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Research report

Investigating the differential contributions of sex and brain size to gray matter asymmetry

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ABSTRACT

Scientific reports of sex differences in brain asymmetry – the difference between the two hemispheres – are rather inconsistent. Some studies report no sex differences whatsoever, others reveal striking sex effects, with large discrepancies across studies in the magnitude, direction, and location of the observed effects. One reason for the lack of consistency in findings may be the confounding effects of brain size as male brains are usually larger than female brains. Thus, the goal of this study was to investigate the differential contributions of sex and brain size to asymmetry with a particular focus on gray matter. For this purpose, we applied a well-validated workflow for voxel-wise gray matter asymmetry analyses in a sample of 96 participants (48 males/48 females), in which a subsample of brains (24 males/24 females) were matched for size. By comparing outcomes based on three different contrasts – all males versus all females; all large brains versus all small brains; matched males versus matched females – we were able to disentangle the contributing effects of sex and brain size, to reveal true (size-independent) sex differences in gray matter asymmetry: Males show a significantly stronger rightward asymmetry than females within the cerebellum, specifically in lobules VII, VIII, and IX. This finding agrees closely with prior research suggesting sex differences in sensorimotor, cognitive and emotional function, which are all moderated by the respective cerebellar sections. No other significant sex effects were detected across the remainder of the brain.

1. Introduction

Sex differences in brain anatomy are manifold and have been described in an abundance of studies, in which the most consistent observation is a larger brain size, on average, in males than in females (Giedd, Raznahan, Mills, & Lenroot, 2012; Gong, He, & Evans, 2011; Luders & Toga, 2010; Sacher, Neumann, Okon-Singer, Gotowiec, & Villringer, 2013). Another frequently assessed feature with respect to the sexual dimorphism of the human brain is its asymmetry. Interestingly, while some studies detected no significant

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differences between male and female brains, others revealed striking sex effects on brain asymmetry, where there are large discrepancies in findings with respect to effect magnitude, direction, and location (Fan et al., 2010; Geschwind & Galaburda, 1985b; Good et al., 2001; Guadalupe et al., 2016; Jancke, Schlaug, Huang, & Steinmetz, 1994; Kovalev, Kruggel, & von Cramon, 2003; Kurth, Jancke, & Luders, 2017; Luders, Gaser, Jancke, & Schlaug, 2004; Luders, Narr, Thompson, et al., 2006; Savic, 2014; Takao et al., 2011; Toga, Narr, Thompson, & Luders, 2009; Toga & Thompson, 2003; Watkins et al., 2001; Wisniewski, 1998; Yucel et al., 2001; Zilles et al., 1997). A few asymmetry studies have specifically focused on mapping gray matter differences between the hemispheres using voxel-based morphometry (VBM). However, outcomes are similarly inconsistent, ranging from no sex differences whatsoever to significant sex differences in various gray matter regions, not necessarily overlapping across studies and with conflicting findings in terms of whether male or female brains are more asymmetric (Fan et al., 2010; Good et al., 2001; Luders et al., 2004; Savic, 2014; Takao et al., 2011; Watkins et al., 2001).

