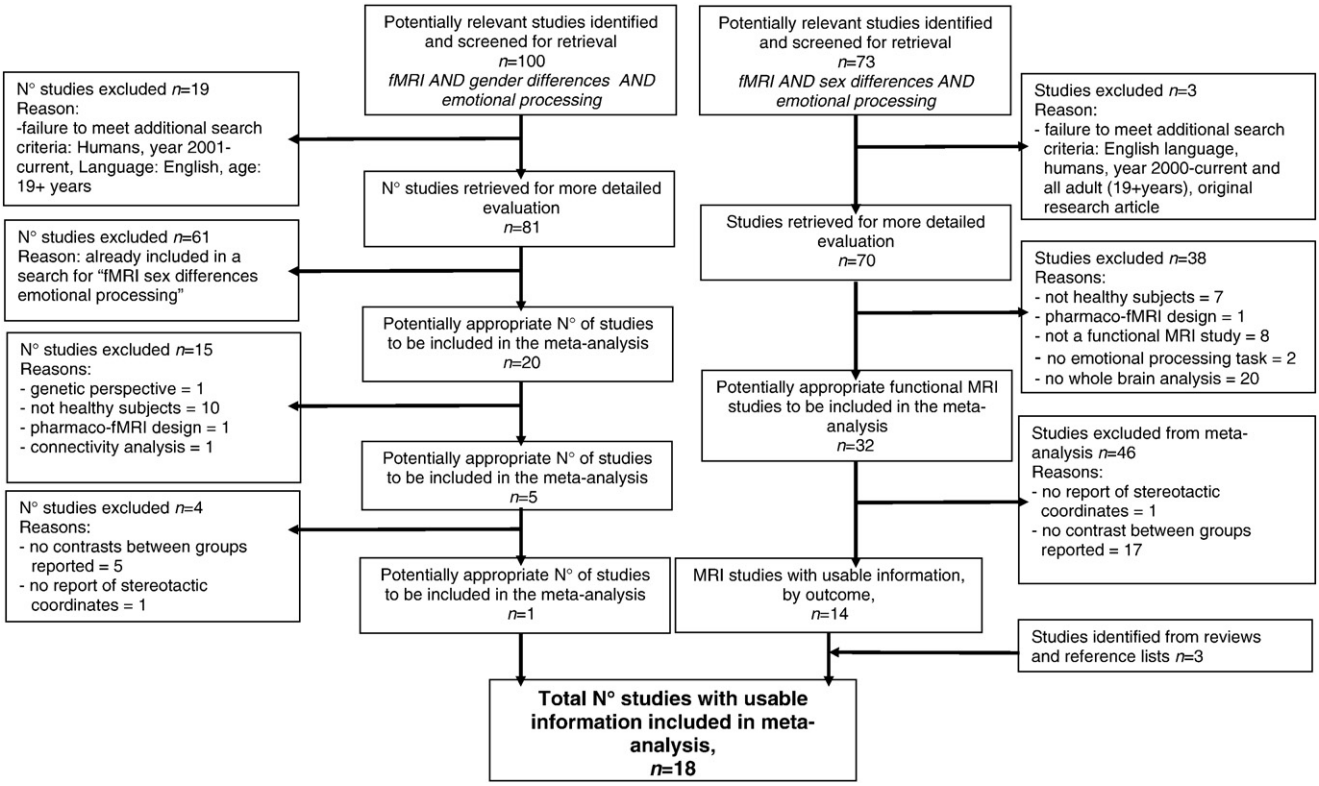

Table 2
Studies included in meta-analysis

Study	Sample size Males vs females	Mean age±S.D.	Contrasts Men versus women/women versus men	Task
fMR studies during emotional processing task				
Mercadillo et al., *Brain and Cognition*, 2011.	12 vs. 12	27±3	Women>men	Experience of compassion while viewing pictures representing suffering vs. objects
Rahko et al., *Brain Imaging and Behaviour*, 2010.	18 vs. 9	12–17	Men>women	During viewing of happy stimuli (facial expressions)
Derntl et al., *Psychoneuro endocrinology*, 2010.	12 vs. 12	28±7	Men>women	Emotional recognition
			Women>men	
			Women>men	Emotional perspective taking
			Men>women	
			Women>men	Affective responsiveness
Harenski et al., *Scan*, 2008.	14 vs. 16	26	Women>men	Positive modulation of moral severity ratings (IAPS pictures)
			Men>women	
Koch et al., *Neuropsychologia*, 2007.	21 vs. 19	31±10	Women>men	Contrast of negative emotions (rotten yeast, olfactory stimulus)
			Men>women	
			Women>men	Interaction between working memory and negative emotion
Caseras et al., *Biol Psychiatry*, 2007.	17 vs. 17	30±9	Women>men	Disgusting versus neutral pictures
Hofer et al., *Psych Medicine*, 2007.	18 vs. 18	20–48	Women>men	Positive mood induction versus reference coordination
			Men>women	
			Women>men	Negative mood induction versus reference condition
Takahashi et al., *Neuroimage*, 2006.	11 vs. 11	21±1	Men>women	Sexual infidelity minus neutral
			Women>men	
			Men>women	Emotional infidelity minus neutral
			Women>men	
Hofer et al., *Neuroimage*, 2006.	19 vs. 19	20–48	Women>men	Positive mood induction versus reference condition
			Women>men	Negative mood induction versus reference condition
Shirao et al., *British J Psych*, 2005.	13 vs. 13	21–30	Men>women	Emotional decision task consisting of unpleasant words concerning body image and neutral words
Butler et al., *Neuroreport*, 2005.	13 vs. 10	27–60	Women>men	Activation during threat (color cues for electrodermal stimulation, no real electrodermal stimulation occurred)
			Men>women	
Shirao et al., *Eur Arch Psy Clin Neurosci*, 2005.	13 vs. 13	21–30	Women>men	Unpleasant words concerning intrapersonal relationships and neutral words
Klein et al., *Neurosci Letters*, 2003.	10 vs. 10	42±7	Women>men	Negative IAPS pictures>positive IAPS pictures
Wrase et al., *Neurosci Letters*, 2003.	10 vs. 10	42±7	Men>women	Emotionally positive versus neutral stimuli (IAPS pictures)
Kempton et al., *Int J Neuropsychopharm*, 2009.	40 vs. 34	18–65	Women>men	Fearful affect recognition task
			Men>women	
Piefke et al., *Hum Brain Mapping*, 2005.	10 vs. 10	27±3	Men>women	All types of autobiographical memory vs. baseline
			Women>men	
Domes et al., *Hum Brain Mapping*, 2010.	16 vs. 17	25±2	Women>men	Negative>neutral picture processing
			Men>women	Decrease>maintain emotion
			Men>women	Increase>maintain emotion
Hamann et al., *Nat Neuroscience*, 2004.	14 vs. 14	25–45	Men>women	Visual sexual stimuli

