Neuropsychologia xx (2012) xxx–xxx

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Highlights

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

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► Meta-analysis examined sex differences in emotion-related activation. ► Marked sex differences in several emotion processing areas were found. ► Women had greater amygdala activation for negative emotion. ► Men had greater amygdala activation for positive emotion. ► Findings accord with reported behavioral sex differences.

Neuropsychologia xxx (2012) xxx–xxx

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

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ARTICLE INFO

Article history:
Received 11 November 2011
Received in revised form 5 March 2012
Accepted 9 March 2012
Available online xxx

Keywords:
Neuroimaging
Sex differences
Gender differences
Emotion
Amygdala
Meta-analysis

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,

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0028-3932/$ – see front matter © 2012 Published by Elsevier Ltd.
doi:10.1016/j.neuropsychologia.2012.03.011

Codispoti, 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

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Table 1
Studies included in the meta-analysis.

Study	Year	Valence			*N*		Experimental contrast(s)
		Pos	Neg	Combined	Female	Male	
George	1995		x		11		Autobio recall + faces: sadness > neutral
Breiter	1996	x	x			10	Faces: fear > neutral; happy > neutral
Dolan	1996	x				8	Faces: happy > neutral
George	1996	x	x		10	10	Autobio recall + faces: sadness > neutral; happiness > neutral
Kosslyn	1996		x			7	Pictures: negative > neutral; mental imagery: negative > neutral
Baker	1997	x	x			10	Moods elicited before scan: negative (script-driven imagery + music + social interaction) > neutral; positive (script-driven imagery + music + social interaction + monetary gift) > neutral
Beauregard	1997			x		10	Words: emotional > fixation
Lane	1997	x	x		12		Films + autobio recall: disgust > neutral; sadness > neutral; happiness > neutral
Lane	1997	x	x		12		Pictures: negative > neutral; positive > neutral
Reiman	1997			x	12		Films: emotion > neutral; autobio recall: emotion > neutral
Zald	1997		x		12		Odors: negative > no scent
Phillips	1998		x			6	faces: disgust > neutral; fear > neutral; prosody: disgust > neutral; fear > neutral
Taylor	1998		x		8		Pictures: negative > neutral
Blair	1999		x			13	Faces: anger > neutral; negative > neutral
Dougherty	1999		x			8	Autobio recall: anger > neutral
Mayberg	1999		x		8		Autobio recall: sadness > fixation
Morris	1999		x	x		6	Prosody: emotion > neutral; fear > neutral
Nakamura	1999			x		7	Faces: emotion discrim. > background color discrim.
Rauch	1999	x				8	Autobio recall: positive erotic > neutral; positive nonerotic > neutral
Buchanan	2000	x	x	x		10	Prosody: emotional > fixation; happy > fixation; sad > fixation
Dolan	2000			x		10	Picture retrieval: emotional > neutral
Frey	2000		x		11		Environmental sounds: negative > neutral
Liberzon	2000		x		10		Pictures: negative > neutral
Liotti	2000		x		8		Autobio recall: sadness > neutral
Royet	2000			x		12	Odors: emotion > neutral; pictures: emotion > neutral; sounds: emotion > neutral
Shin	2000		x			8	Autobio recall: guilt > neutral
Beauregard	2001	x				10	Films: erotic > neutral
Herpertz	2001		x		6		Pictures: negative > neutral
Tabert	2001		x		9		Words: negative > neutral
Williams	2001		x			11	Faces: fear > neutral
Aalto	2002	x	x		11		Films: sad > neutral; amusing > neutral
Canli	2002		x		12	12	Pictures: correlation with increasing arousal
Hamann	2002(a)	x	x		14		Words: negative > neutral; positive > neutral
Hamann	2002(b)	x	x		9		Pictures: negative > neutral; positive > neutral
Schienle	2002		x		12		Pictures: disgust > neutral; fear > neutral
Abel	2003		x			8	Faces: fear > neutral
Lange	2003		x			9	Faces: fear > neutral
Levesque	2003		x		20		Films: sadness > neutral
Mitterschiffthaler	2003	x		7			Pictures: positive > neutral
Mouras	2003	x				8	Pictures: erotic > neutral
Royet	2003	x	x		14	14	Odors: negative > no scent; positive > no scent
Wicker	2003	x	x			14	Odors: disgust > no scent; dynamic faces: disgust > neutral
Wrase	2003	x	x		10	10	Pictures: negative > neutral; positive > neutral
Cahill	2004		x		11	12	Pictures: correlation with increasing arousal
Herz	2004			x	5		Odors: emotion > neutral
Malhi	2004	x	x		10		Captioned pictures: negative > neutral; positive > neutral
McClure	2004		x		8	9	Faces: anger > fixation; fear > fixation
Ottowitz	2004		x		8		Script-driven imagery: sadness > neutral
Phillips	2004		x			8	Faces: disgust > neutral; fear > neutral
Stark	2004		x			24	Pictures: disgust > neutral; fear > neutral
Goldin	2005	x	x		13		Films: sadness > neutral; amusement > neutral
Habel	2005	x	x			26	Faces: sadness > gender descrim.; happiness > gender descrim.
Schienle	2005		x		63		Pictures: disgust > neutral; fear > neutral
Shirao	2005		x		13		Words: negative > neutral
Harenski	2006		x		10		Pictures: negative (moral) > fixation; negative (non-moral) > fixation
Hofer	2006	x	x		19	19	Pictures: negative > neutral; positive > neutral
Schienle	2006		x		12		Pictures: fear > neutral
Siessmeier	2006			x		13	Pictures: emotional > neutral
Ashwin	2007		x			13	Faces: fear + neutral > scrambled
Cooney	2007		x		14		Films: sad > fixation
Hessl	2007		x			13	Faces: fear > scrambled
Hofer	2007	x	x		19	19	Verbal: negative words > nonwords; positive words > nonwords

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Table 1 (*Continued*)

Study	Year	Valence			*N*		Experimental contrast(s)
		Pos	Neg	Combined	Female	Male	
Malhi	2007		x		10		Faces: disgust > neutral; fear > neutral
Meseguer	2007	x	x			14	Pictures: negative > neutral; positive > neutral
Schienle	2007		x		25		Pictures: negative > neutral
Benuzzi	2008		x		15		Films: disgust > neutral
Deckersbach	2008		x		17		Autobio recall: sad > neutral
Deeley	2008		x			40	Faces: disgust > neutral; fear > neutral
Goldin	2008		x		17		Films: negative > neutral
Herpertz	2008	x	x			22	Pictures: negative > neutral; positive > neutral
Montag	2008	x	x		37		Pictures: negative > neutral; positive > neutral
Wright	2008			x		15	Pictures: emotion rating > frequency rating
McLean	2009	x				9	Sports-related films: positive > neutral
Mériau	2009		x		23		Pictures: negative > neutral
Nielen	2009	x	x		23		Pictures: negative > neutral; positive > neutral
Trautmann	2009	x	x		16		Static faces: disgust > neutral; happiness > neutral; dynamic faces: disgust > neutral; happiness > neutral
Botzung	2010	x				23	Sports-related films: high > low arousal
Frewen	2010	x	x		20		Script-driven imagery: negative, social > neutral; negative, non-social > neutral; positive, non-social > neutral; positive, social > neutral
Reker	2010	x	x		33		Faces: sadness > neutral; happiness > neutral
Zink	2010		x			20	Negative faces > neutral objects
Total # studies		31	65	10	44	44	
Total # participants					656	561	

(Eickhoff et al., 2009). This software uses random-effects inference to determine regions that exhibit a greater convergence of activations across experiments than would be expected by chance. Individual neuroimaging studies contributed one or more sets of activation peaks or foci (stereotaxic *x*, *y*, and *z* coordinates) representing the locations of maximal activation in either Montreal Neurological Institute (MNI) or Talairach space. ALE analyses require that all activation location data be transformed into a common stereotaxic space. We used the Montreal Neurological Institute (MNI) space as the common anatomical reference space and transformed any coordinates of maximal activation that had been reported in Talairach space to MNI space using icbm2tal, a standard transformation program (Lancaster et al., 2007).

For each set of activation maxima from an individual study, a modeled activation (MA) map was generated by convolving the peak coordinates with a 3D Gaussian kernel with a full width half maximum (FWHM) between 9 mm and 11 mm (FWHM calculation depending upon sample size; empirical validation elaborated in Eickhoff et al., 2009). An ALE map of the convergence of activations across studies was calculated as the union across all MA-maps, taken at each voxel. Significant areas of convergence within the ALE map were determined by statistical comparison at each voxel to a null distribution of convergence based on random spatial distribution between experiments (see Eickhoff et al., 2009). ALE maps were thresholded using a voxel-level false discovery rate correction for multiple comparisons (Genovese, Lazar, & Nichols, 2002) pID of .05 and a 100 mm^3 minimum cluster size.

Three emotional valence conditions were examined (negative emotion, positive emotion, and a combination of all emotional responses irrespective of valence: all emotion). For each, one ALE map was constructed for women, one map was constructed for men, and a pooled map was constructed that summarized results irrespective of sex. Sex differences were assessed by computing the voxel-wise difference between the ALE maps for women and men. All MA-maps for the pooled analysis of both women and men were then randomly divided into two groups of the same size as the sets for women and for men, and the voxel-wise difference between the ALE maps for these two randomly assigned datasets was calculated. This process was repeated 10,000 times to create a null distribution of difference scores, and the map of sex differences was compared to this randomly permuted map of differences. Results were thresholded using a false discovery rate (pID) of .05, and a 100 mm^3 minimum cluster size.

ALE meta-analyses summarize regions where activations spatially converge significantly across studies. We use the term "activation" in the current study to refer to regions of significant convergence, to maintain consistency with the terminology used in previous meta-analyses (Friebel, Eickhoff, & Lotze, 2011).

2.3. Analyses controlling for specific emotions and stimulus types

In ALE differential activation analyses, conditions associated with more modeled activation maps are more likely to show activation likelihood differences favoring that condition (Laird et al., 2005). For example, in the current study, for the ALE analysis for negative emotion, if the dataset for women included more MA-maps than the corresponding set for men, then this would introduce an analysis bias towards finding clusters of greater activation likelihood for women, solely because of the imbalance in the number of MA-maps. In addition, because specific emotions (e.g., basic emotions such as happiness and fear) typically recruit partially non-overlapping patterns of brain activation (Vytal & Hamann, 2010), disproportionate inclusion of specific emotion types across groups could also potentially influence the results of an ALE meta-analysis. Though the magnitude of this potential bias is difficult to estimate, it increases with increasingly unbalanced comparisons between conditions or groups. In practice, small imbalances in the number of MA-maps between conditions have typically been viewed in previous ALE meta-analyses as relatively minor potential sources of bias and have been largely ignored. However, in the current study we adopted a conservative approach to this issue and included additional analyses to help establish that our findings were unlikely to be attributable to such imbalances.

