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Meta-analysis reveals a lack of sexual dimorphism in human amygdala volume

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ABSTRACT

The amygdala plays a key role in many affective behaviors and psychiatric disorders that differ between men and women. To test whether human amygdala volume (AV) differs reliably between the sexes, we performed a systematic review and meta-analysis of AVs reported in MRI studies of age-matched healthy male and female groups. Using four search strategies, we identified 46 total studies (58 matched samples) from which we extracted effect sizes for the sex difference in AV. All data were converted to Hedges g values and pooled effect sizes were calculated using a random-effects model. Each dataset was further meta-regressed against study year and average participant age. We found that uncorrected amygdala volume is about 10% larger in males, with pooled sex difference effect sizes of g=0.581 for right amygdala (κ=28, n=2022), 0.666 for left amygdala (κ=28, n=2006), and 0.876 for bilateral amygdala (κ=16, n=1585) volumes (all p values < 0.001). However, this difference is comparable to the sex differences in intracranial volume (ICV; g=1.186, $p < .001$, 11.9% larger in males, κ=11) and total brain volume (TBV; g=1.278, $p < 0.001$, 11.5% larger in males, κ=15) reported in subsets of the same studies, suggesting the sex difference in AV is a product of larger brain size in males. Among studies reporting AVs normalized for ICV or TBV, sex difference effect sizes were small and not statistically significant: g=0.171 for the right amygdala (p=0.206, κ=13, n=1560); 0.233 for the left amygdala (p=0.092, κ=12, n=1512); and 0.257 for bilateral volume (p=0.131, κ=5, n=1629). These values correspond to less than 0.1% larger corrected right AV and 2.5% larger corrected left AV in males compared to females. In summary, AV is not selectively enhanced in human males, as often claimed. Although we cannot rule out subtle male-female group differences, it is not accurate to refer to the human amygdala as "sexually dimorphic."

Introduction

The amygdala is a highly-connected limbic structure that participates in the processing of all types of emotion (Costafreda et al., 2008), face recognition (Haxby et al., 2002), aggression (Rosell and Siever, 2015), sexual arousal (Kuhn and Gallinat, 2011), anxiety, and fear conditioning (Janak and Tye, 2015). In accordance with such roles, amygdala dysfunction has been implicated in several psychiatric disorders, including autism (Cauda et al., 2011), major depressive illness (Sacher et al., 2012), posttraumatic stress disorder (PTSD; O'Doherty et al., 2015), addiction disorders (Hammerslag and Gulley, 2016; Wassum and Izquierdo, 2015), schizophrenia (Wright et al., 2000), bipolar disorder (Hallahan et al., 2011), and borderline personality disorder (BPD; Ruocco et al., 2012). Since many of these behaviors (Hyde, 2014) and diagnoses (Kessler et al., 2005) differ between males and females, it is reasonable to suspect that sex differences in amygdala structure and function contribute to social-emotional sex differences, including the risk for psychiatric disorders.

For example, anxiety and depressive disorders are more common in women than men and could reflect females' higher neural reactivity to social-emotional stimuli (Bangasser and Valentino, 2014). Prior meta-analyses have suggested that amygdala volume is smaller in patients suffering from depression (Hamilton et al., 2008; Sacher et al., 2012), PTSD (O'Doherty et al., 2015) and BPD (Nunes et al., 2009; Ruocco et al., 2012) compared to matched healthy control participants. It is possible that a premorbidly smaller AV contributes to females' higher risk for disorders such as BPD (Ruocco et al., 2012), anxiety and depression (Lenroot and Giedd, 2010). Conversely, a sex difference in AV might also predispose boys and men to diagnoses such as autism (Yu et al., 2011), addiction (Ersche et al., 2013) or impulse control disorders (Fairchild et al., 2011; Pardini et al., 2014), all of which have also been linked to amygdala dysfunction.

Animal studies lay further foundation for suspecting that AV is larger in males. In rats, the medial amygdala has been shown to participate in several behaviors that differ between males and females, including aggression (Wang et al., 2013), rough-and-tumble play

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(Meaney and McEwen, 1986) and sexual performance (Newman, 1999). One portion of the medial amygdala, the posterodorsal zone, has been found to be larger in male rats, compared to females, both before and after puberty (Cooke et al., 2007). This volume difference has been linked to higher synaptic density, larger average soma sizes, and a greater level of neurogenesis in the amygdala of male rats, compared to females (Ahmed et al., 2008; Cooke, 2006). A similar sex difference has been found in the guinea pig, where the larger volume of males' medial amygdala is sufficient to drive a difference in overall AV between males and females (Rowniak, 2013).

The amygdala is a site of high androgen receptor density (Sato et al., 2008; Simerly et al., 1990) and rodent studies have demonstrated that sex differences in medial amygdala morphology and the behaviors it controls are importantly influenced by testosterone. For example, young female rats that received testosterone implants in the medial amygdala shortly after birth exhibited rates of rough-and-tumble play comparable to males (Meaney and McEwen, 1986). Similar research in hamsters found that male sexual behaviors were enhanced by testosterone infused into the medial amygdala (Wood and Newman, 1995). Pubertal testosterone appears to increase neurogenesis in the medial amygdala of male rats (Ahmed et al., 2008) and this and other long-term changes in circulating testosterone level have been shown to influence both the regional volume and cellular morphology of the amygdala in male rats and hamsters, perhaps serving as a neural substrate for sex differences in amygdala-dependent behaviors (Cooke, 2006).

