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Sex differences in brain activation to emotional stimuli: A meta-analysis of neuroimaging studies

Jennifer S. Stevens, Stephan Hamann*

Department of Psychology, Emory University, 36 Eagle Row, Atlanta, GA 30322, United States

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ABSTRACT

Substantial sex differences in emotional responses and perception have been reported in previous psychological and psychophysiological studies. For example, women have been found to respond more strongly to negative emotional stimuli, a sex difference that has been linked to an increased risk of depression and anxiety disorders. The extent to which such sex differences are reflected in corresponding differences in regional brain activation remains a largely unresolved issue, however, in part because relatively few neuroimaging studies have addressed this issue. Here, by conducting a quantitative meta-analysis of neuroimaging studies, we were able to substantially increase statistical power to detect sex differences relative to prior studies, by combining emotion studies which explicitly examined sex differences with the much larger number of studies that examined only women or men. We used an activation likelihood estimation approach to characterize sex differences in the likelihood of regional brain activation elicited by emotional stimuli relative to non-emotional stimuli. We examined sex differences separately for negative and positive emotions, in addition to examining all emotions combined. Sex differences varied markedly between negative and positive emotion studies. The majority of sex differences favoring women were observed for negative emotion, whereas the majority of the sex differences favoring men were observed for positive emotion. This valence-specificity was particularly evident for the amygdala. For negative emotion, women exhibited greater activation than men in the left amygdala, as well as in other regions including the left thalamus, hypothalamus, mammillary bodies, left caudate, and medial prefrontal cortex. In contrast, for positive emotion, men exhibited greater activation than women in the left amygdala, as well as greater activation in other regions including the bilateral inferior frontal gyrus and right fusiform gyrus. These meta-analysis findings indicate that the amygdala, a key region for emotion processing, exhibits valence-dependent sex differences in activation to emotional stimuli. The greater left amygdala response to negative emotion for women accords with previous reports that women respond more strongly to negative emotional stimuli, as well as with hypothesized links between increased neurobiological reactivity to negative emotion and increased prevalence of depression and anxiety disorders in women. The finding of greater left amygdala activation for positive emotional stimuli in men suggests that greater amygdala responses reported previously for men for specific types of positive stimuli may also extend to positive stimuli more generally. In summary, this study extends efforts to characterize sex differences in brain activation during emotion processing by providing the largest and most comprehensive quantitative meta-analysis to date, and for the first time examining sex differences as a function of positive vs. negative emotional valence. The current findings highlight the importance of considering sex as a potential factor modulating emotional processing and its underlying neural mechanisms, and more broadly, the need to consider individual differences in understanding the neurobiology of emotion.

1. Introduction

Among the many psychological differences between men and women, sex differences in emotion have long held special interest for scientists and laypersons alike. In contrast to popular conceptions of sex differences, for example, of women as being uniformly more emotionally responsive than men, empirical studies of affective behavior and psychophysiology have yielded a more complex and nuanced picture. Empirical studies have reported differences between women and men in their psychological and physiological responses to wide range of emotional stimuli. For example, women have been reported to respond more expressively than men to emotional stimuli, to report feeling more emotion, and to display heightened physiological arousal responses (Bradley, Codispoti,

* Corresponding author. Tel.: +1 404 727 4261; fax: +1 404 727 0372.
E-mail address: shamann@emory.edu (S. Hamann).

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Sabatinelli, & Lang, 2001; Grossman & Wood, 1993; Kring & Gordon, 1998). However, the empirical literature remains somewhat inconsistent regarding the nature of these affective sex differences, and the magnitude of observed sex differences has varied widely across studies (Bradley et al., 2001).

A key dimension of emotion that may help explain variability in the experimental literature on affective sex differences is valence, that is, whether an emotion is positive (pleasant) or negative (unpleasant). Sex differences for studies involving negative emotions have been demonstrated more consistently and have been larger on average relative to positive emotions (e.g., Bradley et al., 2001; Davis & Emory, 1995; McManis, Bradley, Berg, Cuthbert, & Lang, 2001; Sharp, Van Goozen, & Goodyer, 2006; Thomsen, Mehlsen, Viidik, Sommerlund, & Zachariae, 2005). Women's affective responses to negative emotional stimuli have been of particular interest because enhanced responses to negative emotional stimuli and stressors have been theorized to contribute to mechanisms underlying the greater prevalence of depression and anxiety disorders in women (Leach, Christensen, Mackinnon, Windsor, & Butterworth, 2008; Nolen-Hoeksema, 2001; Thomsen et al., 2005).

Fewer studies have investigated sex differences in the context of positive emotions. Although there is currently little evidence to suggest the existence of sex differences in affective responses to positive stimuli in general, limited evidence suggests that men are more emotionally aroused by visual erotica, showing higher subjective ratings of affect and greater skin conductance responses (Bradley et al., 2001; Chivers, Seto, Lalumiere, Laan, & Grimbos, 2010).

These affective sex differences in behavioral and physiological responses ultimately arise from differences in brain activity, and thus to fully understand these differences it is necessary to investigate their neural basis. The extent to which sex differences in emotional response are reflected in regional brain activation as assessed by neuroimaging methods remains a largely open question, however. This is in part because only a small number of neuroimaging studies to date have investigated sex differences in emotional responses by directly comparing women and men's emotional and neural responses to the same stimuli. Meta-analytic methods can help overcome these limitations, by allowing the much larger emotion neuroimaging literature comprised of studies of only one sex to be combined with and augment the smaller literature of studies that have directly compared men and women within the same experiment.