IAPS, International affective picture system.

approach: we identified all studies in the last decade that reported sex differences during emotional processing paradigms and conducted a meta-analysis using ALE. This method goes beyond qualitatively pooling results from diverse neuroimaging studies by quantitatively modeling reported brain coordinates and analyzing the locations where individual peak coordinates converge in a standard brain space [1–5]. Concordance between studies is identified by creating statistical probability maps as a measure of likelihood of activation on a voxel-wise level across the entire set of studies entering the meta-analysis. We focused on a selection of fMRI studies investigating paradigms of emotional processing that reported aspects of sexual dimorphism in brain activation patterns in healthy human subjects.

According to the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) guidelines [101], we conducted multiple Medline searches to identify all fMRI studies using an emotional processing paradigm from 2000 to 2011. Keywords used in the search were (fMRI OR functional magnetic resonance imaging) AND (gender differences OR sex differences) AND (emotional processing). Additionally, we searched the reference lists of identified articles and several reviews. Studies had to fulfill the following inclusion criteria: (a) peer-reviewed original research articles, (b) healthy human subjects, (c) reported contrasts as (men versus women) or (women versus men) and (d) results reported as coordinates in a normalized standard stereotactic space (Talairach [102] or Montreal Neurological Institute (MNI) [103] reference system). Moreover, studies had to be available in the English language and to be original research articles. Region-of-interest studies were excluded to enable a data-driven whole-brain approach for the meta-analysis.

Literature search, selection of studies according to the inclusion and exclusion criteria, and compilation of coordinates for the several

contrasts were performed independently by two investigators, and any disagreements were resolved by consensus. Multiple articles referring to the same patient data set were only included once. Following the PRISMA statement [101], the flowchart (Table 1) provides information about the numbers of studies identified, included and excluded and the reasons for exclusion of studies. A summary of all studies included in the meta-analysis is provided in Table 2. A total of 173 studies were initially identified. After limiting the results by criteria displayed in detail in the flowchart (Table 1), 18 studies were considered eligible to enter the meta-analysis, including 484 subjects entering the contrasted analysis for men versus women and 656 subjects entering the contrasted analysis for women versus men.

For the contrast showing neural regions that were more activated in men versus women, in 13 studies, a total of 72 peak coordinates from 16 individual contrasts were reported in brain areas including anterior cingulate cortex, superior frontal cortex, hippocampus, amygdala, insula, posterior cingulate cortex, superior temporal cortex, inferior OFC, putamen, globus pallidus, caudate, supramarginal gyrus, parahippocampal gyrus, visual cortex, thalamus, dorsal midbrain, vermis and DLPFC. For the contrast showing neural regions that were more activated in women versus men, 14 studies provided a total of 80 peak coordinates in 21 individual contrasts with changes in brain areas including frontal gyrus, thalamus, paracingulate gyrus, temporoparietal junction, superior occipital lobe, amygdala, OFC, insula, hippocampus, cerebellum, rostral anterior cingulated cortex and caudal DLPFC. Results are reported as consistent activation increases.

Reported coordinates were analyzed for convergence across studies using the software package GingerALE (http://brainmap.org/ale/index.html, Version 2.1.1). For each experiment, every reported activation maximum was modeled by a three-dimensional Gaussian probability distribution centered at the given coordinate. The width of the Gaussian probability distribution was determined individually for each experiment based on empirical estimates of between-subject variability, taking into account the number of subjects in each experiment [1]. Voxel-wise ALE scores were calculated from the union of the Gaussian probability distributions within and across experiments. In a random-effects analysis, ALE scores were tested against a null hypothesis of random distribution across the brain [1], thereby identifying those regions where empirical ALE values were higher than could be expected by chance. The resulting ALE map was thresholded at $P<.05$ (corrected for multiple comparisons by false discovery rate). Statistically significant voxels represent the convergence of the investigated effect across the several studies. ALE results were overlaid onto an optimized individual anatomical T1 template (www.brainmap.og/ale/Colin1.1.nii) in MNI space for display.

As illustrated in Fig. 1A and B, we found the main significant increases in activity in male healthy subjects versus female healthy subjects in the left amygdala (cluster size: 848 mm^3, center: x: −18, y: −4, z: −16, with a maximum ALE value of 0.017) and right amygdala (cluster size: 328 mm^3, center: x: 19, y: 1, z: −15, with a maximum ALE value of 0.011). The amygdala has multiple functions: one interpretation is that the observed amygdala activation represents a greater appetitive incentive value of visual sexual stimuli [92], a pattern that could be learned and potentially socially rewarding for men. Most stimuli used in this context in the meta-analysis were of a sexual nature [92,93], although not all of the paradigms supporting these results were based on erotic visual material [104]. This phenomenon can be paralleled with increased feelings of arousal but does not necessarily correlate with arousal ratings in every study [92]. Animal data support this concept as the amygdala has been shown to be receptive to testosterone-induced increases of vasopressin levels in monkeys [105], and vasopressin has been found to play an important role for pair-bonding in male monkeys [105]. A second potential explanation is in line with previous findings on the central role of the amygdala in processing of positive emotions [96,106] and views this brain region as the key player in mediating sex differences in response to appetitive, emotionally positive stimuli. Notably, increased amygdala activity