Accordingly, to address this potential source of bias, we conducted our ALE analysis in two different ways. We first analyzed the complete set of MA-maps from our selected studies, and then repeated the analysis with a balanced set of MA-maps that controlled for the overrepresentation of specific emotions. This balanced dataset was created by matching comparisons between women and men on emotion type (e.g., sadness, happiness) and stimulus type (e.g., pictures, words). In the few cases for which stimulus matching was not possible, comparisons were matched for sensory modality of stimuli. As a result of this matching procedure, MA-maps from studies of responses to erotic stimuli were excluded from the balanced dataset. Fig. 2b shows the distribution of specific emotions in the balanced data set. In addition, the balanced dataset better equated the number of female vs. male participants contributing to each MA-map. The average sample size for MA-maps included in the complete dataset was $M(SD) = 15.7(10.5)$ for women and 16.7(11.6) for men. The average sample size for MA-maps included in the balanced dataset was

Table 2
Number of modeled activation (MA) maps contributing to the meta-analysis.

	Complete dataset		Balanced dataset[a]	
	Women	Men	Women	Men
Negative emotion	51	41	32 (.63)	32 (.78)
Positive emotion	18	22	16 (.89)	16 (.73)
All emotion	72	71	51 (.71)	51 (.72)

[a] # maps (proportion of complete dataset).

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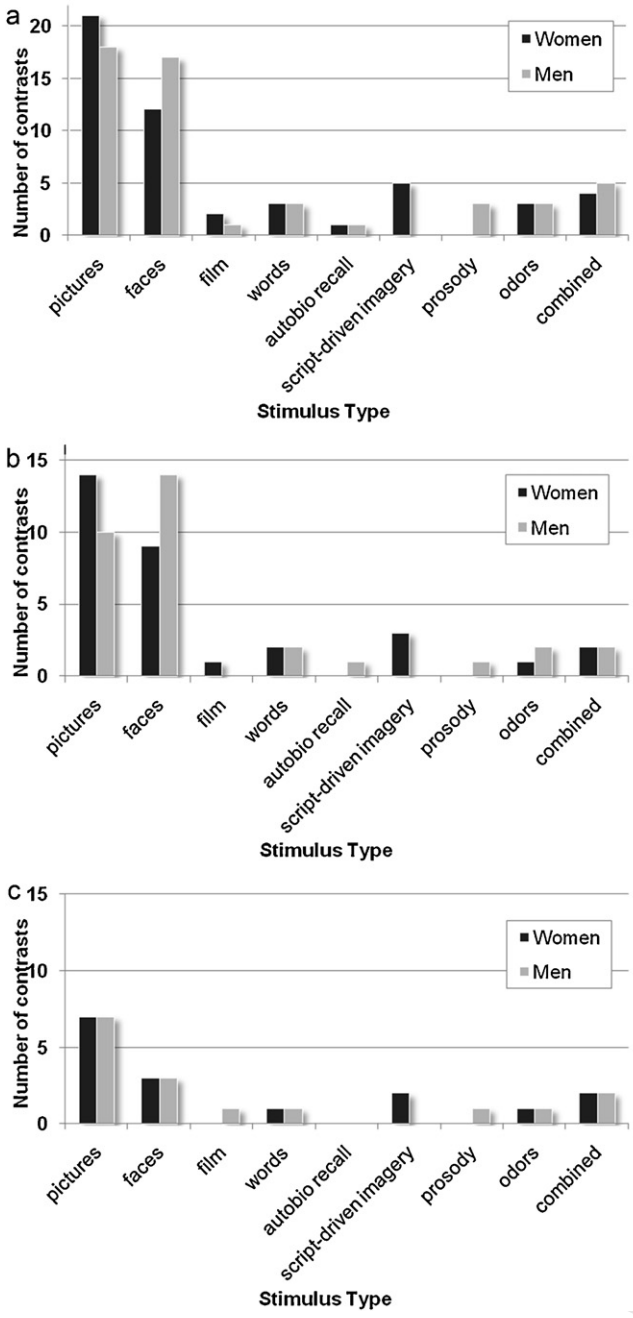

Fig. 1. Frequency distribution of stimulus types used for emotion induction, for the studies included in the ALE meta-analyses of the balanced dataset equated for the frequency of specific emotion types across women and men. (a) All emotion. (b) Negative emotion. (c) Positive emotion.

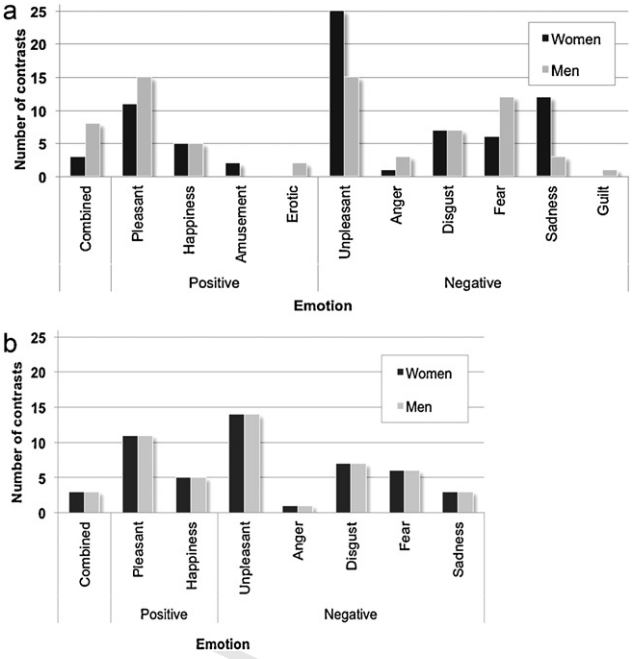

Fig. 2. Frequency distributions of specific emotion types included in the meta-analyses, for women and men. "Combined" indicates studies that included both positive and negative emotional stimuli. Negative emotion analyses included activation contrasts from the set of negative emotions. Positive emotion analyses included activation contrasts from the set of positive emotions. All-emotion analyses included all emotion types illustrated here, regardless of emotion category (combined emotion, positive emotion, and negative emotion). (a) Activation contrasts included in the meta-analyses of the complete dataset. (b) The subset of activation contrasts included in the meta-analyses of the balanced dataset.

$M(SD)$ = 13.0(6.9) for women and 13.6(6.6) for men. The average ages of female and male samples were comparable in both the complete and balanced datasets. 36 of 45 studies of women, and 33 of 44 studies of men reported the mean age of participants. The average age of participants in the complete dataset was $M(SD)$ = 28.1(5.6) for women and 30.8(7.0) for men. The average age of participants in the balanced dataset was 28.0(5.7) for women and 31.9(7.5) for men.

As detailed in Section 3, the ALE analysis using the carefully balanced data sets in fact yielded very similar results to those obtained with the complete data set of all MA-maps. In general, the results with the balanced data set constituted a subset of the results obtained with the complete data set, yielding ALE clusters with slightly smaller spatial extent. Because the ALE results with the balanced data set were highly similar to those obtained with the complete data set and were less likely to be affected by bias, in the current report we focus primarily on the ALE results from the balanced data set. For completeness, the results from the analysis of the complete dataset are presented in Supplemental Tables, and we describe any important differences in findings between the two analyses in Section 3.

3. Results

3.1.1. Negative emotion: sex differences

Significant differences between women's and men's responses to negative stimuli are shown in Fig. 3a and Table 3. Women showed greater activation than men in a cluster that had peaks in the left amygdala and hippocampus (cluster 1). Prominent clusters were also observed in the hypothalamus in the approximate region of the left mammillary body and in the medial dorsal nucleus of the left thalamus (cluster 2), in right middle occipital gyrus, and middle and inferior temporal gyri (BA37, 19, cluster 3), and medial frontal and anterior cingulate gyri (BA10, 32, 9; cluster 4).

Men showed greater activation than women in a large cluster containing peaks in right precentral gyrus, inferior frontal gyrus, and insula (BA6, 9, 13, 44; cluster 1). Prominent clusters were also observed in right superior temporal gyrus and right putamen (BA38, cluster 2), posterior cingulate gyrus (BA23, 29; cluster 3), and left middle temporal gyrus and fusiform gyrus (BA37, 19; cluster 4).

3.1.2. Negative emotion: women

Results are shown in Fig. 3b (list of clusters in Table S1). A large cluster contained peaks in both the left and the right amygdala, left hippocampus, left thalamus, right subthalamic nucleus, right superior temporal gyrus (BA38), left mammillary body, left caudate head, and left putamen (cluster 1). Other prominent clusters were observed in left middle and inferior frontal gyri, and insula (BA46, cluster 2; BA47, 13, cluster 5). A major cluster had activation

