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A meta-analysis of sex differences in human brain structure☆

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ABSTRACT

The prevalence, age of onset, and symptomatology of many neuropsychiatric conditions differ between males and females. To understand the causes and consequences of sex differences it is important to establish where they occur in the human brain. We report the first meta-analysis of typical sex differences on global brain volume, a descriptive account of the breakdown of studies of each compartmental volume by six age categories, and whole-brain voxel-wise meta-analyses on brain volume and density. Gaussian-process regression coordinate-based meta-analysis was used to examine sex differences in voxel-based regional volume and density. On average, males have larger total brain volumes than females. Examination of the breakdown of studies providing total volumes by age categories indicated a bias towards the 18–59 year-old category. Regional sex differences in volume and tissue density include the amygdala, hippocampus and insula, areas known to be implicated in sex-biased neuropsychiatric conditions. Together, these results suggest candidate regions for investigating the asymmetric effect that sex has on the developing brain, and for understanding sex-biased neurological and psychiatric conditions.

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1. Introduction

The prevalence, age of onset, and symptomatology of many neurological and psychiatric conditions differ substantially between males and females (Bao and Swaab, 2010; Baron-Cohen et al., 2011; Central Brain Tumour Registry of the United States, 2012; Paus et al., 2008; Rutter et al., 2003). Examples of male-biased conditions include autism, attention deficit/hyperactivity disorder, conduct disorder, specific language impairment, Tourette syndrome, and dyslexia, and examples of female-biased conditions include depression, anxiety disorder, and anorexia nervosa (Bao and Swaab, 2010; Baron-Cohen et al., 2011; Rutter et al., 2003). Factors influencing the asymmetric effect that sex has on brain development may help us understand how and why male and female brains differ in their predisposition for risk for or resilience to such conditions. Identifying where and in what way male and female brains differ will help illuminate these factors and associated mechanisms. Previous whole-brain and region-of-interest studies on sex differences in typically developing human brains show contradictory results, which may be due to small sample sizes and/or variability in age range of the sample in individual studies, leading to opposing or non-significant findings. To summarize the evidence, we report the first meta-analysis of overall and voxel-wise regional brain structure of sex differences in the typically developing human brain and provide a descriptive account of the breakdown of studies providing overall volumes by age category.

Understanding the influence of sex on the developing brain can provide insight into what is happening during the development of psychopathological conditions that are asymmetrically affected between sexes. Sex differences in brain structure are a product of the interaction of biological and environmental influences on brain development (McCarthy and Arnold, 2011). Animal studies have shown that (prenatal) hormones (Arnold and Breedlove, 1985; Phoenix et al., 1959), sex chromosomes (Arnold and Chen, 2009; De Vries et al., 2002), and the immune system (Lenz et al., 2013) all have early roles in the development of neural sexual differentiation. In addition, brain development is also influenced by factors such as sex-biased gene expression (Kang et al., 2011), steroid hormones (Giedd et al., 2012), early life programming such as prenatal nutrition/starvation (DeLong, 1993; Heijmans et al., 2008), stress and maternal infections (Bale et al., 2010), and postnatal factors such as early child care (Center on the Developing Child, 2012; Cicchetti, 2013; Rutter et al., 2003).

Meta-analysis is a statistical framework summarizing themes from the existent literature. Within this framework bias and variability is characterized and quantified leading to a reliable consensus. Recent extension of meta-analysis to brain imaging datasets has identified key regions of structure and function that are consistently detected in a wide range of psychiatric disorders (Etkin and Wager, 2007; Menzies et al., 2008; Valera et al., 2007). However, although a variety of phenomena differ in many psychiatric conditions as a function of sex (Bao and Swaab, 2010; Baron-Cohen et al., 2011; Paus et al., 2008; Rutter et al., 2003), and sex differences in brain function have been systematically reviewed in the typically developing population (Giedd et al., 2012; Sacher et al., 2013; Stevens and Hamann, 2012), to our knowledge no meta-analysis has been conducted on overall or regional voxel-based structural brain differences between human males and females.

In the current study, we carried out two types of meta-analysis. First, we examined sex differences in overall brain volumes. As development and ageing have a large influence on total brain volume, we also investigated if different age categories were well represented in the literature by providing a description of the number of articles, number of total participants and weighted mean volume of each compartmental volume for each of the six age categories. Next, we conducted foci-based meta-analyses on regional differences between males and females, one with voxel-based studies of volume and one with voxel-based studies of tissue density. Gaussian-process regression coordinate-based meta-analysis (GPR-CBMA) was used for the voxel-based meta-analyses, as this new technique allows for relatively more accurate results by incorporating effect-size estimates from source data (Salimi-Khorshidi et al., 2011). Furthermore, GPR-CBMA is also advantageous because its output includes meta-analytic effects in both positive and negative directions as well as an estimate of magnitude models censoring within the source data (i.e., reporting significant foci only), infers the smoothness of meta-analytic statistic images, and provides an effect-size map (i.e., *T*- and/or *Z*-stat) across the entire intra-cranial space.

2. Methods

2.1. Systematic literature search

The literature search was conducted according to PRISMA guidelines (Moher et al., 2009) for reporting meta-analyses and systematic reviews. The search, conducted in PubMed, Web of Knowledge and Scopus, included articles published between 1990 and January 2013. Search terms used were "brain" AND (sex OR gender OR sex difference OR gender difference) AND (voxel* OR morphometry OR diffusion tensor imaging OR magnetic resonance imaging OR DTI or MRI OR VBM). MeSH terms for "brain" and "sex differences" were also included in the PubMed search.

Authors were contacted if articles were not available online and/or if there was a question about the data presented in the article (e.g., when parameters needed for the meta-analysis, such as effect size information or standard deviations, were not reported in the article). Only articles written in English were included in this analysis. Unpublished materials were not explored and publications performing region-of-interest analysis were excluded. Publications were first selected based on title and then imported into EndNote X4 for abstract selection. After abstract selection, publications were checked for inclusion criteria and reference lists of included articles were crosschecked for potential articles.

2.2. Selection criteria

Articles were included in the overall volumes analyses if they explicitly provided (1) any of the following raw (not corrected for age, body size, etc.) mean brain volumes for typically developing males and females: intracranial volume (ICV), total brain volume (TBV), cerebrum (Cb), grey matter (GM), white matter (WM), cerebrospinal fluid (CSF), or cerebellum (Cbl) and (2)