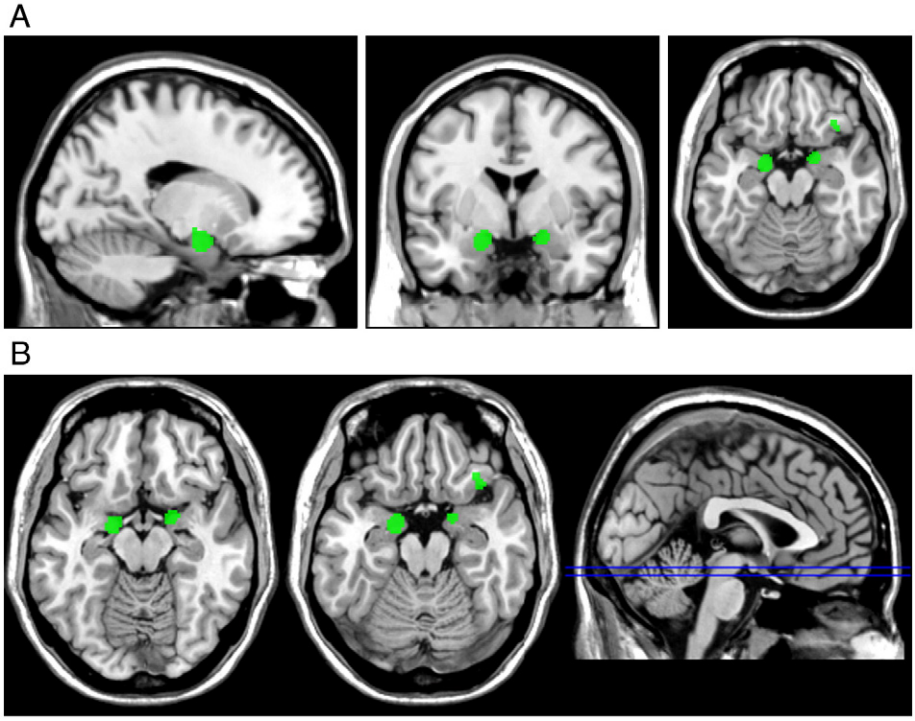

Fig. 1. Significant activation likelihood estimation (ALE) meta-analysis results for differences in blood oxygenation level dependent (BOLD) activation for the contrast men vs. women overlaid onto a single-subject Montreal Neurological Institute (MNI) template. Significant clusters include amygdala bilaterally and left orbito-frontal cortex (OFC). (A) Sagittal ($x=-17$), coronal ($y=-2$) and axial ($z=-17$) view. (B) Sagittal view of all identified clusters.

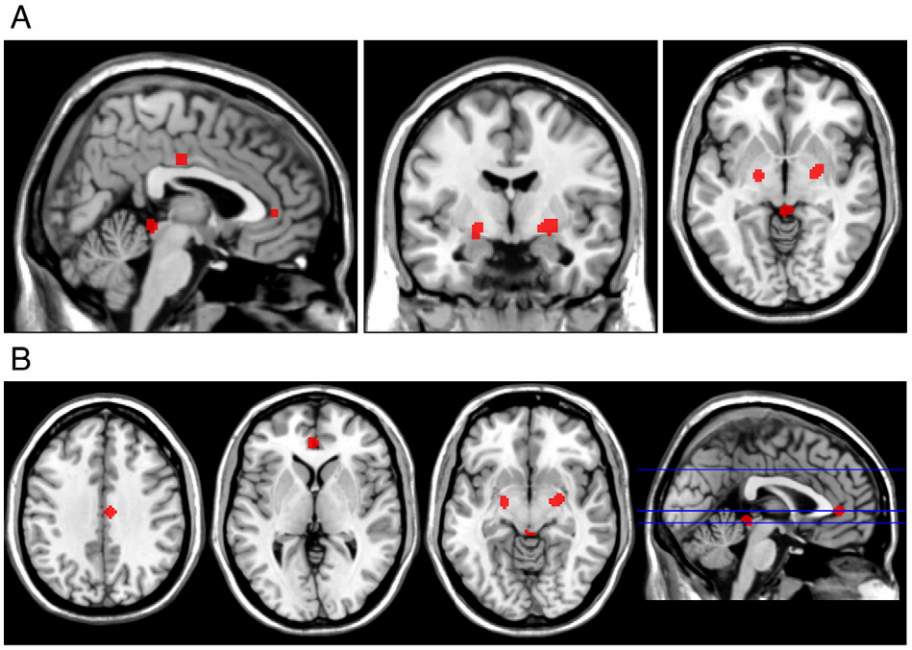

Fig. 2. Significant ALE meta-analysis results for differences in BOLD activation for the contrast women vs. men overlaid onto a single-subject MNI template. Significant clusters include globus pallidus/putamen bilaterally, anterior and posterior cingulate, bilateral thalamic regions and midbrain. (A) Sagittal ($x=3$), coronal ($y=-5$) and axial ($z=-4$) view. (B) Sagittal view of the main clusters.

has also been detected as a response to negative stimuli in men during cognitively increasing emotional responses [104]. Those results have been interpreted as a potential aspect in aggressive male behavior and might be a vulnerability trait for maladaptive behavior [104]. The amygdala is known to be involved in emotional perception and as a region that initiates an emotional reaction [107].

A third cluster of increased signal in males versus females was identified within the left OFC (cluster size: 160 mm^3, center: x: 35, y: 24, z: −19, with a maximum ALE value of 0.01). The OFC has been implicated in the control and inhibition of emotional associations with visual stimuli and in decision making [107,108]. It has further been demonstrated to be reciprocally and strongly connected with the amygdala activation during negative emotional stimulation [107]. The OFC and the amygdala both show high densities of Gamma-aminobutyric acid (GABA)-A receptors [109,110], and the GABA-A receptor system has been observed to be sexually dimorphic in certain brain areas: in a rat model, cortical GABA-A receptors have been found to be up-regulated by testosterone [111]. The left lateralization found in the meta-analysis is not in line with the evidence cited before showing stronger lateralization in neural functions (though in emotional memory and executive functions) for men in the right hemisphere and for women in the left hemisphere. However, differences between tasks related to emotional processing and tasks related to memory and executive functions may underlie this discrepancy.