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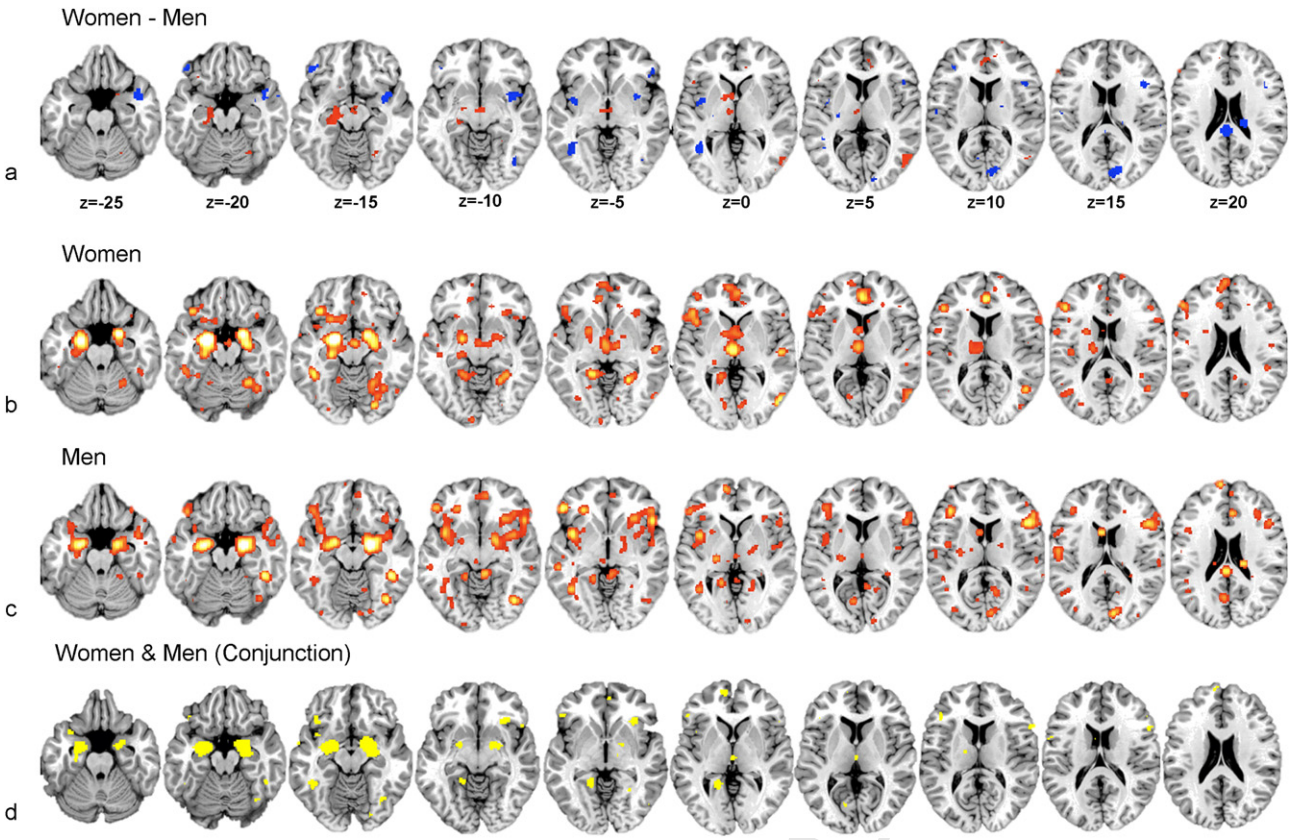

Fig. 3. Regions of significant activation ($p < .05$, FDR-corrected for multiple comparisons) for negative emotion, overlaid on a representative single-subject structural anatomical image template in MNI space. (a) Significant differences in activation for negative emotion in women vs. men. (b) Significant activation clusters for negative emotion in women. (3) Significant activation clusters for negative emotion in men. Red color scale: greater activation for women than men. Blue color scale: greater activation for men than women. Brighter colors indicate greater activation likelihood. Axial slices are shown in neurological orientation (left side of image = left hemisphere; top of image = rostral). (For interpretation of the references to color in this figure legend, the reader is referred to the web version of the article.)

Table 3
Peak coordinates for sex differences in negative emotion (analysis of balanced dataset).

Region (>100 mm³)	BA(s)[a]	X[b]	Y	Z	Peak value	Vol. (mm³)	Pic/face/other
Females > Males							
1 Hippocampus, Amygdala	35	−20	−19	−16	2.64	2112	
2 Hypothalamus-Mammillary body, Thalamus-Medial dorsal nucleus	*	−1	−13	−7	2.39	1344	
3 Middle occipital gyrus, middle temporal gyrus, inferior temporal gyrus	37, 19	52	−69	4	2.59	976	
4 Right medial frontal gyrus, left medial frontal gyrus, left anterior cingulate	10, 32, 9	4	47	8	2.50	648	
5 Medial globus pallidus, Lateral Globus Pallidus	*	−9	4	−1	2.39	624	
6 Middle frontal gyrus	9	−50	28	24	2.04	280	
7 Cerebellum-declive	*	26	−62	−19	2.04	208	
8 Middle frontal gyrus	46	−57	33	18	2.12	112	
Males > Females							
Precentral gyrus, inferior frontal gyrus, Insula	6, 9, 13, 44	44	10	28	2.99	3144	
2 Superior temporal gyrus, putamen	38	41	4	−18	2.88	2576	
3 Posterior cingulate	23, 29	−2	−36	24	3.16	2048	
4 Middle temporal gyrus, fusiform gyrus	37, 19	−41	−56	−3	2.40	1328	
5 Cuneus, lingual gyrus	17, 18	10	−83	14	2.67	1240	
6 Inferior frontal gyrus	47	−46	36	−16	2.56	752	
7 Claustrum	*	−39	−1	−3	2.19	744	
8 Thalamus-pulvinar	*	18	−27	19	3.72	696	
9 Fusiform gyrus	19	41	−72	−11	1.91	360	
10 Inferior frontal gyrus	10	−36	37	9	2.18	208	
11 Inferior frontal gyrus	45, 47	51	31	−7	1.96	200	
12 Putamen	*	−27	−18	5	2.14	152	

[a] BA: Brodmann's area, if applicable.
[b] *X*, *Y*, and *Z* coordinates represent weighted central activation likelihood focus in MNI space.
* Clusters demonstrating significant concordance across studies ($p < .05$, FDR-corrected for multiple comparisons). For each cluster, labels denote regions which contained the peak ALE activation, and regions which contained secondary peaks; clusters may extend across non-labeled regions between peaks and the extent is best characterized in Fig. 3.

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peaks in anterior cingulate gyrus and medial frontal gyrus (BA32, 10, cluster 4).

3.1.3. Negative emotion: men

Results are shown in Fig. 3c and Table S1. This analysis revealed a large cluster with activation maxima in right amygdala, precentral gyrus, superior temporal gyrus, inferior frontal gyrus, claustrum, middle temporal gyrus, and insula (BA 6, 38, 44, 47, 45, 21, 13; cluster 1). A similar cluster in the left hemisphere contained an activation peak in left amygdala with additional peaks in left inferior frontal gyrus and insula, left middle frontal gyrus, superior temporal gyrus, putamen, and hippocampus (BA45, 13, 46, 38, 47; cluster 2). Prominent clusters were also observed in medial cingulate and superior frontal gyri (BA32, 6, 24; cluster 3), left middle temporal gyrus and fusiform gyrus (BA37, 19; cluster 4), left inferior frontal gyrus and precentral gyrus (BA9, 6, 44, cluster 5), and posterior cingulate gyrus (BA23, cluster 6). Two clusters had peaks in right fusiform gyrus (BA19, cluster 7; BA37, cluster 8).

3.1.4. Negative emotion: women and men

To investigate the brain regions reliably activated across studies for negatively valenced emotions, regardless of the sex of participants, we conducted an analysis on MA-maps from all studies of negative emotion, collapsing across female and male samples. Results are shown in Figure S1a and Table S1. Peaks were observed in the amygdala bilaterally (right hemisphere: cluster 1, left hemisphere: cluster 2). The largest cluster also included peaks in bilateral thalamus, left caudate body and head, right precentral gyrus (BA6), right inferior frontal gyrus (BA47, 44, 45, 13), right middle frontal gyrus (BA9, 46), right claustrum, right superior temporal gyrus (BA38), left mammillary body and red nucleus, and left medial globus pallidus (cluster 1). A similar but left-lateralized cluster had peaks in left inferior frontal gyrus (BA47, 9, 46), left superior temporal gyrus (BA38), left insula (BA13), the ventral posterior lateral nucleus of the left thalamus, and left putamen (cluster 2). A prominent cluster in frontal cortex had peaks in cingulate gyrus, superior frontal gyrus and anterior cingulate gyrus (BA32, 6, 24; cluster 3).

3.1.5. Positive emotion: sex differences

Significant differences between women's and men's responses to positive stimuli are shown in Fig. 4a (list of clusters in Table 4). Women showed greater activation than men in small clusters in right middle and inferior temporal gyrus (cluster 1), left superior temporal gyrus (cluster 2), and dorsomedial frontal gyrus (BA32, 6, cluster 3).

Men showed greater activation than women in a cluster covering left subcallosal gyrus (BA34), left uncus (BA28), and left amygdala (cluster 1). Prominent clusters contained peaks in inferior frontal gyrus (BA47, 13, right: cluster 4, left: clusters 2, 3), and superior temporal gyrus (BA38; cluster 2). Other prominent clusters contained peaks in right fusiform gyrus (BA37, cluster 5), and left middle frontal gyrus (BA8, cluster 6).

3.1.6. Positive emotion: women

Results for positive emotion for women are shown in Fig. 4b and Table S2. The largest cluster appeared in the ventral anterior nucleus of the left thalamus, and extended into the head of the caudate (cluster 1). Clusters were also observed bilaterally in the amygdala (right: cluster 15, left: cluster 5). Other prominent clusters included right lingual gyrus (BA18; cluster 2), left fusiform gyrus (BA19) and inferior occipital gyrus (BA18; cluster 4), left medial frontal gyrus (BA9; cluster 3), left anterior cingulate gyrus (BA32; cluster 6).

3.1.7. Positive emotion: men

Results for positive emotion for men are shown in Fig. 4c and Table S2. Large clusters appeared in left amygdala extending into left inferior frontal gyrus and the lateral globus pallidus (cluster 1), and in right amygdala extending into right entorhinal cortex (BA34, cluster 3). Prominent clusters were also observed in bilateral inferior frontal gyri/insula (left: BA13, 45, 47 clusters 2, 6; right: BA46, cluster 9), and bilateral fusiform gyri (BA19, right: cluster 5, left: cluster 4). An additional cluster had its maximum in the posterior cingulate gyrus (BA30, cluster 7).

3.1.8. Positive emotion: women and men

To investigate the brain regions reliably activated across studies for positive emotions, regardless of sex, we analyzed the MA-maps from all studies of positive emotion, collapsing across the female and male groups. Results are shown in Figure S1b and Table S2. Prominent clusters had peak activations in the bilateral amygdala (right: cluster 5, left: cluster 2), the ventral anterior nucleus of the left thalamus (cluster 1), head of the caudate (cluster 1), medial frontal gyrus (BA9, cluster 4), bilateral inferior frontal gyrus/insula (BA 45, 13, right: cluster 9, left: cluster 3), left anterior cingulate (BA32, cluster 1), and bilateral fusiform gyri (BA19, right: cluster 13, left: cluster 12).

3.1.9. All emotion: sex differences

Significant differences between women's and men's responses to all emotional stimuli are shown in Fig. 5a and Table 5. Women showed greater activation than men in an extended cluster with peaks in the left thalamus and subthalamic nuclei, lateral globus pallidus, left caudate head, left anterior cingulate (BA25), and the left mammillary body (cluster 1). Prominent clusters were also observed in the left hippocampus (cluster 2), and in right middle occipital gyrus and inferior temporal gyrus (BA37, cluster 3). Women's emotion-related activations also differed from men's in several additional frontal regions, including a cluster in anterior cingulate and medial frontal gyrus (BA32, 24, 10; cluster 4), in medial and superior frontal gyri (BA9, 10, 6; clusters 5, 7, 8), and in left middle and inferior frontal gyri (BA46, 9; cluster 6).

