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Sex differences in emotional perception: Meta analysis of divergent activation

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ABSTRACT

Behavioral and physiological sex differences in emotional reactivity are well documented, yet comparatively few neural differences have been identified. Here we apply quantitative activation likelihood estimation (ALE) meta-analysis across functional brain imaging studies that each reported clusters of activity differentiating men and women as they participated in emotion-evoking tasks in the visual modality. This approach requires the experimental paradigm to be balanced across the sexes, and thus may provide greater clarity than previous efforts. Results across 56 emotion-eliciting studies (n=1907) reveal distinct activation in the medial prefrontal cortex, anterior cingulate cortex, frontal pole, and mediodorsal nucleus of the thalamus in men relative to women. Women show distinct activation in bilateral amygdala, hippocampus, and regions of the dorsal midbrain including the periaqueductal gray/superior colliculus and locus coeruleus. While some clusters are consistent with prevailing perspectives on the foundations of sex differences in emotional reactivity, thalamic and brainstem regions have not previously been highlighted as sexually divergent. These data strongly support the need to include sex as a factor in functional brain imaging studies of emotion, and to extend our investigative focus beyond the cortex.

1. Introduction

Many human imaging studies have explored sex differences in the neural correlates of emotional reactivity (Kogler et al., 2015; Lee et al., 2014; Young et al., 2013). Often, the results of these efforts highlight the role of the amygdala (Andreano et al., 2014; Domes et al., 2010; Schneider et al., 2011; Williams et al., 2005) However, recent structural neuroimaging (Ingalhalikar et al., 2014; Simmonds et al., 2014) and resting-state functional imaging studies (Tomasi and Volkow, 2012) suggest that sex differences are widespread across the cortex, reflecting subtle yet distinct regional and intra/interhemispheric connectivity patterns. An accounting of these modest distinctions with large functional imaging datasets may thus help to define sex-specific emotional reactivity.

Indeed, there have been recent attempts to analyze and review sex differences in the neural foundations of emotional processing using qualitative (Kret and De Gelder, 2012; Whittle et al., 2011) and quantitative methods (Stevens and Hamann 2012). Each of these works has yielded a valuable contribution based on an integration of a wide range of published experiments, all having some relevance to emotional processing, broadly defined. However, as the empirical works from which these reviews are based are seldom focused on the question of sex differences, it is essential that the review process involves the assumption of equivalence among studies of emotion that sampled women with studies of emotion that sampled men.

Here, we use Activation Likelihood Estimation (ALE) methods (Eickhoff et al., 2012) to combine studies published over a 20-year period that report direct contrasts between men and women participating in the same emotion-eliciting task within each study. In this way, any variation that exists across individual experiments in experimental paradigm, data collection, and analysis methods are balanced across sex. Thus, the sample population and size are likely to be more consistent across sex than has been achieved in past efforts to meta analyze sex differences in emotional processing.

Moreover, since differences in neural activation across studies may also be due to disparity in the methods of emotion elicitation (e.g., via

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autobiographical memory, stress, pain), here we limited our analysis to studies using emotion elicited with visual cues in an effort to reduce the potential for heterogeneity of neural recruitment.

We expect that by requiring each study to report direct contrasts between men and women engaged in the same emotion-eliciting task within the visual modality (e.g. faces, scenes, text), a more reliable pattern of results may be revealed. This level of confound control may result in the identification of novel cortical and subcortical regions that differentiate the emotional processes of men and women, and foster the development of new research targets.

2. Methods

Articles from January 1 1995 through March 1 2015 were identified using a specific search string in the PubMed database:

((((emotion*[Title/Abstract] OR affectiv*[Title/Abstract] OR fear*[Title/Abstract] OR disgust*[Title/Abstract] OR reward*[Title/Abstract] OR aversive*[Title/Abstract] OR appetitiv*[Title/Abstract])) AND (fMRI OR "functional magnetic resonance imaging"[Title/Abstract] OR "functional MRI"[Title/Abstract] OR neuroimaging[Title/Abstract] OR "neural correlates"[Title/Abstract] OR "brain imaging"[Title/Abstract])) AND (sex*[Title/Abstract] OR gender*[Title/Abstract] OR men[Title/Abstract] OR male[Title/Abstract] OR males[Title/Abstract] OR women[Title/Abstract] OR female[Title/Abstract] OR females[Title/Abstract])) AND ("1995/01/01"[Date - Publication]: "2015/03/01"[Date - Publication]).

Published journal articles were included if: 1) authors reported whole-brain fMRI contrast results in Talairach or MNI space 2) sampled at least five adult participants of each sex, and 3) used an emotion eliciting paradigm in the visual domain. Studies of clinical populations were excluded; however, clinical studies that reported sex differences amongst a healthy control group were included if listed separately. Articles that met these criteria were reviewed by at least two authors to evaluate the appropriateness of inclusion.