For increased neural activation in women versus men during paradigms of emotional processing (depicted in Fig. 2), we primarily observed differences in activity in the corticolimbic network: a total of seven clusters, namely, subcortical brain areas, including the right and left globus pallidus and putamen (right: cluster size: 584 mm^3, center: x: 24, y: −6, z: −6, with a maximum ALE value of 0.017; left: cluster size: 408 mm^3, center: x: −20, y: −8, z: −7, with a maximum ALE value of 0.015). Lesions of the basal ganglia such as the putamen can result in decreased recognition of emotional facial expression of anger, disgust and fear [112]. Dopaminergic activity in the putamen might modulate the pathway between areas processing analytic facial recognition associated with the appraisal of multiple emotional inputs: an interesting study in Parkinson patients could link significant decrease of recognition of emotional but not nonemotional gestures with decreased dopaminergic transporter (DAT) levels in the putamen [113]. It is of particular relevance to the current finding that dopaminergic function has been hypothesized to be enhanced in women compared to men [8] and that overall DAT levels tend to be higher in women compared with men [51,71,72].

In addition, bilateral thalamic regions (cluster size: 280 mm^3, center: x: 2, y: −34, z: −5, with a maximum ALE value of 0.012) were shown to be more activated in women compared to men. The thalamus has been discussed as a relevant subcortical structure in the fear circuitry [114] and has also been included in the core limbic group of emotion processing networks, mediating signal transmission from subcortical areas to further interaction with cortical areas [96]. The pulvinar thalamic nucleus has recently been suggested as a core region in the neural network mediating reactions to negative stimuli [115].

Another cluster that was more activated in female than male participants includes areas in the anterior and posterior cingulate (ventral and dorsal ACC, Brodmann areas 24, 32: cluster size: 320 mm^3, center: x: −2, y: 41, z: 3, with a maximum ALE value of 0.014; posterior cingulate, Brodmann area 23: cluster size: 264 mm^3, center: x: 6, y: −16, z: 36, with a maximum ALE value of 0.018), as well as a smaller cluster in the left frontal cortex (Brodmann area 11, cluster size: 160 mm^3, center: x: −27, y: 37, z: −21, with a maximum ALE value of 0.011). One approach to understanding the role of more prominent ACC activation in female subjects in the processing of emotional stimuli [116,117] is to regard this pattern as a neurobiological correlate of enhanced attention towards unpleasant stimuli, emphasizing a sex-specific difference in the balance between competing demands of emotion and cognition and the brain circuits involved in managing this competition. Anatomical studies have been able to show larger volumes for both posterior and anterior parts of the cingulate cortex in women [8,118].

Finally, a smaller cluster in the midbrain (cluster size: 256 mm^3, center: x: 29, y: −93, z: -15, with a maximum ALE value of 0.018) was more activated in women than men. This region has been

associated with the raphe area, a region very rich in serotonin innervation and thus prone to sexual dimorphism: several studies suggest higher baseline serotonin function in women compared to men [8], and estrogens have been demonstrated to regulate serotonergic transmission in the raphe nuclei in rodent models [119,120].

4. Summary and outlook

In this paper, we reviewed evidence on sex differences in neural structure, function, metabolism and chemistry of the human brain. Evidence for sex differences stems from anatomical studies examining gray and white matter, functional neural connectivity analyses, PET studies measuring differences in neurochemistry and fMRI studies examining differences in neural activation during tasks. Overall, the various methods highlight robust sex-specific differences in human neural anatomy and function, and suggest that sex should be considered as a modulating factor in studies of the human brain.

Structural studies revealed that men have larger brain volumes than women, and women have a larger gray matter–white matter ratio compared to men. Sex differences in white matter microstructure were revealed in the corpus callosum and the cingulate cortex, suggesting differences in myelination between male and female. Resting-state studies have further identified sex differences in neural connectivity. Specifically, sex differences in connectivity were shown in several regions, including the corpus callosum, the ACC, the insula, the OFC and the PAG, in line with studies using different methods. It was further shown that men exhibit stronger connectivity in the right hemisphere, while women show enhanced connectivity in the left hemisphere. fMRI studies detected sex differences in emotional perception and memory, fear conditioning and visuospatial abilities. These results were corroborated by our meta-analysis of fMRI studies examining emotional processing, which found consistent enhanced activation in male compared to women in bilateral amygdala and left OFC, and in women compared to men in several clusters, including bilateral globus pallidus and putamen, bilateral thalamus, anterior and posterior cingulate cortex, and the midbrain.

Sex differences in neural structure and function can be related to various factors and causes, which should be carefully studied in future experiments. Factors that have been suggested are: neural hormones, personality characteristics that differ between male and female subjects, social learning that can differ according to sex and different evolution-related factors in specific sex roles. Several directions for further work in this intriguing field of research follow from the summary and the discussion provided above: (a) including sex as a covariate in the analysis if possible to disentangle the impact of sex on various perceptual, emotional and cognitive functions; (b) the study of specific subject samples to ask questions about the potential impact of sex hormones on the female brain across healthy hormonal transition phases, such as the postpartum or the perimenopausal period, but also across more subtle hormonal changes, such as the regular menstrual cycle; (c) the development of multimodal imaging designs to understand the stages of neuroplasticity that can be influenced by sex hormones and that might affect neurochemical, neurofunctional and neurostructural properties in a synergistic manner; (d) the development of novel PET radiotracers suitable to visualize steroid hormonal target sites in the human brain; (e) the integration of postmortem studies to establish a more global understanding of the physiology of sexual dimorphism in the human brain to inform the design of genetic, neuroimaging and neuropsychological studies; (f) the application of pharmacological challenges to evaluate the interaction between neurotransmitter systems and hormonal alteration in a controlled design and (g) the study of populations at risk for developing psychiatric disorders that show a substantial sex disparity in prevalence rate, like major depressive disorder, at different stages across the lifespan to complement the studies of sex differences in pathologies.

Acknowledgments

This research received project and salary support from the Alexander von Humboldt Foundation (AvH) fellowship and from the Society in Science, The Branco Weiss Fellowship, administered by the ETH Zürich, to J.S. and the Federal Ministry of Education and Research (BMBF), Germany (FKZ: 01EO1001), research grant to J.N.