Men showed greater activation than women in bilateral inferior frontal gyrus (right: BA45, 47, clusters 1, 15, 18; left: BA47, clusters 7, 12, 13, 21). A prominent cluster in posterior cingulate was also more activated in men than women (BA23, 29, 31; cluster 2). A large cluster overlapped right superior temporal gyrus, claustrum, putamen, and right amygdala (BA38, cluster 3). Other prominent clusters appeared in right fusiform gyrus (BA19, 20, cluster 5, 9), and left insula (BA13, cluster 1).

3.1.10. All emotion: women

Results are shown in Fig. 5b and Table S3. For studies of emotional responses in women, ALE analysis revealed a large cluster covering the left thalamus, and extending to the left caudate head, left putamen, bilateral amygdala, bilateral hippocampus, and mammillary bodies (cluster 1). Several large medial frontal clusters contained activation peaks in superior frontal gyrus, anterior cingulate, and medial frontal gyrus (BA9, 32, 10; clusters 2 and 5). Another cluster had peaks left middle frontal gyrus, inferior frontal gyrus, and insula (BA9, 47, 45, 46, 13, 9; cluster 3). A large cluster

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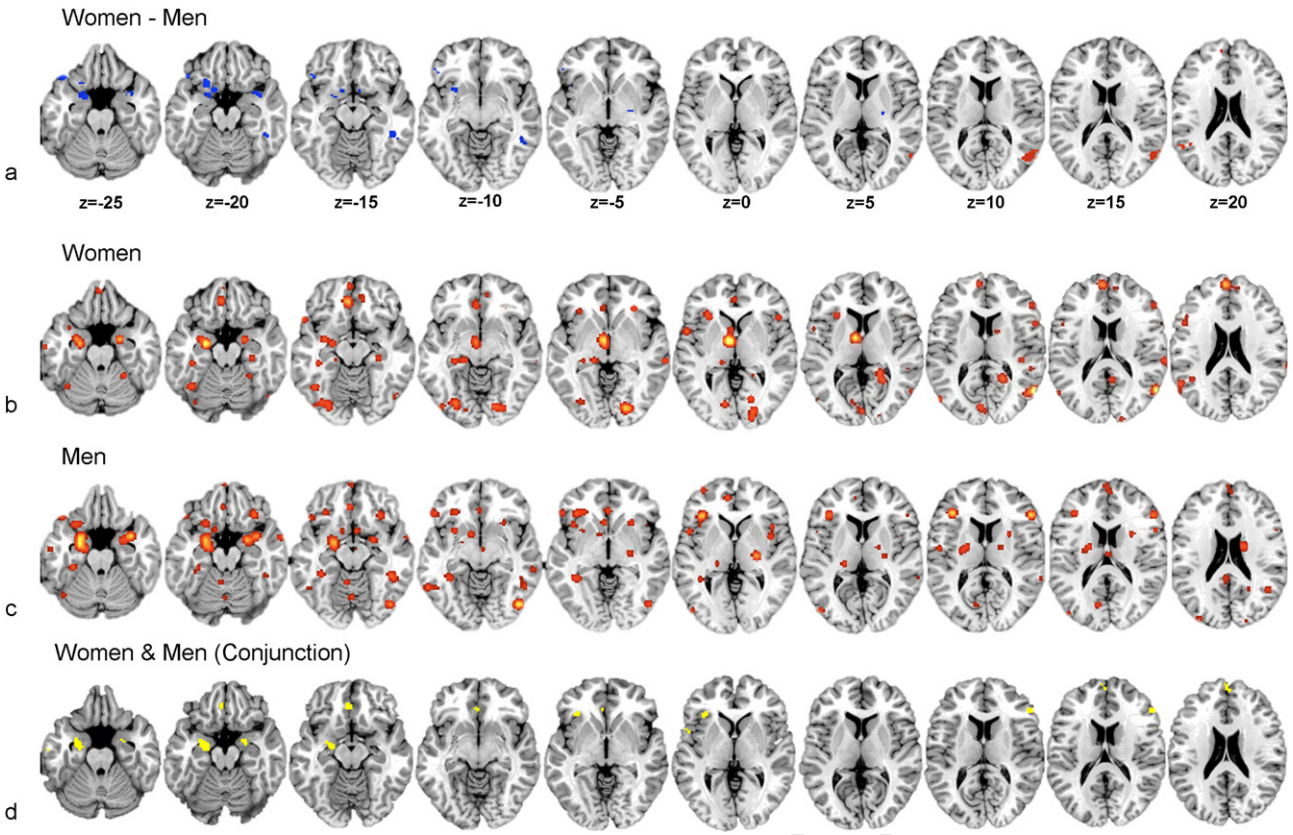

Fig. 4. Regions of significant activation ($p < .05$, corrected) for positive emotion, overlaid on a representative single-subject structural anatomical image template in MNI space. (a) Significant differences in activation for positive emotion in women vs. men. (b) Significant activation clusters for positive emotion in women. (c) Significant activation clusters for positive emotion in men. Red color scale: greater activation for women than men. Blue color scale: greater activation for men than women. Brighter colors indicate greater activation likelihood. Images are presented in neurological orientation. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of the article.)

had peaks in right fusiform gyrus, lingual gyrus, culmen, and the declive of the cerebellar vermis (BA19, 18, 37; cluster 4).

3.1.11. *All emotion: men*

Results are shown in Fig. 5c (list of clusters in Table S3). For studies of emotional responses in men, ALE analysis revealed an extended cluster covering left amygdala, left inferior frontal gyrus, insula, and postcentral gyrus (BA13, 47, 45, 43; cluster 1). Another prominent cluster peaked in right amygdala, and extended into right inferior frontal gyrus, precentral gyrus, superior temporal gyrus, claustrum, thalamus, precentral gyrus, lateral globus pallidus, and insula (BA45, 6, 38, 47; cluster 2). Substantial clusters were also observed in posterior cingulate and cuneus (BA23, 30, 29; cluster 3), and left middle temporal gyrus and fusiform gyrus (BA19, 37; cluster 4). Other notable clusters were observed in right

Table 4
Peak coordinates for sex differences in positive emotion (analysis of balanced dataset).

Region (>100 mm^3)	BA(s)[a]	X[b]	Y	Z	Peak value	Vol. (mm^3)
Females > Males						
1 Middle temporal gyrus, inferior temporal gyrus	39, 37	53	−66	10	1.89	1296
2 Superior temporal gyrus	39, 22	−55	−56	22	2.08	352
3 Medial frontal gyrus, superior frontal gyrus	32, 6	2	16	51	2.05	328
Males > Females						
1 Subcallosal gyrus, entorhinal cortex, amygdala	34, 28	−20	3	−24	2.44	792
2 Inferior frontal gyrus, superior temporal gyrus	47, 38	−44	25	−25	2.59	752
3 Inferior frontal gyrus	47	−23	18	−20	2.22	376
4 Inferior frontal gyrus	13	35	6	−21	2.71	360
5 Fusiform gyrus	37	46	−41	−17	2.04	360
6 Middle frontal gyrus	8	−27	35	41	2.08	320
7 Subcallosal gyrus	34	−13	10	−19	2.50	280
8 Fusiform gyrus	37	50	−48	−12	1.84	232
9 claustrum	*	−28	10	−10	2.13	168
10 Lateral globus pallidus, medial globus pallidus	*	26	−13	−4	1.86	104

[a] BA: Brodmann's area, if applicable.
[b] *X*, *Y*, and *Z* coordinates represent weighted central activation likelihood focus in MNI space. Clusters demonstrating significant concordance across studies ($p < .05$, FDR-corrected for multiple comparisons).
[*] For each cluster, labels denote regions which contained the peak ALE activation, and regions which contained secondary peaks; clusters may extend across non-labeled regions between peaks and the extent is best characterized in Fig. 4.

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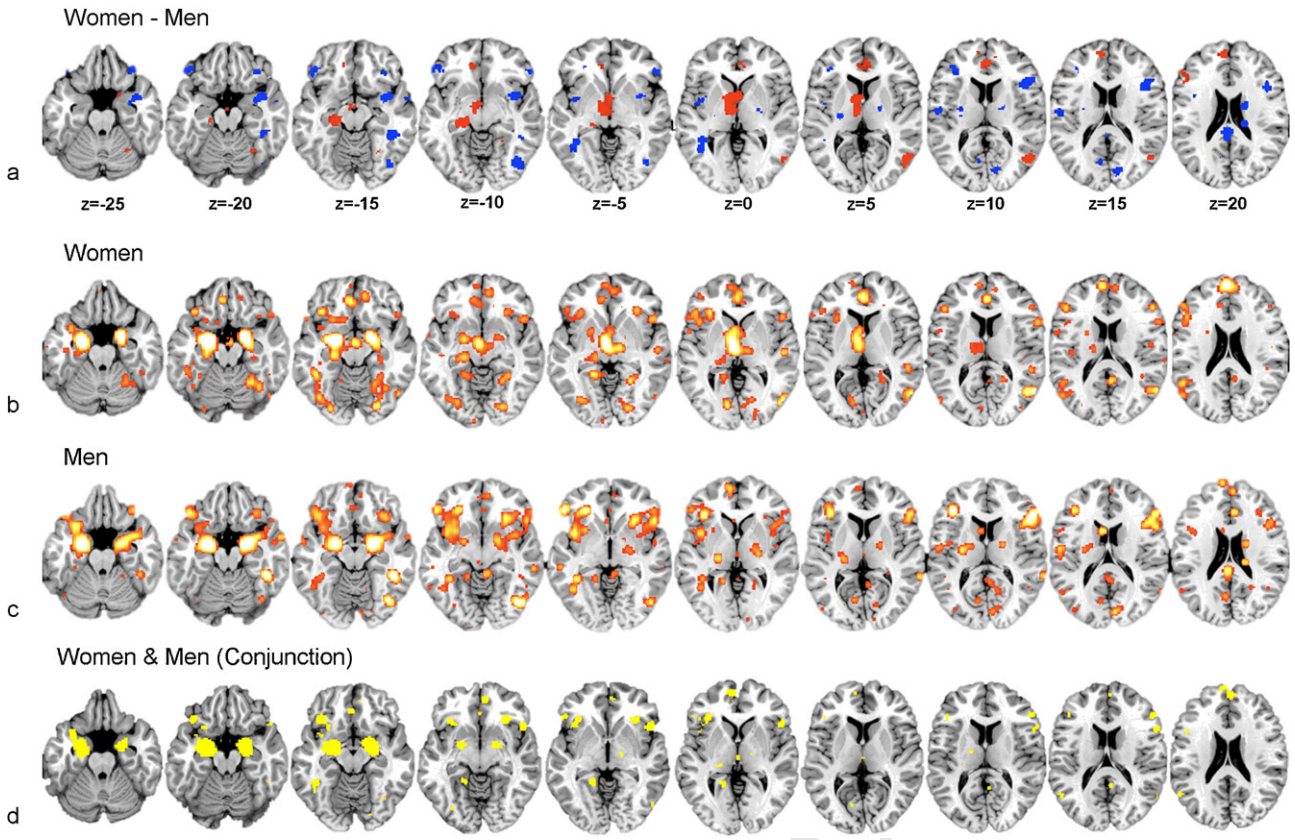

Fig. 5. Regions of significant activation ($p < .05$, corrected) for all emotion, collapsed across positive and negative emotion stimuli, overlaid on a representative single-subject structural anatomical image template in MNI space. (a) Significant differences in activation for all emotion in women vs. men. (b) Significant activation clusters for all emotion in women. (c) Significant activation clusters for all emotion in men. Red color scale: greater activation for women than men. Blue color scale: greater activation for men than women. Brighter colors indicate greater activation likelihood. Images are presented in neurological orientation. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of the article.)

fusiform gyrus (BA19; clusters 6), dorsomedial prefrontal cortex (BA32, 6; cluster 5), and in the left thalamus extending into the putamen (cluster 9).