It is not entirely clear if sex-specific gray matter asymmetries reflect sex differences in the performance of tasks that are lateralized (Shaywitz et al., 1995), whether they are a sequel of sex differences in brain connectivity (Ingalhalikar et al., 2014), or both. In addition, there may be yet another reason to expect sex differences in brain asymmetry, namely the sex-specific brain size, which is typically larger in males. According to the Ringo hypothesis (Ringo, 1991; Ringo, Doty, Demeter, & Simard, 1994), larger brains are differently connected than smaller brains, to ensure that computational efforts are distributed most efficiently. In larger brains, for example, this might manifest as more connections within one hemisphere but fewer connections across hemispheres, ultimately resulting in an increased hemispheric specialization and potentially stronger asymmetry (Hanggi, Fovenyi, Liem, Meyer, & Jancke, 2014; Jancke & Steinmetz, 2003; Jancke, Staiger, Schlaug, Huang, & Steinmetz, 1997; Ringo, 1991; Ringo et al., 1994). This hypothesis matches well with some reports that male brains are more asymmetric, in some respects, than female brains (Shaywitz et al., 1995; Toga & Thompson, 2003; Toga et al., 2009). Surprisingly though, while analyses have been conducted to assess sex differences in gray matter asymmetry (Fan et al., 2010; Geschwind & Galaburda, 1985b; Good et al., 2001; Kovalev et al., 2003; Luders et al., 2004; Luders, Narr, Thompson, et al., 2006; Savic, 2014; Takao et al., 2011; Toga et al., 2009; Toga & Thompson, 2003; Watkins et al., 2001; Wisniewski, 1998; Yucel et al., 2001; Zilles et al., 1997), there is a lack of studies systematically investigating how much of this apparent sex difference in gray matter asymmetry is attributable to the typical sex difference in brain size. In other words, it still remains to be addressed if there are any sex differences in gray matter asymmetry after properly accounting for the sex differences in brain size. Similarly, it needs to be resolved if male or female brains show a stronger gray matter asymmetry, and which brain regions are affected in particular.

Thus, the goal of the current study was to investigate the differential contributions of sex and brain size on gray matter asymmetry. For this purpose, we applied a well-validated workflow for voxel-wise asymmetry analyses (Kurth, Gaser, & Luders, 2015) and compiled a sample of 96 participants (48 males/48 females), in which a subsample of brains (24 males/24 females) were matched for size. By contrasting outcomes based on three different contrasts – all males versus all females; all large brains versus all small brains; matched males versus matched females – we were able to disentangle the contributing effects of sex and brain size, revealing true (size-independent) sex differences in gray matter asymmetry.

2. Methods

2.1. Study sample and imaging parameters

High-resolution T1-weighted images ($n = 153$) were obtained from the ICBM database (www.loni.usc.edu/ICBM) of healthy participants rigorously screened and medically evaluated (Mazziotta et al., 2009). To minimize the influence of age-related brain atrophy, participants older than 70 years were excluded for the current study, leaving 145 participants altogether (72 males/73 females) aged 18–69 years. This sample was then further reduced to 96 participants (48 males/48 females) as detailed in the next section. All images were acquired on the same Siemens Sonata 1.5 T MRI system at UCLA using an 8-channel head coil and the same T1-weighted MPRAGE sequence with the following parameters: TR = 1900 ms, TE = 4.38 ms, flip angle = 15°, 160 contiguous 1 mm sagittal slices, FOV = 256×256 mm^2, voxel dimensions = $1.0 \times 1.0 \times 1.0$ mm^3. All participants gave informed consent according to UCLA's Institutional Review Board.

2.2. Brain sizes and (sub)samples

Brain size was estimated using SPM8 (http://www.fil.ion.ucl.ac.uk/spm) and the VBM8 Toolbox (http://dbm.neuro.uni-jena.de/vbm.html) as detailed elsewhere (Luders, Gaser, Narr, & Toga, 2009). Briefly, the T1-weighted images were segmented into gray matter, white matter, and cerebrospinal fluid, and the respective tissue volumes were added up to calculate the total intracranial volume (TIV) in milliliters (ml). The resulting TIVs were then used to create the size-matched subsample consisting of 24 males and 24 females; the TIV difference within each matched pair was minute (≤5.16 ml). In addition, the resulting TIVs were used to identify 24 extremely small female brains as well as 24 extremely large male brains. Then, by adding the 48 brains of the extreme sample to the 48 brains of the matched sample, we created the whole sample ($n = 96$), which was representative in terms of sex-typical brain sizes (i.e., smaller brains in females, larger brains in males). Table 1 summarizes the TIVs for both matched sample ($n = 48$) and whole sample ($n = 96$).

2.3. Image preprocessing

Image preprocessing followed an established protocol for voxel-wise asymmetry analyses (Kurth et al., 2015). In short, using SPM8 (http://www.fil.ion.ucl.ac.uk/spm) and the VBM8

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