References

[1] Eickhoff SB, Laird AR, Grefkes C, Wang LE, Zilles K, Fox PT. Coordinate-based activation likelihood estimation meta-analysis of neuroimaging data: a random-effects approach based on empirical estimates of spatial uncertainty. Hum Brain Mapp 2009;30(9):2907–26.
[2] Neumann J, von Cramon DY, Lohmann G. Model-based clustering of meta-analytic functional imaging data. Hum Brain Mapp 2008;29(2):177–92.
[3] Sacher J, Neumann J, Funfstuck T, Soliman A, Villringer A, Schroeter ML. Mapping the depressed brain: a meta-analysis of structural and functional alterations in major depressive disorder. J Affect Disord 2012;140(2):142–8. Epub 2011 Sep 3.
[4] Schroeter ML, Stein T, Maslowski N, Neumann J. Neural correlates of Alzheimer's disease and mild cognitive impairment: a systematic and quantitative meta-analysis involving 1351 patients. Neuroimage 2009;47(4):1196–206.
[5] Turkeltaub PE, Eden GF, Jones KM, Zeffiro TA. Meta-analysis of the functional neuroanatomy of single-word reading: method and validation. Neuroimage 2002;16(3 Pt 1):765–80.
[6] Chen X, Sachdev PS, Wen W, Anstey KJ. Sex differences in regional gray matter in healthy individuals aged 44–48 years: a voxel-based morphometric study. Neuroimage 2007;36(3):691–9.
[7] Allen JS, Damasio H, Grabowski TJ, Bruss J, Zhang W. Sexual dimorphism and asymmetries in the gray–white composition of the human cerebrum. Neuroimage 2003;18(4):880–94.
[8] Cosgrove KP, Mazure CM, Staley JK. Evolving knowledge of sex differences in brain structure, function, and chemistry. Biol Psychiatry 2007;62(8):847–55.
[9] Luders E, Steinmetz H, Jancke L. Brain size and grey matter volume in the healthy human brain. Neuroreport 2002;13(17):2371–4.
[10] Nopoulos P, Flaum M, O'Leary D, Andreasen NC. Sexual dimorphism in the human brain: evaluation of tissue volume, tissue composition and surface anatomy using magnetic resonance imaging. Psychiatry Res 2000;98(1):1–13.
[11] Shin YW, Kim DJ, Ha TH, et al. Sex differences in the human corpus callosum: diffusion tensor imaging study. Neuroreport 2005;16(8):795–8.
[12] Goldstein JM, Seidman LJ, Horton NJ, et al. Normal sexual dimorphism of the adult human brain assessed by in vivo magnetic resonance imaging. Cereb Cortex 2001;11(6):490–7.
[13] Gur RC, Turetsky BI, Matsui M, et al. Sex differences in brain gray and white matter in healthy young adults: correlations with cognitive performance. J Neurosci 1999;19(10):4065–72.
[14] Luders E, Narr KL, Thompson PM, et al. Mapping cortical gray matter in the young adult brain: effects of gender. Neuroimage 2005;26(2):493–501.
[15] Filipek PA, Richelme C, Kennedy DN, Caviness Jr VS. The young adult human brain: an MRI-based morphometric analysis. Cereb Cortex 1994;4(4):344–60.
[16] Passe TJ, Rajagopalan P, Tupler LA, Byrum CE, MacFall JR, Krishnan KR. Age and sex effects on brain morphology. Prog Neuropsychopharmacol Biol Psychiatry 1997;21(8):1231–7.
[17] Im K, Lee JM, Lee J, et al. Gender difference analysis of cortical thickness in healthy young adults with surface-based methods. Neuroimage 2006;31(1):31–8.
[18] Luders E, Narr KL, Thompson PM, et al. Gender effects on cortical thickness and the influence of scaling. Hum Brain Mapp 2006;27(4):314–24.
[19] Sowell ER, Peterson BS, Kan E, et al. Sex differences in cortical thickness mapped in 176 healthy individuals between 7 and 87 years of age. Cereb Cortex 2007;17(7):1550–60.
[20] Witte AV, Savli M, Holik A, Kasper S, Lanzenberger R. Regional sex differences in grey matter volume are associated with sex hormones in the young adult human brain. NeuroImage 2010;49(2):1205–12Epub 2009 Sep 28.
[21] van Amelsvoort T, Compton J, Murphy D. In vivo assessment of the effects of estrogen on human brain. Trends Endocrinol Metab 2001;12(6):273–6.
[22] Brun CC, Lepore N, Luders E, et al. Sex differences in brain structure in auditory and cingulate regions. Neuroreport 2009;20(10):930–5.
[23] Keller K, Menon V. Gender differences in the functional and structural neuroanatomy of mathematical cognition. Neuroimage 2009;47(1):342–52.
[24] Assaf Y, Pasternak O. Diffusion tensor imaging (DTI)-based white matter mapping in brain research: a review. J Mol Neurosci 2008;34(1):51–61.