3.1.12. *All emotion: women and men*

To characterize patterns of activation independent of sex differences, primarily for purposes of comparison to previous studies, we conducted an analysis on all MA-maps, collapsing across positive and negative valence, and across female and male groups. Results are shown in Figure S1c and Table S3. In part because of the large number of maps entering into this analysis and attendant increase in statistical power, several activation clusters were relatively large and extended across multiple brain regions. Among these activation clusters, clusters of activation were observed in several regions associated with emotion and reward, including the bilateral amygdala (cluster 1), bilateral thalamus (cluster 1), mammillary bodies (cluster 1), bilateral insula (cluster 1) and left caudate (cluster 1). Activation clusters in prefrontal cortex associated with emotion included bilateral inferior frontal gyri (left: cluster 1, right: cluster 2), anterior cingulate (clusters 4, 14, 26, 39, 44) and left medial frontal gyrus (cluster 4).

3.2. *Results for the complete dataset*

As described in Section 2, to help reduce potential biasing effects of systematic differences in stimuli and emotion type and number of MA-maps between the data sets for women and men, our primary analyses focused on a balanced data set that minimized such effects by matching between women and men on these factors. However, because this procedure necessarily excluded a proportion of studies, it was important to determine whether our primary findings were also observed in the complete dataset comprised of all studies that met our inclusion criteria. This analysis of the complete dataset yielded results that were highly similar to the findings obtained with the smaller, balanced data set (detailed results for the complete dataset are presented in Supplemental Tables). In general, highly similar activation clusters were observed in the complete analysis and the balanced dataset, but with greater spatial extent for the complete dataset in many cases, extending across adjacent brain regions.

A few notable additional sex differences were observed in the analysis of the complete dataset. For negative emotion, women showed greater activation than men in the left substantia nigra, left hypothalamus, and left subcallosal gyrus (cluster 1). Men showed greater activation than women for negative emotion in additional clusters in right entorhinal cortex (BA28; cluster 7) and in left insula (BA13, cluster 8). Table S4 and Figure S2a present the full results for the complete analysis of negative emotion. For positive emotion stimuli, women showed greater activation than men in the following additional brain regions: left thalamus, subthalamic nucleus, hypothalamus, and medial globus pallidus (cluster 1), right superior temporal gyrus (BA42, 13, 22, cluster 4; BA41, cluster 6). No additional clusters of greater activation for men were observed in the complete analysis. Table S5 and Figure S2b present the full results for the complete analysis of positive emotion. No additional brain regions were activated in the complete analysis relative to the balanced analysis, but as with the examination of

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Table 5
Peak coordinates for sex differences for all-emotion condition (analysis of balanced dataset).

Region (>100 mm³)	BA(s)[a]	X[b]	Y	Z	Peak value	Vol. (mm³)
Females > Males						
1 Subthalamic nucleus, thalamus, Lateral globus pallidus, caudate head, anterior cingulate, hypothalamus-mammillary body	25	−5	−5	−3	3.16	6096
2 Hippocampus	*	−21	−26	−13	2.85	1944
3 Middle occipital gyrus, inferior temporal gyrus	37	50	−68	7	3.72	1832
4 Left anterior cingulate, right anterior cingulate, right medial frontal gyrus	32, 24, 10	3	43	6	2.58	1696
5 Left medial frontal gyrus, right superior frontal gyrus	9	−5	55	19	2.47	1184
6 Middle frontal gyrus, Inferior frontal gyrus	46, 9	−50	27	23	2.33	1152
7 Medial frontal gyrus	10	−10	39	−10	2.00	424
8 Superior frontal gyrus	6	4	26	59	2.01	416
9 Cerebellum-declive, dentate gyrus	*	29	−59	−21	2.05	264
10 Uncus	34	19	4	−25	1.88	112
Males > Females						
1 Insula, inferior frontal gyrus, precentral gyrus, Middle frontal gyrus	13, 45, 9, 6	45	17	17	3.54	2968
2 Posterior cingulate	23, 29, 31	−2	−39	24	3.72	2880
3 Superior temporal gyrus, claustrum, putamen, amygdala	38	38	2	−17	3.35	2672
4 Middle occipital gyrus, middle temporal gyrus	19, 37	−40	−51	−2	3.04	1632
5 Fusiform gyrus	19	42	−74	−11	2.95	1504
6 Precentral gyrus, insula, claustrum	6, 13	−47	−6	5	2.59	1488
7 Inferior frontal gyrus, middle frontal gyrus	47, 11	−47	34	−16	3.35	1360
8 Middle frontal gyrus	8	−26	37	38	2.61	1336
9 Fusiform gyrus	37, 36	44	−41	−15	2.31	1280
10 Cuneus	17	11	−82	14	3.16	824
11 Caudate body	*	19	−6	22	2.95	776
12 Inferior frontal gyrus, middle frontal gyrus	10	−36	36	8	2.49	696
13 Precentral gyrus, inferior frontal gyrus	6, 9	−38	5	27	2.10	640
14 Putamen	*	−27	−15	7	2.77	632
15 Inferior frontal gyrus	47	34	32	−21	2.39	592
16 Thalamus-pulvinar	*	18	−27	20	3.72	528
17 Supramarginal gyrus, superior temporal gyrus	40, 39	42	−46	31	2.10	512
18 Inferior frontal gyrus	47	55	32	−7	2.43	448
19 Thalamus-ventral lateral nucleus, lateral globus pallidus	*	22	−10	4	2.54	424
20 Posterior cingulate	30	−8	−70	14	2.22	320
21 Inferior frontal gyrus	47	−44	26	−27	2.04	208

[a] BA: Brodmann's area, if applicable.
[b] *X*, *Y*, and *Z* coordinates represent weighted central activation likelihood focus in MNI space.
* Clusters demonstrating significant concordance across studies ($p < .05$, FDR-corrected for multiple comparisons). For each cluster, labels denote regions which contained the peak ALE activation, and regions which contained secondary peaks; clusters may extend across non-labeled regions between peaks and the extent is best characterized in Fig. 5.

negative and positive emotion, significant activation clusters were greater in extent. Table S6 and Figure S2c present the full results for the complete analysis of all emotion, combined across positive and negative valence.

4. Discussion

The primary goal of this study was to examine and characterize sex differences in brain activation during the processing of positive and negative emotion. We used a quantitative meta-analytic approach, summarizing and analyzing activation findings from the relevant fMRI and PET neuroimaging literature. This analysis characterized differences between women and men in regional activation likelihood for positive and negative emotion separately as well as for both types of emotion combined. A major finding was that, in line with our predictions, sex differences varied markedly as a function of negative vs. positive emotional valence. The majority of sex differences favoring women were observed for negative emotion, whereas relatively few sex differences favoring men were observed for the analysis of negative emotion. Conversely, the majority of the sex differences favoring men were observed for positive emotion, whereas relatively few sex differences favoring women were observed for positive emotion.

This valence-specificity of sex differences in regional activation was particularly evident for the amygdala, a key region for emotion processing. Women exhibited greater activation than men in the left amygdala for negative emotion, consistent with previous evidence suggesting that women are more psychologically and neurally responsive to stimuli and situations that elicit negative emotion. Conversely, men exhibited greater activation than women in the left amygdala for positive emotion. Notably, this greater amygdala activation for men was found in the balanced dataset that did not include any studies of sexually arousing stimuli, suggesting that this sex difference in amygdala response previously reported for sexually arousing stimuli generalizes to other types of positive emotional stimuli. No sex differences in amygdala activation were observed when all studies were analyzed regardless of valence.

This study extends previous efforts to characterize sex differences in brain activation during emotion processing in several important ways. Our meta-analysis is the most comprehensive such attempt to date, including a substantially larger and more complete set of relevant studies than in previous meta-analyses. This study also represents the first quantitative meta-analytic review to our knowledge that has investigated such sex differences separately for studies of positive and negative emotional valence. A third key feature of our study was that it is the first such neuroimaging meta-analysis to use recently developed whole-brain random-effects statistical meta-analytic methods, as opposed to fixed-effects methods that have been used in previous relevant meta-analyses. Fixed-effects meta-analysis methods are limited because inferences based on them are strictly valid only for the population included in the analysis (i.e., the specific neuroimaging studies included), although in practice this limitation has been frequently overlooked. The random-effects meta-analysis method used in the current study allows valid statistical inference about the

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general population, thereby substantially broadening the scope and generality of our conclusions.

To control for possible bias related to greater representation of specific emotions across groups, as described in Section 2, we conducted our ALE analysis in two different ways and focused our interpretation on results obtained with the more conservative, balanced method that controlled for bias. The results of the two analyses were in fact highly similar, with slightly more extensive activation clusters observed with the less conservative method. Because similar meta-analysis results were obtained with both analysis methods, this suggests that our findings are relatively robust to minor variations in the specific studies sampled.

In the next sections we discuss these sex differences in brain activations in greater detail, focusing on activations in regions involved in emotion and emotion regulation.