Turning to human research, many reviews of human brain sex difference single out the amygdala as a structure that is larger in males, even when corrected for individual differences in overall brain volume (Andreano and Cahill, 2009; Cahill, 2006; Durston et al., 2001; Giedd et al., 2012; Hines, 2011). However, the sources for this claim rarely go beyond one or two very early imaging studies (Giedd et al., 1996; Goldstein et al., 2001). An early meta-analysis (Brierley et al., 2002) similarly reported that AV is larger in males, but this was based on relatively few studies and, importantly, compared men and women across different studies, not those explicitly matched within individual studies. By contrast, several recent and very large studies have reported no sex difference in AV (Inano et al., 2013), or very small differences (Fjell et al., 2009) with sex accounting for no more than 1% of the variance (Jäncke et al., 2015) in AV across the population. The range of findings across these various studies suggests that narrative reviews may be missing negative findings and calls out for a more thorough analysis.

We therefore undertook systematic meta-analysis of the sex difference in human AV, exploiting the large number of recent morphometry studies to quantify the difference in AV between age-matched samples of healthy males and females. Our data sweep captured studies that reported both "raw" or native AV measures as well as AVs that were corrected for individual differences in TBV or ICV. Such overall brain measures average some 10–14% larger in men, so any comparison of regional volumes between males and females must take allometric scaling into account (Lüders et al., 2002; Leonard et al., 2008; Voevodskaya et al., 2014; de Jong et al., 2016). We therefore separately analyzed sex differences in raw and corrected AVs. We further tested for age effects on AV sex differences, based on prior studies suggesting that a sex difference in corrected AV emerges only at puberty in humans (Giedd et al., 1996; Neufang et al., 2009).

Material and methods

This study was performed according to Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (Moher et al., 2009).

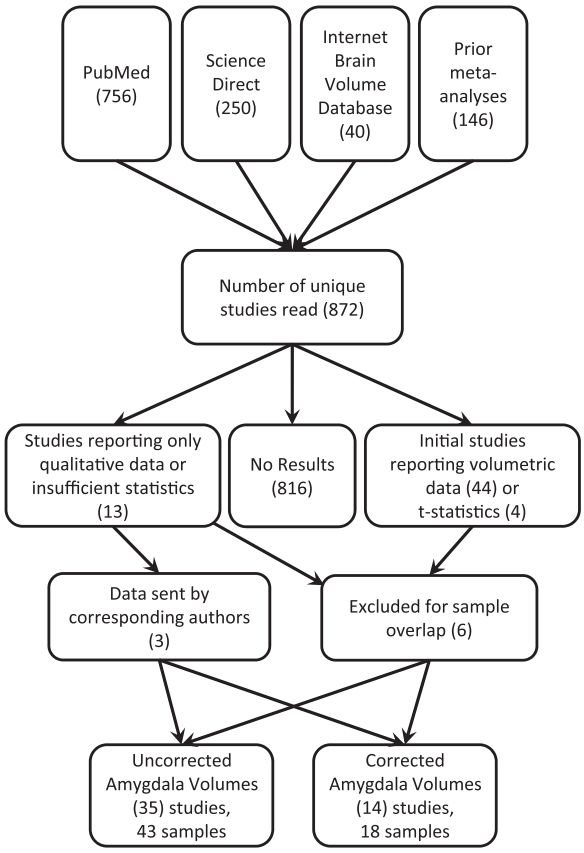

Fig. 1. Search strategies and results, with parentheses indicating the number of studies at each step.

Search strategy

We used four approaches to search the literature for studies reporting amygdala volumes (AVs) from age-matched groups of healthy males and females (Fig. 1). The primary search was in PubMed and included all results through January 1, 2015 for English-language articles using the terms: amygdala AND MRI AND volume AND (sex OR gender OR (male AND female) OR (males AND females)). The second approach employed a full-text search of the ScienceDirect database using the search terms: amygdala AND (sex OR gender) AND volume AND (MRI OR magnetic resonance). The first 250 hits from this search, sorted by "relevance" as of September 15, 2014 were included. Third, we searched the Internet Volume Brain Database (http://www.cma.mgh.harvard.edu/ibvd/search.php) for studies that published male and female AVs of healthy controls as of August 21, 2014. Fourth, we hand-searched 27 prior meta-analyses of amygdala volume (listed in Supplementary material) to find primary studies that reported data by sex or gender for healthy participants.

Data extraction and elimination of duplication

These four search strategies netted 872 unique papers that were read in full. Of these, 44 papers reported the mean AVs ± SD in age-matched samples of healthy males and females, with a minimum sample size of eight participants. Four other papers reported t-values for the between-group comparison of amygdala volume in matched samples of males and females. We further identified 13 publications that reported qualitative data, insufficient statistics, or graphical comparisons of matched male-female groups, but did not publish numerical volumes or t-values. Among these, we emailed the authors of all but two of the studies (published in 2000 or earlier) to request mean ± SD amygdala volumes for male and female groups. Authors of