[25] Feldman HM, Yeatman JD, Lee ES, Barde LH, Gaman-Bean S. Diffusion tensor imaging: a review for pediatric researchers and clinicians. J Dev Behav Pediatr 2010;31(4):346–56.
[26] Fields RD. White matter in learning, cognition and psychiatric disorders. Trends Neurosci 2008;31(7):361–70.
[27] Gong G, He Y, Evans AC. Brain connectivity: gender makes a difference. Neuroscientist 2011;17(5):575–91Epub 2011 Apr 28.
[28] Chou KH, Cheng Y, Chen IY, Lin CP, Chu WC. Sex-linked white matter microstructure of the social and analytic brain. NeuroImage 2011;54(1): 725–33Epub 2010 Jul 12.
[29] Menzler K, Belke M, Wehrmann E, et al. Men and women are different: diffusion tensor imaging reveals sexual dimorphism in the microstructure of the thalamus, corpus callosum and cingulum. NeuroImage 2011;54(4): 2557–62. Epub 2010 Nov 16.
[30] Westerhausen R, Walter C, Kreuder F, Wittling RA, Schweiger E, Wittling W. The influence of handedness and gender on the microstructure of the human corpus callosum: a diffusion-tensor magnetic resonance imaging study. Neurosci Lett 2003;351(2):99–102.
[31] Westerhausen R, Kreuder F, Dos Santos Sequeira S, et al. Effects of handedness and gender on macro- and microstructure of the corpus callosum and its subregions: a combined high-resolution and diffusion-tensor MRI study. Brain Res Cogn Brain Res 2004;21(3):418–26.
[32] Liu F, Vidarsson L, Winter JD, Tran H, Kassner A. Sex differences in the human corpus callosum microstructure: a combined T2 myelin-water and diffusion tensor magnetic resonance imaging study. Brain Res 2010;1343:37–45. Epub 2010 May 27.
[33] Westerhausen R, Kompus K, Dramsdahl M, et al. A critical re-examination of sexual dimorphism in the corpus callosum microstructure. NeuroImage 2011; 56(3):874–80Epub 2011 Mar 21.
[34] Gong G, Rosa-Neto P, Carbonell F, Chen ZJ, He Y, Evans AC. Age- and gender-related differences in the cortical anatomical network. J Neurosci 2009;29(50): 15684–93.
[35] Yan C, Gong G, Wang J, et al. Sex- and brain size-related small-world structural cortical networks in young adults: a DTI tractography study. Cereb Cortex 2011; 21(2):449–58. Epub 2010 Jun 18.
[36] Gusnard DA, Raichle ME. Searching for a baseline: functional imaging and the resting human brain. Nat Rev Neurosci 2001;2(10):685–94.
[37] Liu H, Stufflebeam SM, Sepulcre J, Hedden T, Buckner RL. Evidence from intrinsic activity that asymmetry of the human brain is controlled by multiple factors. Proc Natl Acad Sci U S A 2009;106(48):20499–503.
[38] Biswal BB, Mennes M, Zuo XN, et al. Toward discovery science of human brain function. Proc Natl Acad Sci U S A 2010;107(10):4734–9. Epub 2010 Feb 22.
[39] Zuo XN, Kelly C, Di Martino A, et al. Growing together and growing apart: regional and sex differences in the lifespan developmental trajectories of functional homotopy. J Neurosci 2010;30(45):15034–43.
[40] Kong J, Tu PC, Zyloney C, Su TP. Intrinsic functional connectivity of the periaqueductal gray, a resting fMRI study. Behav Brain Res 2010;211(2):215–9. Epub 2010 Mar 27.
[41] Tian L, Wang J, Yan C, He Y. Hemisphere- and gender-related differences in small-world brain networks: a resting-state functional MRI study. NeuroImage 2011;54(1):191–202. Epub 2010 Aug 3.
[42] Weissman-Fogel I, Moayedi M, Taylor KS, Pope G, Davis KD. Cognitive and default-mode resting state networks: do male and female brains "rest" differently? Hum Brain Mapp 2010;31(11):1713–26.
[43] Devous Sr MD, Stokely EM, Chehabi HH, Bonte FJ. Normal distribution of regional cerebral blood flow measured by dynamic single-photon emission tomography. J Cereb Blood Flow Metab 1986;6(1):95–104.
[44] Gur RC, Gur RE, Obrist WD, et al. Sex and handedness differences in cerebral blood flow during rest and cognitive activity. Science 1982;217(4560): 659–61.
[45] Baxter Jr LR, Mazziotta JC, Phelps ME, Selin CE, Guze BH, Fairbanks L. Cerebral glucose metabolic rates in normal human females versus normal males. Psychiatry Res 1987;21(3):237–45.
[46] Andreason PJ, Zametkin AJ, Guo AC, Baldwin P, Cohen RM. Gender-related differences in regional cerebral glucose metabolism in normal volunteers. Psychiatry Res 1994;51(2):175–83.
[47] Azari NP, Rapoport SI, Grady CL, et al. Gender differences in correlations of cerebral glucose metabolic rates in young normal adults. Brain Res 1992; 574(1–2):198–208.
[48] Kuhl DE, Metter EJ, Riege WH, Phelps ME. Effects of human aging on patterns of local cerebral glucose utilization determined by the [18F]fluorodeoxyglucose method. J Cereb Blood Flow Metab 1982;2(2):163–71.
[49] Reiman EM, Armstrong SM, Matt KS, Mattox JH. The application of positron emission tomography to the study of the normal menstrual cycle. Hum Reprod 1996;11(12):2799–805.
[50] Jovanovic H, Lundberg J, Karlsson P, et al. Sex differences in the serotonin 1A receptor and serotonin transporter binding in the human brain measured by PET. Neuroimage 2008;39(3):1408–19.
[51] Staley JK, Krishnan-Sarin S, Zoghbi S, et al. Sex differences in [123I]beta-CIT SPECT measures of dopamine and serotonin transporter availability in healthy smokers and nonsmokers. Synapse 2001;41(4):275–84.
[52] Kornstein SG, Schatzberg AF, Thase ME, et al. Gender differences in treatment response to sertraline versus imipramine in chronic depression. Am J Psychiatry 2000;157(9):1445–52.
[53] Rasgon NL, Dunkin J, Fairbanks L, et al. Estrogen and response to sertraline in postmenopausal women with major depressive disorder: a pilot study. J Psychiatr Res 2007;41(3–4):338–43.