4.1. Greater activations for women

A primary finding was that women showed greater left amygdala activation for negative emotion, relative to men. This finding supported our prediction that, relative to men, women would show stronger responses to negative emotion in key brain regions associated with emotion processing and parallels findings from the behavioral and psychophysiological literature (Bradley et al., 2001; Fujita, Diener, & Sandvik, 1991; McClure et al., 2004; McManis et al., 2001; Thomsen et al., 2005). These results are also consistent with the findings of some individual neuroimaging studies that have reported greater amygdala activations in women relative to men to negative emotional stimuli, using direct within-experiment comparisons (Domes et al., 2009; Hofer et al., 2006). The activation cluster showing greater activation for women vs. men for negative emotion also contained additional, secondary activation maxima in the anterior hippocampus (Fig. 6). Greater activation for women vs. men in the left hippocampus was also observed when all emotion studies (regardless of valence) were analyzed.

These sex differences in amygdala and hippocampal activation are notable in part because interactions between the amygdala and hippocampus are known to be a primary mechanism by which emotion modulates episodic memory (memory for events) (Cahill et al., 1996; Canli, Desmond, Zhao, & Gabrieli, 2002; Hamann, Ely, Grafton, & Kilts, 1999). These greater amygdala and hippocampal activations for women are consistent with previous findings of enhanced emotional memory for women relative to men (Seidlitz & Diener, 1998). Neuroimaging studies have also identified consistent sex differences in the amygdala's contribution to successful memory encoding for negative stimuli (Cahill et al., 2001; Cahill, Uncapher, Kilpatrick, Alkire, & Turner, 2004; Canli et al., 2002), such that right amygdala activation is associated with successful memory encoding in men for negative stimuli, whereas left amygdala activation is associated with successful encoding in women for negative stimuli.

In addition to the left amygdala, women also exhibited greater activation to negative stimuli in the anterior cingulate and medial prefrontal cortex, in BAs 9, 32, and 10. Neuroimaging studies of depression and induced sad mood have linked negative affect and depression to increased subgenual anterior cingulate cortex and medial prefrontal activation (Mayberg et al., 1997, 1999) as well as a temporally prolonged amygdala response (Siegle, Steinhauer, Thase, Stenger, & Carter, 2002). Activity in the medial prefrontal cortex and anterior cingulate has been associated with several cognitive processes linked to depression, including representation of mental states (Abu-Akel, 2003), default-mode resting state activity (Buckner, Andrews-Hanna, & Schacter, 2008), and rumination, the tendency to recollect and focus on negative events and feelings (Denson, Pedersen, Ronquillo, & Nandy, 2009; Ray et al., 2005). Increased rumination in women relative to men has been linked to the higher prevalence of depression in women (Leach et al., 2008; Thomsen et al., 2005). The greater activation we observed in medial prefrontal and anterior cingulate regions is consistent with the higher prevalence of depression and anxiety disorders observed among women relative to men (American Psychiatric Association, 2000; Nolen-Hoeksema, 2001).

Greater responses to negative stimuli in women were also observed in the left medial dorsal nucleus of the thalamus and the hypothalamus, with an activation maximum located near the mammillary bodies. A sex difference in hypothalamic activation is consistent with sex differences in the distribution of hormone receptors in the brain. The hypothalamus and amygdala are densely populated with steroid hormone receptors (Clark et al., 1988; MacLusky et al., 1986), and these regions are thus especially sensitive to hormone levels which differ between women and men. Sex differences in receptor density are greatest in the mammillary bodies relative to other hypothalamic nuclei (Fernández-Guasti, Kruijver, Fodor, & Swaab, 2000). In addition, functional connectivity between the left amygdala and the hypothalamus has been shown be stronger in women than men (Kilpatrick, Zald, Pardo, & Cahill, 2006).

For positive stimuli, there were substantially fewer sex differences favoring women, and these differences were observed in regions that have been less specifically associated with emotion processing. Women were more likely than men to exhibit activation in a few clusters in the right temporal gyrus and right medial and superior frontal gyrus. For all emotional stimuli (see Table 5 and Fig. 5c), a number of regions showed clusters of greater activation for women, including the left hippocampus (a region also showing sex differences favoring women for negative stimuli) and the bilateral anterior cingulate cortex. Because these sex differences in activation for all emotional stimuli were a composite of the sex differences observed for negative and positive emotion (together with a small number of studies that combined positive and negative stimuli) and markedly different sex differences were found as a function of negative vs. positive valence, we focus our interpretation on the valence specific sex differences and include the results for the analysis of all emotions primarily for comparison to previous studies. In addition, because there were substantially more studies of negative emotion than of positive emotion in the sampled neuroimaging literature, the overall results for all emotion necessarily reflect the contribution of negative emotion studies significantly more than positive emotion studies, complicating the interpretation of the overall results for all emotions.

4.2. Greater activations for men

For studies of positive emotion, men exhibited greater ALE activation than women in the left amygdala. Our predictions regarding possible greater activations for men for positive stimuli were initially more tentative than our corresponding predictions for women and negative stimuli, because of less extant evidence for such a difference from behavioral and neuroimaging studies. The current findings provide further support for this previously suggested sex difference, and are consistent with findings from some individual neuroimaging studies of men's responses to positive stimuli, which have found left-lateralized amygdala activity (Hamann & Mao, 2002; Hamann, Ely, Hoffman, & Kilts, 2002), and larger left amygdala responses in men than women (Wrase et al., 2003).

These results parallel sex differences previously observed in appetitive responses to a specific type of appetitive stimuli, erotic stimuli, for which men show greater activation relative to women in the bilateral amygdala (Hamann et al., 2004), visual cortex (Sabatinelli, Flaisch, Bradley, Fitzsimmons, & Lang, 2004), and show stronger emotional physiological responses as indexed by skin

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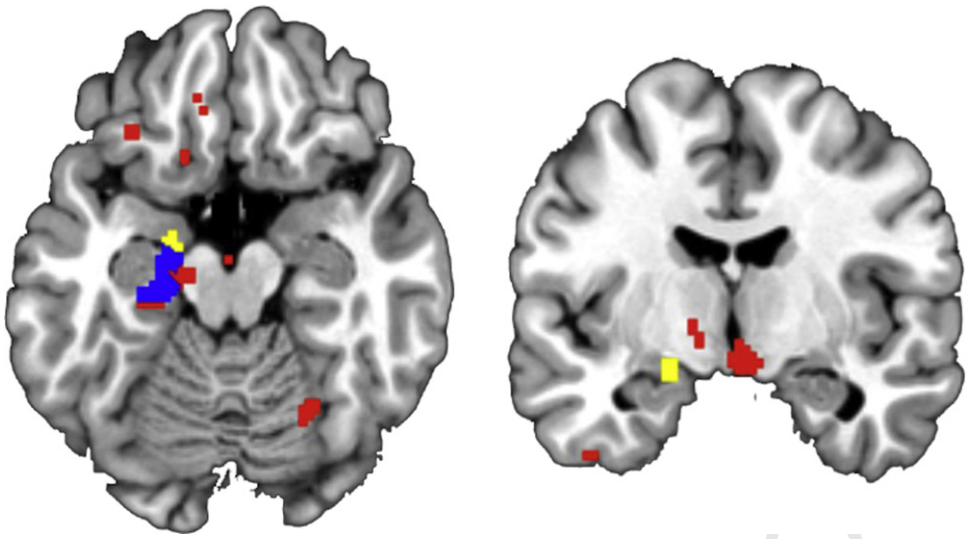

Fig. 6. Regions of significantly greater activation for women than for men ($p < 0.05$, corrected) for negative emotion, highlighting regional overlap with the amygdala and the hippocampus, overlaid on a representative single-subject structural anatomical image template in MNI space. Left panel: axial view at $z = -19$; right panel: coronal view at $y = -7$. Yellow regions: overlap with the amygdala; blue regions: overlap with the hippocampus and hippocampal–amygdala transition zone; red: regions where significant ALE voxels were observed outside of the amygdala and hippocampus. Amygdala and hippocampal ROIs were constructed from a digital neuroanatomy atlas based on postmortem brain data, as implemented in the Anatomy Toolbox (Eickhoff et al., 2005). Images are presented in neurological orientation. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of the article.)

conductance responses (Bradley et al., 2001). Our findings suggest that greater amygdala activation to positive emotional stimuli for men extends beyond sexually arousing stimuli, to other types of positive emotional stimuli. The activation cluster showing greater amygdala activation to positive emotional stimuli for men also overlapped with the entorhinal cortex (Fig. 7), a region of the medial temporal lobe which plays an important role in episodic memory supporting successful encoding and retrieval of declarative memory (for reviews, see Eichenbaum, Yonelinas, & Ranganath, 2007; Squire, Wixted, & Clark, 2007).

Men were also more likely than women to exhibit activation in the insula and lateral prefrontal cortex, in response to both positive and negative stimuli, with activation maxima in bilateral inferior frontal gyrus in BA47 and 45, extending into right anterior insula in BA13. The anterior insula and ventrolateral prefrontal regions have been implicated in representing emotional states (Critchley, Wiens, Rotshtein, Ohman, & Dolan, 2004; Wicker et al., 2003), and in emotion recognition (Adolphs, Damasio, Tranel, Cooper, & Damasio, 2000; Kringelbach & Rolls, 2003).

For negative emotion, there were substantially fewer sex differences favoring men. Men were more likely than women to exhibit activation in left posterior cingulate, for negative stimuli. This region is preferentially active for emotional stimuli (Damasio et al., 2000; Maddock, Garrett, & Buonocore, 2003) and has been implicated in integrating the emotional value of stimuli with sensory information in memory and spatial orientation tasks (Vogt,

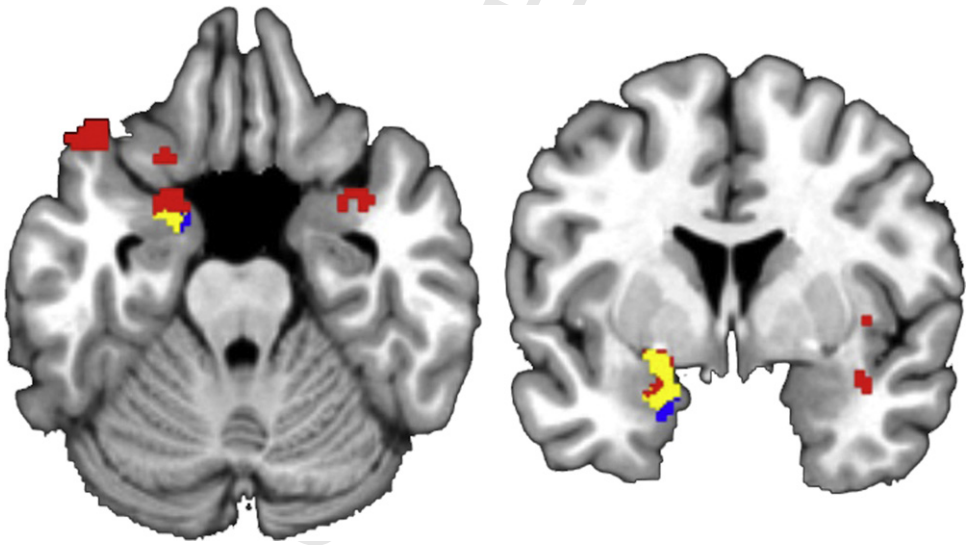

Fig. 7. Regions of significantly greater activation likelihood for men than for women ($p < 0.05$, corrected) for positive emotion, highlighting regional overlap with the amygdala and the hippocampus, overlaid on a representative single-subject structural anatomical image template in MNI space. Left panel: axial view at $z = -25$; right panel: coronal view at $y = 1$. Yellow regions: overlap with the amygdala; blue regions: overlap with the hippocampus and hippocampal–amygdala transition zone; red: regions where significant ALE voxels were observed outside of the amygdala and hippocampus. Amygdala and hippocampal ROIs were constructed from a digital neuroanatomy atlas based on postmortem brain data, as implemented in the Anatomy Toolbox (Eickhoff et al., 2005). Images are presented in neurological orientation. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of the article.)