2.1. Contrast inclusion details

All contrasts reflected statistically significant whole brain clusters active during emotional stimuli compared to neutral stimuli in men and women. Direct contrasts of men > women and/or women > men were required for inclusion in the analysis (see Table 1). For studies in which multiple contrasts are reported, the contrast representing a visual emotional cue was chosen. For studies in which multiple visual-modality contrasts are reported, the contrast representing the most experimentally basic or simple contrast was chosen (e.g., highly evocative scene vs. neutral scene, rather than highly evocative scene vs. moderately evocative scene). A description of each chosen contrast is listed in Table 1.

2.2. ALE meta analysis process

Activation likelihood estimation (ALE; Laird et al., 2005; Turkeltaub et al., 2002) is a coordinate-based quantitative meta-analysis method that can be used to identify consistent locations of brain activation elicited across studies employing similar tasks. In ALE, activation foci reported in published studies are treated as probability distributions centered at the reported coordinates. Activation probabilities are then calculated for each standard-space voxel to construct ALE maps for contrasts of interest. To determine the reliability of the ALE map, null-distributions are generated by analyzing the distribution of ALE values across independent studies, which is conceptually similar to using permutation tests of individual voxels across experiments. The observed values in the ALE distribution are then compared to the null distribution in order to assign probability estimates to the observed (experimental) data (Eickhoff et al., 2012). Here we used GingerALE v2.3.2 (http://www.brainmap.org) with a conservative mask size and use of the Eickhoff ALE method, a variable FWHM spatial filter kernel (Eickhoff et al., 2009), and a cluster-based multiple comparisons correction in which an uncorrected threshold of $p < .01$ was permuted 100 times to arrive at a minimum cluster volume that guarantees a $p < .005$ probability of a false-positive. Two separate analyses were conducted to examine regions during which men exhibited increased activation relative to women (men > women) and regions during which women exhibited increased activation relative to men (women > men). All ALE coordinate clusters are reported in Talairach space. A detailed description of the ALE process and analysis procedures and correction methods can be found on the Brainmap website (http://www.brainmap.org/ale/manual.pdf).

3. Results

3.1. Article Inclusion

The final analysis included 56 fMRI experiments of visually-evoked emotion. Included studies are listed by publication year in Table 1. The total n = 1908, including 947 men and 961 women. There was no significant difference in the number of women relative to men (X^2 (1, N=1908)=0.1, p=.777). Ages of subjects ranged from 18–65. Average ages for each sex in each study can be found in Table 1. There was no significant difference in the ages of men and women included within each study. Some of the included studies also matched subjects based on years of education (N=22) or evaluated other factors such as intelligence (N=8), but this was not consistent across studies. A total of 46% of studies included only unpleasant emotional stimuli, 36% studies included both pleasant and unpleasant stimuli, and 18% included only pleasant stimuli. Across the study pool, 52 contrasts yielded coordinates in which men showed greater activity than women, and 54 contrasts yielded coordinates in which women showed greater activity than men. The total number of foci entered into the ALE analysis was 773, including 435 foci representing clusters in men greater than women, and 338 foci representing clusters in women greater than men.

3.2. Emotional activation

An overlay of ALE maps for men and women is shown in Fig. 1. Orange clusters represent areas of activation that were greater in women compared to men (women > men) whereas blue clusters represent regions with greater activation in men compared to women (men > women). ALE superclusters, large clusters comprised of several distinct regions, resulting from *men > women* and *women > men* contrasts can be found in Table 2, and the regions which make up the associated superclusters can be found in Table 3. The neuroanatomical region names are derived from the output of the ALE software.

3.3. Men > Women

Men exhibited increased activation relative to women in several regions including the mediodorsal nucleus of the thalamus (MDN) (TAL: −2, −16, 10), bilateral pulvinar (right, TAL: 8, −18, 18; left, TAL: −12, −16, 10), frontal pole (TAL: −2, 60, 22 & −14, 50, 18), and a cluster that included the right ACC (TAL: 20, 44, 6) and right mPFC (TAL: 18, 38, 18).

3.4. Women > Men

Women exhibited increased activation relative to men in bilateral amygdala (right, TAL: 32, −2, −12; left, TAL: −18, −4, −10), and left hippocampus (TAL: −34, 24, 10). In addition, women exhibited increased activation in several regions of the dorsal midbrain including the periaqueductal gray/superior colliculus (TAL: 2, −28, 4) and locus coeruleus (TAL: −8, −24, −16).