[54] Halbreich U, Borenstein J, Pearlstein T, Kahn LS. The prevalence, impairment, impact, and burden of premenstrual dysphoric disorder (PMS/PMDD). Psychoneuroendocrinology 2003;28(Suppl. 3):1–23.
[55] Parsey RV, Oquendo MA, Simpson NR, et al. Effects of sex, age, and aggressive traits in man on brain serotonin 5-HT1A receptor binding potential measured by PET using [C-11]WAY-100635. Brain Res 2002;954(2):173–82.
[56] Biver F, Lotstra F, Monclus M, et al. Sex difference in 5HT2 receptor in the living human brain. Neurosci Lett 1996;204(1–2):25–8.
[57] Adams KH, Pinborg LH, Svarer C, et al. A database of [(18)F]-altanserin binding to 5-HT(2A) receptors in normal volunteers: normative data and relationship to physiological and demographic variables. Neuroimage 2004;21(3):1105–13.
[58] Frokjaer VG, Mortensen EL, Nielsen FA, et al. Frontolimbic serotonin 2A receptor binding in healthy subjects is associated with personality risk factors for affective disorder. Biol Psychiatry 2008;63(6):569–76.
[59] Stein P, Savli M, Wadsak W, et al. The serotonin-1A receptor distribution in healthy men and women measured by PET and [carbonyl-11C]WAY-100635. Eur J Nucl Med Mol Imaging 2008;35(12):2159–68.
[60] Rabiner EA, Messa C, Sargent PA, et al. A database of [(11)C]WAY-100635 binding to 5-HT(1A) receptors in normal male volunteers: normative data and relationship to methodological, demographic, physiological, and behavioral variables. Neuroimage 2002;15(3):620–32.
[61] Meyer JH, Kapur S, Houle S, et al. Prefrontal cortex 5-HT2 receptors in depression: an [18F]setoperone PET imaging study. Am J Psychiatry 1999; 156(7):1029–34.
[62] Rosier A, Dupont P, Peuskens J, et al. Visualisation of loss of 5-HT2A receptors with age in healthy volunteers using [18F]altanserin and positron emission tomographic imaging. Psychiatry Res 1996;68(1):11–22.
[63] Moses-Kolko EL, Price JC, Shah N, et al. Age, sex, and reproductive hormone effects on brain serotonin-1A and serotonin-2A receptor binding in a healthy population. Neuropsychopharmacology 2011;36(13):2729–40doi: 10.1038/npp.2011.163. Epub 2011 Aug 17.
[64] Frokjaer VG, Erritzoe D, Juul A, et al. Endogenous plasma estradiol in healthy men is positively correlated with cerebral cortical serotonin 2A receptor binding. Psychoneuroendocrinology 2010;35(9):1311–20Epub 2010 Mar 30.
[65] Kugaya A, Epperson CN, Zoghbi S, et al. Increase in prefrontal cortex serotonin 2A receptors following estrogen treatment in postmenopausal women. Am J Psychiatry 2003;160(8):1522–4.
[66] Moses EL, Drevets WC, Smith G, et al. Effects of estradiol and progesterone administration on human serotonin 2A receptor binding: a PET study. Biol Psychiatry 2000;48(8):854–60.
[67] van Dyck CH, Seibyl JP, Malison RT, et al. Age-related decline in striatal dopamine transporter binding with iodine-123-beta-CITSPECT. J Nucl Med 1995;36(7):1175–81.
[68] Best SE, Sarrel PM, Malison RT, et al. Striatal dopamine transporter availability with [123I]beta-CIT SPECT is unrelated to gender or menstrual cycle. Psychopharmacology (Berl) 2005;183(2):181–9.
[69] Pohjalainen T, Rinne JO, Nagren K, Syvalahti E, Hietala J. Sex differences in the striatal dopamine D2 receptor binding characteristics in vivo. Am J Psychiatry 1998;155(6):768–73.
[70] Kaasinen V, Nagren K, Hietala J, Farde L, Rinne JO. Sex differences in extrastriatal dopamine d(2)-like receptors in the human brain. Am J Psychiatry 2001; 158(2):308–11.
[71] Lavalaye J, Booij J, Reneman L, Habraken JB, van Royen EA. Effect of age and gender on dopamine transporter imaging with [123I]FP-CIT SPET in healthy volunteers. Eur J Nucl Med 2000;27(7):867–9.
[72] Mozley LH, Gur RC, Mozley PD, Gur RE. Striatal dopamine transporters and cognitive functioning in healthy men and women. Am J Psychiatry 2001; 158(9):1492–9.
[73] Laakso A, Vilkman H, Bergman J, et al. Sex differences in striatal presynaptic dopamine synthesis capacity in healthy subjects. Biol Psychiatry 2002;52(7): 759–63.
[74] Wong DF, Broussolle EP, Wand G, et al. In vivo measurement of dopamine receptors in human brain by positron emission tomography. Age and sex differences. Ann N Y Acad Sci 1988;515:203–14.
[75] Sacher J, Wilson AA, Houle S, et al. Elevated brain monoamine oxidase A binding in the early postpartum period. Arch Gen Psychiatry 2010;67(5):468–674.
[76] Zubieta JK, Dannals RF, Frost JJ. Gender and age influences on human brain mu-opioid receptor binding measured by PET. Am J Psychiatry 1999; 156(6):842–8.
[77] Smith YR, Zubieta JK, del Carmen MG, et al. Brain opioid receptor measurements by positron emission tomography in normal cycling women: relationship to luteinizing hormone pulsatility and gonadal steroid hormones. J Clin Endocrinol Metab 1998;83(12):4498–505.
[78] Smith YR, Minoshima S, Kuhl DE, Zubieta JK. Effects of long-term hormone therapy on cholinergic synaptic concentrations in healthy postmenopausal women. J Clin Endocrinol Metab 2001;86(2):679–84.
[79] Yoshida T, Kuwabara Y, Sasaki M, et al. Sex-related differences in the muscarinic acetylcholinergic receptor in the healthy human brain — a positron emission tomography study. Ann Nucl Med 2000;14(2):97–101.
[80] Hu X, Erb M, Ackermann H, Martin JA, Grodd W, Reiterer SM. Voxel-based morphometry studies of personality: issue of statistical model specification — effect of nuisance covariates. NeuroImage 2011;54(3):1994–2005. Epub 2010 Oct 20.