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Finch, & Olson, 1992). For all emotional stimuli (see Table 5 and Fig. 5c), a number of emotion-related regions showed clusters of greater activation for men, including the right insula and right inferior frontal gyrus, posterior cingulate, and right superior temporal gyrus.

4.3. Similar activations for women and men

As expected, in addition to these sex differences, we also observed many similarities between women and men in emotion-related brain activation. Sex differences were typically manifested as greater or more extensive activations for one group in regions where both sexes exhibited significant ALE activation clusters. Activations for each group are presented in Table S1 and Fig. 3b and c for negative emotion, Table S2 and Fig. 4b and c for positive emotion, and Table S3 and Fig. 5b and c for all emotions combined. Figs. 3d, 4d, and 5d show the conjunction of significant activations for women and men. Some prominent common activations for both sexes for negative emotion and positive emotion included large activation clusters the in the bilateral amygdala, anterior cingulate cortex, and bilateral insula.

4.4. Relationships to previous studies

As noted previously, the current meta-analysis represents the most comprehensive such review to date. Three previous quantitative neuroimaging meta-analyses of emotion each considered sex differences, but have some limitations relative to the current study. A major limitation of previous meta-analyses is that they did not analyze sex differences as a function of positive and negative emotional valence. As is evident from the current results, patterns of observed sex differences differed markedly depending on emotional valence. Previous meta-analyses on this topic have also included a substantially smaller number of studies. Specifically, Fusar-Poli et al. (2009), limited their analysis to only include neuroimaging studies of facial expression, Sergerie, Chochol, and Armony (2008) limited their analysis to only include studies that reported significant amygdala activation and examined only the amygdala region, and Wager et al. (2003) only included studies published prior to 2002, thereby including approximately 50% fewer studies than in the current meta-analysis. A third highlight of the current study is its use of a random-effects model, which enabled broader inferences relative to previous whole-brain meta-analyses that have used fixed-effects models.

Although direct comparisons between these previous studies and the current study are complicated by important differences in the number and type of studies included and the methodology, some general comparisons can be made at the level of brain regions implicated in sex differences. For example, previous meta-analyses have implicated the amygdala in sex differences in neural responses to emotion, combining across emotional valence, with greater activation for men than women reported by one study in the right amygdala (Fusar-Poli et al., 2009), and in a region adjacent to the amygdala in another study (Wager et al., 2003). In addition, Wager et al. (2003) reported evidence that women were more likely than men to activate the left extended amygdala, but not the amygdala proper. These meta-analysis results are also in line with the findings of individual neuroimaging studies that have reported greater amygdala activations in women relative to men to negative emotional stimuli, in direct within-experiment comparisons (Domes et al., 2009; Hofer et al., 2006).

4.5. Potential mechanisms for observed sex differences

What factors could potentially contribute to the sex differences in brain activation to emotional stimuli observed in the current meta-analytic review? A number of possible relevant factors have been suggested in previous studies. One factor that has received considerable attention and discussion, and has perhaps the most empirical support to date, is the possibility that systematic differences in emotional reactivity between women and men may contribute to systematic differences in regional brain activation such as those observed here. Greater subjective and physiological responses to negative emotional stimuli have indeed been reported for women relative to men in several previous studies (Bradley et al., 2001; Grossman & Wood, 1993; Hess et al., 2000; Kring & Gordon, 1998; Nolen-Hoeksema, 2001; Sharp et al., 2006), and some limited evidence suggests that this sex difference is reversed for positive emotional stimuli (Bradley et al., 2001; Hess et al., 2000). Systematic differences in intensity or arousal across studies between women and men would be expected to result in corresponding differences in regional brain activation, both in arousal-related regions such as the amygdala, hypothalamus, and brainstem, and regions associated specifically with positive or negative emotion. The general pattern of the sex differences in amygdala activation and other regions observed in the current study is generally in line with this possibility.

The extent to which differences in subjective or physiological emotional responses contributed to the differences observed in the current study is difficult to assess. Individual studies included in the meta-analysis varied widely in whether they included subjective or physiological emotion measures. In addition, for those studies that did include such measures, the size of reported sex differences in emotional responses varied considerably. Further studies of sex differences in emotion-elicited brain activation should include measures of subjective and physiological response, to help determine the role of sex differences in emotional response in contributing to regional brain activation differences.

Other factors in addition to emotional reactivity are also likely to contribute significantly to the sex differences in activation we observed. Individual neuroimaging studies have reported sex differences in regional brain activation in regions associated with emotion such as the anterior cingulate and insula, in the absence of sex differences in emotional responses (Fine, Semrud-Clikeman, & Zhu, 2009; George, Ketter, Parekh, Herscovitch, & Post, 1996). Several differences in the neural mechanisms by which women and men process emotion have been proposed that highlight the role of cognitive and other factors. These have included a variety of proposed differences in the cognitive representation and processing of emotional stimuli, ranging from differences in attentional biases (Schirmer et al., 2008), effects of previous experience on perception and memory (Cahill & van Stegeren, 2003; Seidlitz & Diener, 1998) to differences in emotional executive control processes such as regulation (Domes et al., 2009; McRae, Ochsner, Mauss, Gabrieli, & Gross, 2008) and frequency of rumination about past emotional experiences (Thomsen et al., 2005). Additional sources of sex differences have also been proposed, including differences in lateralization of emotion processing (Canli et al., 2002; Fine et al., 2009; Wager et al., 2003) and temporal characteristics of the emotional response (e.g., prolonged emotional responses; Gard & Kring, 2007). Multiple factors may contribute to particular observed sex differences, and these factors may also interact, for example, sex differences in the effectiveness of emotion regulation (e.g., Domes et al., 2009; McRae et al., 2008) may amplify differences in more basic emotional responsiveness.

Although the ultimate causal factors responsible for sex differences in brain responses to emotional stimuli have yet to be delineated, the categories of likely potential factors are the same as those previously theorized for other sex differences in psychological and brain function: biological mechanisms such as genetic and hormonal influences and associated evolutionary factors, differences between the sexes in socialization and prior experience,

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and the interaction of these factors. Our results are compatible with any of these potential causal factors. A question for future study is the extent to which each the sex differences in regional activation observed here are valid cross-culturally and can be modified by experience.

4.6. Limitations

A number of limitations related to the current study should be noted. The meta-analysis results are based on summary information from individual neuroimaging studies, not the original raw data. Re-analysis of original raw data would be preferable, but this approach is precluded by the fact that such data are generally unavailable for most studies (Salimi-Khorshidi, Smith, Keltner, Wager, & Nichols, 2009). The ALE method retains key aspects of the reported findings in each study, but like most neuroimaging meta-analysis methods, does not differentially weight information regarding activation statistics beyond requiring that each activation cluster exceeds the significance threshold used in each study. Another limitation concerned the fact that there were substantially fewer studies that could be included that examined positive emotion than examined negative emotion. Thus, there was lower power to detect sex differences for positive emotion studies relative to negative emotion studies.

In addition, the neuroimaging studies contributing to the meta-analysis varied widely in their stimuli, experimental methods, and scanning parameters. Although we took steps to minimize the possible contribution of such factors, it remains possible that systematic differences in such factors may have contributed to some of the observed differences. Future neuroimaging studies examining these issues should include a wider range of stimulus modalities and tasks to enable potential interactions with stimulus and task factors. Another limitation was that, in line with previous meta-analyses, our analysis only considered differences at the level of individual voxels and brain regions. However, meta-analyses that consider functional connectivity and other methods of characterizing distributed networks involved in emotion are a promising avenue for further study, particularly in light of sex differences in amygdala functional connectivity reported in individual neuroimaging studies (Kilpatrick et al., 2006; Savic & Lindstrom, 2008).

In the current study, our analysis focused on examining sex differences as a function of positive and negative emotional valence. This approach was motivated in part by the considerable evidence demonstrating that emotional valence is a key dimension of emotion and the neural representation of emotion (Feldman Barrett & Russell, 1999; Lang, Bradley, & Cuthbert, 1998; Nielen et al., 2009). However, positive and negative valence categories can be further subdivided into more specific emotion types, for example, basic emotions (happiness, fear, etc.; Darwin, 1873; Ekman, 1999) and other classifications such as threat, dominance, and sexual arousal. The extent to which the valence-specific sex differences observed in this study generalize to other emotion categories is an important question for further study.

5. Conclusions

In conclusion, the current findings provide new meta-analytic evidence that regional brain activations elicited during emotion differ in several important ways between the sexes. These sex differences in regional activation were substantial and were observed in key regions associated with emotion processing, most strikingly the left amygdala, which showed greater activation for women for negative emotion studies, but greater activation for men for positive emotion studies. Other substantial sex differences were found in additional regions involved in emotion and memory, including the hippocampus, insula, hypothalamus, and medial prefrontal cortex. As expected, these sex differences were found against a background of broad similarities between the sexes in the basic regions recruited during positive and negative emotion processing.