Accordingly, we conducted a quantitative meta-analysis of neuroimaging studies of emotion, that allowed us to substantially increase statistical power to detect sex differences by combining emotion studies that explicitly examined sex differences with the much larger number of studies that examined only one sex. We used a voxel-based meta-analysis approach (Activation Likelihood Estimation, ALE; Eickhoff et al., 2009) to characterize sex differences in the likelihood of regional brain activation elicited by emotional stimuli relative to non-emotional stimuli. Because we hypothesized that sex differences would differ by valence, we examined sex differences separately for positive and negative emotions, in addition to examining differences across all emotions combined. To our knowledge, all previous neuroimaging meta-analyses examining sex differences in emotion have combined positive and negative stimuli together when contrasting women and men, precluding examination of sex differences that vary by emotional valence.

The current study used ALE to synthesize and analyze neuroimaging results bearing on sex differences in emotional brain responses. Among regions that support emotion, we predicted that the amygdala, hypothalamus, ventral striatum, anterior cingulate, orbitofrontal cortex, and insula would exhibit sex differences, on the basis of previous neuroimaging studies of sex differences in emotional responses (e.g., Hamann, Herman, Nolan, & Wallen, 2004; Schienle, Schäfer, Stark, Walter, & Vaitl, 2005; Wrase et al., 2003) and on the distribution of gonadal hormone receptors in the brain (Clark, Maclusky, & Goldman-Rakic, 1988; MacLusky, Naftolin, & Goldman-Rakic, 1986; Roselli, Klosterman, & Resko, 2001). We predicted that sex differences in brain response would differ by emotional valence, with women showing increased activation likelihood in regions associated with emotion, for negative but not for positive emotion. As noted previously, men have been found to be more responsive to specific types of appetitive, positive emotional stimuli and therefore would be expected to show increased activation likelihood for positive emotion. However, because considerably less evidence supports the view that men are more responsive to positive stimuli, our predictions for such increased activations for men were more tentative than our corresponding predictions for women.

2. Methods

2.1. Study selection

To help ensure a representative sample of emotion studies, we used relatively broad inclusion criteria to select studies for inclusion in the analysis. Neuroimaging contrasts contributing to the analysis spanned a variety of types of stimuli and specific emotions (see Table 1 and Fig. 1). For example, several studies included in the analysis examined emotional responses to affectively pleasant or unpleasant stimuli, whereas other studies examined responses to specific emotions such as anger, disgust, fear, happiness or sadness (Table 1 and Fig. 2a).

Candidate studies were selected through searches of PubMed and ISI Web of Science, for publication years 1990–June 2010, to cover the period of investigation from the earliest PET and fMRI studies of healthy emotional brain function in the early 1990s through the present day. The search was restricted to English language studies with human participants. Search terms were applied to all fields: "emotions" OR "emotion" AND ("magnetic resonance imaging" OR "fMRI" OR "PET"). The search yielded 2473 studies. From among this group of studies, we included only those which reported maximal coordinates from female-only and/or male-only samples, and reported coordinates for whole-brain activation maxima in either Talairach space (Talairach & Tournoux, 1988) or Montreal Neurological Institute (MNI) space. No coordinates from ROI analyses were included. Data from patient groups, and participants under the age of 18 or over the age of 55 were excluded. Studies were included only if the experimental task elicited emotion, and included no significant component of other types of cognition such as reasoning. Data was included from studies that examined negative emotions, positive emotions, or a combination of several emotions. In total, 44 studies of women and 44 studies of men contributed one or more sets of activation maxima to the current meta-analysis (a 147% increase in the number of studies since the most recent comparable meta-analysis; Wager, Phan, Liberzon, & Taylor, 2003). Data for women and men were extracted from within-groups results (women-only, or men-only) and no data from comparisons between women and men were included in the meta-analyses. Table 2 summarizes the characteristics of the data set.

Emotions evoked in each neuroimaging study were classified as negative if they were either specific emotions commonly classified in the emotion literature as negative in affective valence, such as anger, fear, disgust, guilt, or sadness, or were reported as having significantly negative valence in the original study from which the emotion contrast was selected. The corresponding classification for the positive emotion condition included responses to pleasant, emotionally arousing stimuli, including responses to erotic stimuli, as well stimuli eliciting happiness or amusement. Task conditions that were not specifically associated with emotional responses were omitted. In addition studies of fear conditioning or appetitive conditioning were not included, because these tasks include a significant learning component. No studies of reasoning about emotional situations (e.g., moral dilemmas, theory of mind tasks, empathy tasks) were included, because these tasks include a significant reasoning component. Neuroeconomic studies involving gambling tasks or social games were not included, because they involve a significant decision-making component. Studies of surprise were also omitted, primarily because of the small number of relevant neuroimaging studies. No studies of hunger, thirst, pain, visceral stimulation, were included, because they involved more basic motivational processes. Deactivations associated with emotion were not included, because few relevant studies have reported deactivations and the interpretation of relative deactivations is relatively unclear in comparison with activations. Each set of activation maxima represented a contrast between an emotionally arousing condition vs. a non-emotional baseline condition.

2.2. Analytic approach

All meta-analyses of functional neuroimaging studies of emotion in women and men were conducted using GingerALE 2.1 software; http://brainmap.org/ale