[81] Fusar-Poli P, Placentino A, Carletti F, et al. Functional atlas of emotional faces processing: a voxel-based meta-analysis of 105 functional magnetic resonance imaging studies. J Psychiatry Neurosci 2009;34(6):418–32.
[82] Schroeder U, Hennenlotter A, Erhard P, et al. Functional neuroanatomy of perceiving surprised faces. Hum Brain Mapp 2004;23(4):181–7.
[83] Lee TM, Liu HL, Hoosain R, et al. Gender differences in neural correlates of recognition of happy and sad faces in humans assessed by functional magnetic resonance imaging. Neurosci Lett 2002;333(1):13–6.
[84] Aleman A, Swart M. Sex differences in neural activation to facial expressions denoting contempt and disgust. PLoS One 2008;3(11):e3622.
[85] McClure EB, Monk CS, Nelson EE, et al. A developmental examination of gender differences in brain engagement during evaluation of threat. Biol Psychiatry 2004;55(11):1047–55.
[86] Fischer H, Sandblom J, Herlitz A, Fransson P, Wright CI, Backman L. Sex-differential brain activation during exposure to female and male faces. Neuroreport 2004;15(2):235–8.
[87] Lee TM, Liu HL, Chan CC, Fang SY, Gao JH. Neural activities associated with emotion recognition observed in men and women. Mol Psychiatry 2005;10(5):450–5.
[88] Schirmer A, Zysset S, Kotz SA, Yves von Cramon D. Gender differences in the activation of inferior frontal cortex during emotional speech perception. Neuroimage 2004;21(3):1114–23.
[89] Royet JP, Plailly J, Delon-Martin C, Kareken DA, Segebarth C. fMRI of emotional responses to odors: influence of hedonic valence and judgment, handedness, and gender. Neuroimage 2003;20(2):713–28.
[90] Bunzeck N, Wuestenberg T, Lutz K, Heinze HJ, Jancke L. Scanning silence: mental imagery of complex sounds. Neuroimage 2005;26(4):1119–27.
[91] Reinholz J, Pollmann S. Differential activation of object-selective visual areas by passive viewing of pictures and words. Brain Res Cogn Brain Res 2005;24(3):702–14.
[92] Hamann S, Herman RA, Nolan CL, Wallen K. Men and women differ in amygdala response to visual sexual stimuli. Nat Neurosci 2004;7(4):411–6.
[93] Takahashi H, Matsuura M, Yahata N, Koeda M, Suhara T, Okubo Y. Men and women show distinct brain activations during imagery of sexual and emotional infidelity. Neuroimage 2006;32(3):1299–307.
[94] Cahill L. Sex-related influences on the neurobiology of emotionally influenced memory. Ann N Y Acad Sci 2003;985:163–73.
[95] Cahill L, Uncapher M, Kilpatrick L, Alkire MT, Turner J. Sex-related hemispheric lateralization of amygdala function in emotionally influenced memory: an FMRI investigation. Learn Mem 2004;11(3):261–6.
[96] Canli T, Desmond JE, Zhao Z, Gabrieli JD. Sex differences in the neural basis of emotional memories. Proc Natl Acad Sci U S A 2002;99(16):10789–94.
[97] Mackiewicz KL, Sarinopoulos I, Cleven KL, Nitschke JB. The effect of anticipation and the specificity of sex differences for amygdala and hippocampus function in emotional memory. Proc Natl Acad Sci U S A 2006;103(38):14200–5.
[98] Koscik T, Bechara A, Tranel D. Sex-related functional asymmetry in the limbic brain. Neuropsychopharmacology 2010;35(1):340–1.
[99] Gur RC, Alsop D, Glahn D, et al. An fMRI study of sex differences in regional activation to a verbal and a spatial task. Brain Lang 2000;74(2):157–70.
[100] Hugdahl K, Thomsen T, Ersland L. Sex differences in visuo-spatial processing: an fMRI study of mental rotation. Neuropsychologia 2006;44(9):1575–83.
[101] Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. PLoS Med 2009;6(7):e1000097.
[102] Talairach J, Tornoux P. Co-planar stereotaxic atlas of the human brain : 3-dimensional proportional system : an approach to cerebral imaging. Stuttgart: Georg Thieme; 1988 [122 p.p.].
[103] Mazziotta J, Toga A, Evans A, et al. A probabilistic atlas and reference system for the human brain: International Consortium for Brain Mapping (ICBM). Philos Trans R Soc Lond B Biol Sci 2001;356(1412):1293–322.
[104] Domes G, Schulze L, Bottger M, et al. The neural correlates of sex differences in emotional reactivity and emotion regulation. Hum Brain Mapp 2010;31(5):758–69.
[105] Young LJ, Wang Z. The neurobiology of pair bonding. Nat Neurosci 2004;7(10):1048–54.
[106] Cahill L, Haier RJ, White NS, et al. Sex-related difference in amygdala activity during emotionally influenced memory storage. Neurobiol Learn Mem 2001;75(1):1–9.
[107] LeDoux JE. Emotion circuits in the brain. Annu Rev Neurosci 2000;23:155–84.
[108] Bechara A, Damasio H, Damasio AR. Emotion, decision making and the orbitofrontal cortex. Cereb Cortex 2000;10(3):295–307.
[109] Davis M, Rainnie D, Cassell M. Neurotransmission in the rat amygdala related to fear and anxiety. Trends Neurosci 1994;17(5):208–14.
[110] Veselis RA, Reinsel RA, Beattie BJ, et al. Midazolam changes cerebral blood flow in discrete brain regions: an H2(15)O positron emission tomography study. Anesthesiology 1997;87(5):1106–17.
[111] Zhang L, Chang YH, Feldman AN, et al. The expression of GABA(A) receptor alpha2 subunit is upregulated by testosterone in rat cerebral cortex. Neurosci Lett 1999;265(1):25–8.
[112] Cheung CC, Lee TM, Yip JT, King KE, Li LS. The differential effects of thalamus and basal ganglia on facial emotion recognition. Brain Cogn 2006;61(3):262–8.
[113] Lotze M, Reimold M, Heymans U, Laihinen A, Patt M, Halsband U. Reduced ventrolateral fMRI response during observation of emotional gestures related to the degree of dopaminergic impairment in Parkinson disease. J Cogn Neurosci 2009;21(7):1321–31.
[114] Gorman JM, Kent JM, Sullivan GM, Coplan JD. Neuroanatomical hypothesis of panic disorder, revised. Am J Psychiatry 2000;157(4):493–505.
[115] Pessoa L, Adolphs R. Emotion processing and the amygdala: from a 'low road' to 'many roads' of evaluating biological significance. Nat Rev Neurosci 2010;11(11):773–83.
[116] Klein S, Smolka MN, Wrase J, et al. The influence of gender and emotional valence of visual cues on FMRI activation in humans. Pharmacopsychiatry 2003;36(Suppl. 3):S191–4.
[117] Wrase J, Klein S, Gruesser SM, et al. Gender differences in the processing of standardized emotional visual stimuli in humans: a functional magnetic resonance imaging study. Neurosci Lett 2003;348(1):41–5.
[118] Mann SL, Hazlett EA, Byne W, et al. Anterior and posterior cingulate cortex volume in healthy adults: effects of aging and gender differences. Brain Res 2011;1401:18–29. Epub 2011 May 27.
[119] Donner N, Handa RJ. Estrogen receptor beta regulates the expression of tryptophan-hydroxylase 2 mRNA within serotonergic neurons of the rat dorsal raphe nuclei. Neuroscience 2009;163(2):705–18.
[120] Hiroi R, McDevitt RA, Neumaier JF. Estrogen selectively increases tryptophan hydroxylase-2 mRNA expression in distinct subregions of rat midbrain raphe nucleus: association between gene expression and anxiety behavior in the open field. Biol Psychiatry 2006;60(3):288–95.