Our findings are consistent the findings of previous individual neuroimaging studies that have directly contrasted women and men in within-experiment comparisons. However, the nature and generality of the findings of these individual studies has remained unclear, in large part because of the small number of studies to date that have examined these differences. The limitations associated with a limited number of studies are particularly prominent for studies of positive emotion (Fine et al., 2009; Hofer et al., 2007; Killgore & Yurgelun-Todd, 2001; Wrase et al., 2003). Here, by taking a meta-analytic approach we were able to make a comprehensive summary assessment of the relevant affective neuroimaging literature. Although the meta-analytic approach has several advantages, it also has significant limitations, highlighting the need to broaden the current neuroimaging literature on affective sex differences with new studies investigating the questions and issues we have examined.

The current findings underscore 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. Approaches that integrate knowledge of individual differences will ultimately provide a more complete account than those that regard individual differences as uninteresting or merely as statistical noise to be filtered out in the search for putative universal psychological and neurobiological mechanisms (Cahill, 2006; Hamann & Canli, 2004). For example, in cases where a regional brain activation effect is present in either women or men, but is either absent or reversed in the other group, examination of results combined across the sexes will produce an incomplete characterization of brain activations. These issues are particularly salient when considering individual differences that are related to depression, anxiety disorders, and other forms of psychopathology. There is growing evidence that women and men differ importantly in psychological and neurobiological mechanisms related to the development of a range of psychopathologies. Understanding the role of these individual differences will foster a better understanding of the neural mechanisms of both healthy and disordered emotional function.

Uncited reference

Q3

Bechara, Damasio, and Damasio (2000).

Acknowledgements

We thank Patricia Bauer, Stella Lourenco, Irwin Waldman, and Kim Wallen for feedback on this paper.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.neuropsychologia.2012.03.011.

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Please cite this article in press as: Stevens, J. S., & Hamann, S. Sex differences in brain activation to emotional stimuli: A meta-analysis of neuroimaging studies. *Neuropsychologia* (2012), doi:10.1016/j.neuropsychologia.2012.03.011

Figure S1. ALE maps for analyses of emotion across all participants (analysis of the balanced dataset)

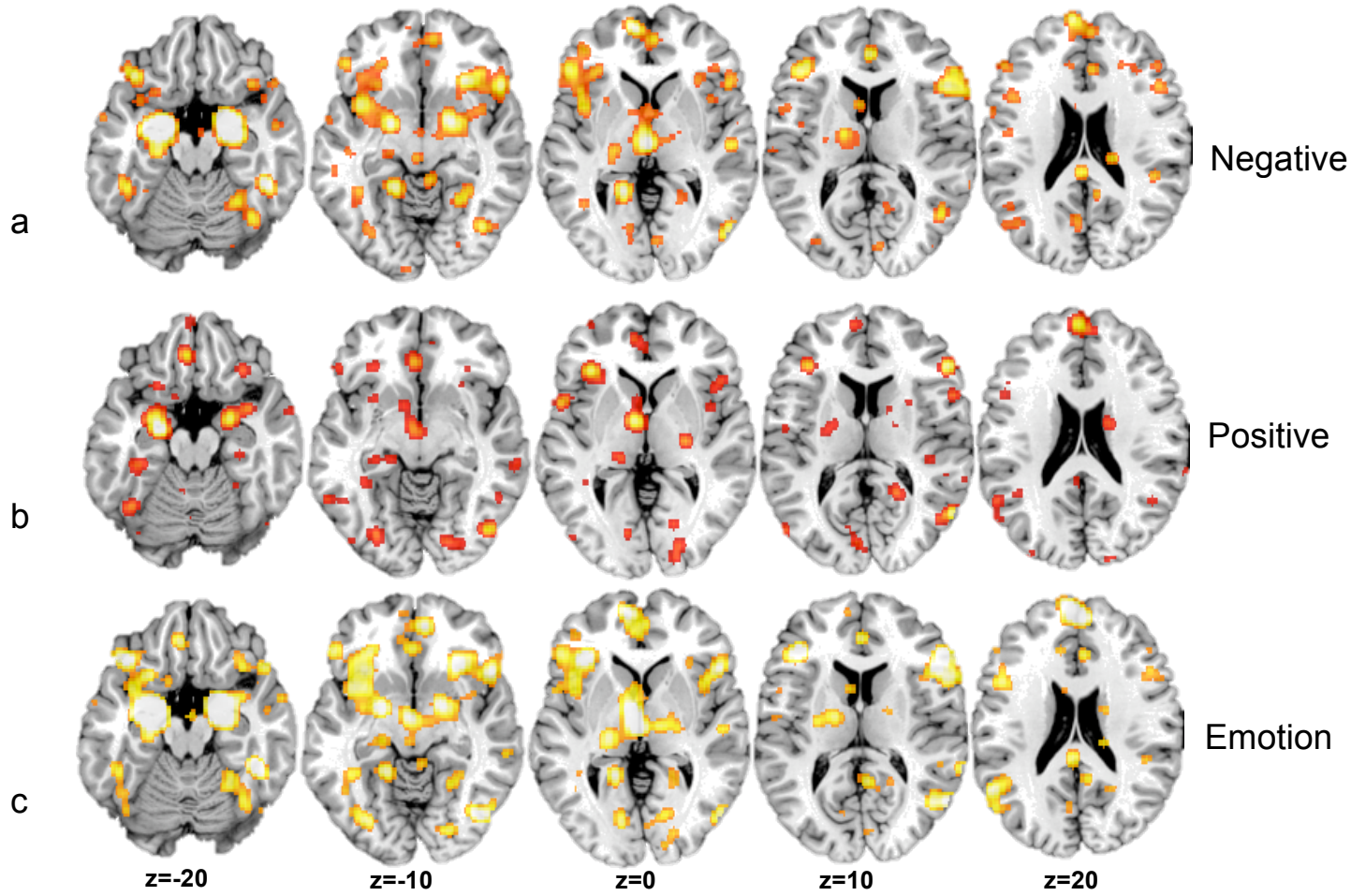

Figure S1. Regions of significant activation likelihood ($p < 0.05$, FDR-corrected for multiple comparisons) for contrasts collapsed across studies of women and men, overlaid on a representative single-subject structural anatomical image template in MNI space. S1a: Significant ALE clusters for negative emotional contrasts. S1b: Significant ALE clusters for positive emotional contrasts. S1c: Significant ALE clusters for all emotional contrasts (positive and negative emotion stimuli). Images are presented in neurological orientation. Brighter colors indicate greater activation likelihood.

Figure S2. ALE maps of sex differences (analysis of the complete dataset)

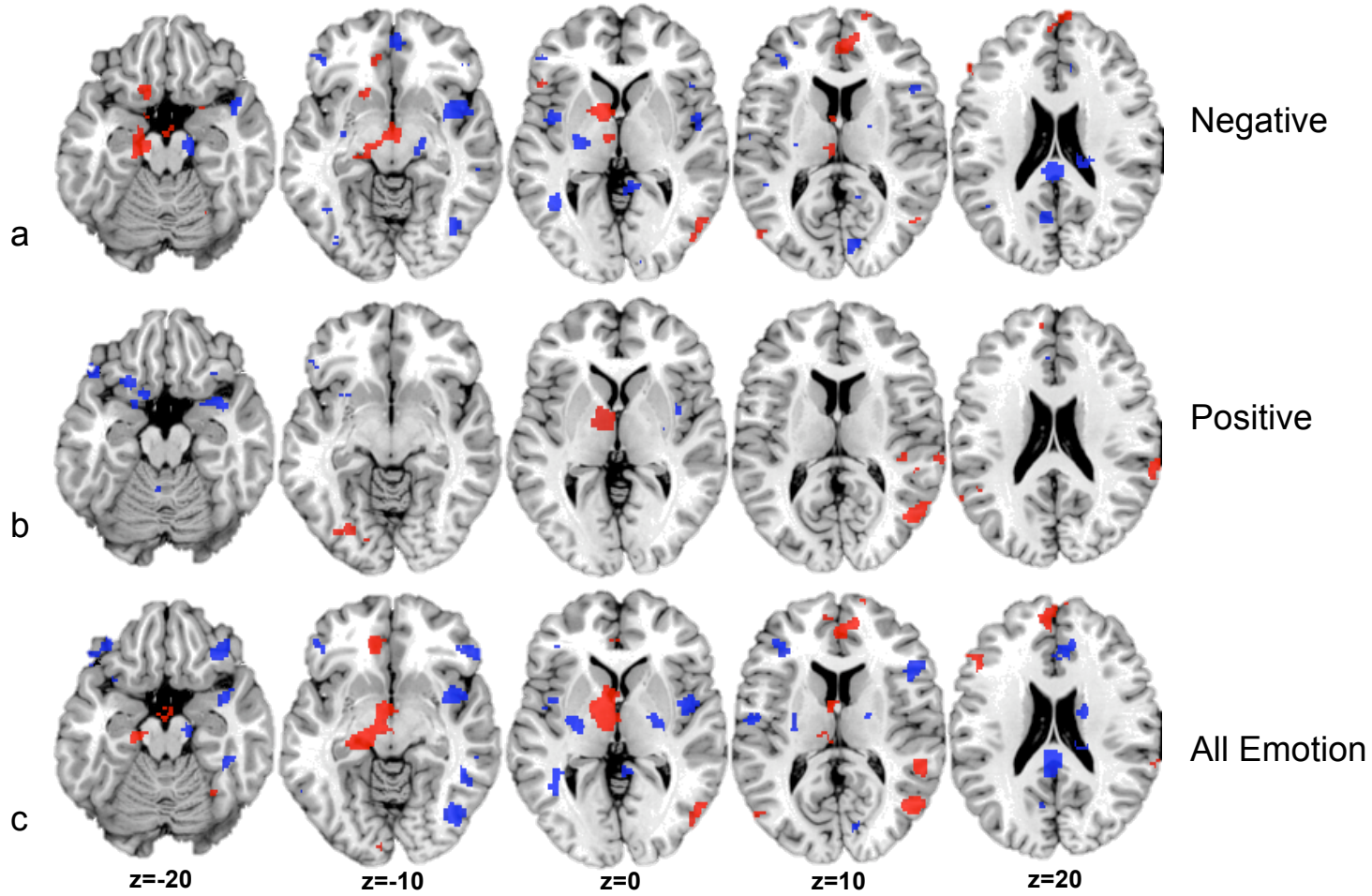

Figure S2. Regions of significant differences in activation likelihood for women vs. men ($p < 0.05$, corrected). S2a: Sex differences in activation likelihood for contrasts of negative emotion. Red color scale: greater activation for women than men. S2c: Sex differences in activation likelihood for all emotional contrasts, collapsed across positive and negative valences. S2b: Sex differences in activation likelihood for contrasts of positive emotion. Blue color scale: greater activation for men than women. Images presented in neurological orientation. Brighter colors indicate greater activation likelihood.