

# Sex differences in the persistence of the amygdala response to negative material

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**Previous studies have indicated that men and women have different amygdala responses to novel (vs familiar) and valenced (positive vs negative) material. It is not known, however, whether these affective sex differences are related. In this study, we tested whether women have more persistent amygdala responses to familiar, negative material than men do. During fMRI, male and female participants viewed evocative images that varied in novelty and valence. Women and men showed equivalent responses to novel negative material, but women showed a sustained amygdala response to familiar negative material relative to men, indicating that women's amygdala responses were more persistent over multiple repetitions of negative material. Individuals with more persistent amygdala responses also reported greater levels of negative affect. These findings have implications for sex differences in the incidence of affective disorders.**

**Keywords:** amygdala; sex; habituation

## INTRODUCTION

Sex differences in the brain's response to affective stimuli have been frequently reported (Cahill, 2006; Stevens and Hamann, 2012). Contrary to the popular belief that women are generally more emotionally reactive than men (Birnbaum and Croll, 1984; Shields, 1991), neuroimaging studies show that these differences are complex and region-specific, such that the direction of sex differences vary in functionally distinct areas of the brain (Wager *et al.*, 2003). One area that has been a frequent subject of sex differences research is the amygdala, a structure known to be involved in the processing of affective information (Costafreda *et al.*, 2008; Kober *et al.*, 2008; Sergerie *et al.*, 2008) and the enhancement of memory consolidation by arousal (McGaugh, 2004; LaBar and Cabeza, 2006).

Research on sex differences in the amygdala has produced conflicting results. Multiple studies report increased amygdala activity during the processing of affective scenes in men relative to women (Schenle *et al.*, 2005; Goldstein *et al.*, 2010), and meta-analysis supports this view, showing larger effect sizes in studies of affective processing including only men compared with those including only women (Sergerie *et al.*, 2008). However several studies using similar stimuli have reported a larger amygdala response in women (Klein *et al.*, 2003; McClure *et al.*, 2004; Hofer *et al.*, 2006; Domes *et al.*, 2010), and others have reported no sex difference at all (Wrase *et al.*, 2003; Caseras *et al.*, 2007; Aleman and Swart, 2008).

A possible explanation for these inconsistent results is that sex differences in amygdala response are valence-dependent. Studies that have distinguished between negative and positive affect have generally indicated that women exhibit a relatively larger amygdala response to negative material, while the amygdalae of men respond preferentially to positivity. Both significant amygdala responses to negativity in women but not men (Hofer *et al.*, 2006), and significant responses to positivity in men but not women (Killgore and Yurgelun-Todd, 2001) have been reported. Similarly, the difference in amygdala signal between negative and positive items was found to be significantly larger in

women than in men (Klein *et al.*, 2003). A recent meta-analysis (including numerous studies using single sex populations as well as studies of sex differences) indicates that in studies where negative affect was induced, the average amygdala response was larger in women, while studies of positive affect show larger responses in men (Stevens and Hamann, 2012). Consistent with this view, multiple studies of the amygdala response to high arousal positive stimuli (erotica) show a larger amygdala response in men relative to women (Hamann *et al.*, 2004; Rupp and Wallen, 2008)

Yet, valence is not the whole story when considering sex differences in amygdala response. The amygdala, along with other limbic structures, respond robustly to novel information (Schwartz *et al.*, 2003b; Gur *et al.*, 2007; Wright *et al.*, 2008; Weierich *et al.*, 2010; Balderston, *et al.*, 2011; Moriguchi *et al.*, 2011). Novel stimuli produce similar physiological responses to those evoked by stimuli that are strongly valenced or arousing (Mendes *et al.*, 2007). Additionally, stimulus novelty enhances the activity of mesolimbic reward circuitry, suggesting that novelty can affect the rewarding properties of positive stimuli (Krebs *et al.*, 2009). The majority of studies of sex influences on affective processing have used only novel stimuli, potentially confounding the influence of stimulus novelty and valence.

To date, only two studies of which we are aware have considered whether men and women have differential amygdala responses to novel information. Williams and colleagues (2005) measured both amygdala signal and skin conductance changes evoked by faces posing fear repeated 15 times over the course of the experiment. While no sex difference in on either measure was observed when all repetitions were averaged, comparison of the change in these responses between the first and second half of the session showed that both skin conductance and amygdala response declined significantly in men, while persisting in women. Similarly, Thomas and colleagues (2001), found that the amygdala response to fearful faces declined over multiple repetitions in boys, but persisted in girls. Previous research has shown habituation in amygdala signal as stimuli are repeated and become familiar, but these studies have examined only male participants (Breiter *et al.*, 1996; Fischer *et al.*, 2003; Wedig *et al.*, 2005). Thus, the evidence suggests that both young and adult females are significantly slower to habituate than are males, but the question remains whether this would be observed for all affective stimuli, or for only negative stimuli.

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In the present experiment, we tested the possibility that women show a sustained amygdala response to negative material across repeated presentations relative to men. We predicted that the more persistent female amygdala response observed in the studies described above would be found specifically for affectively negative material, and not for positive or neutral images. In contrast, we predicted that the amygdala response to negative familiar material would be smaller in men relative to women, while men would show a relatively greater amygdala response to positive material. Additionally, we examined whether individuals with a more persistent amygdala response to negative material also reported more intense negative mood, trait anxiety and depressive symptoms. Studies of the neural correlates of depression and anxiety indicate that individuals at higher risk of affective disorder exhibit an insensitivity to novelty differences in the amygdala, particularly in response to affective material (Barrett and Armony, 2009; Blackford *et al.*, 2011). Furthermore, the amygdala is part of a workspace in the brain that is important for creating affective feelings (Barrett and Bliss-Moreau, 2009). We therefore predicted that a more persistent amygdala response to negative stimuli would be associated with higher levels of self-reported negative affect.

## METHODS

### Participants

A total of 45 healthy young participants between the ages of 18 and 35 years (29 female, 16 male) were studied in this experiment. These participants were controls in previous studies of aging and affect, one of which has been previously published (Moriguchi *et al.*, 2011). All participants were right-handed as determined by the Edinburgh Handedness Inventory, and not currently using any psychoactive medications. Additionally, all participants were screened by the Structured Clinical Interview for DSM-IV to confirm the absence of Axis I diagnosis.

### Stimuli

One hundred and thirty two full-color images selected by valence and arousal ratings from the International Affective Picture System (IAPS; Lang, Bradley, & Cuthbert, 2008) were used in this study. Of these 132 images, equal numbers of each of three levels of arousal (high, mid and low) and types of valence (negative, neutral and positive) were included, creating six combinations of arousal and valence (high arousal negative, high arousal positive, mid arousal negative, mid arousal positive, mid arousal neutral and low arousal neutral). It was not possible to fully cross arousal and valence because the IAPS set does not include high arousal neutral or low arousal valenced images. In addition to valence and arousal, images were also classified by novelty. To create a novelty difference, participants were familiarized to two images in each arousal/valence combination, and the remaining images were used as novel images (see 'Experimental Procedure' section). Thus 22 images (20 novel, 2 familiar) from each valence/arousal combination were used.

### Experimental procedure

Prior to scanning, a subset of participants (31 participants, 21 female, 10 male) completed three survey measures of negative affect: the Positive and Negative Affect Schedule (PANAS), State-Trait Anxiety Inventory (STAI) and Center for Epidemiological Studies Depression inventory (CES-D) (Radloff, 1977; Spielberger *et al.*, 1983; Watson and Clark, 1994).

Functional scanning consisted of five event-related fMRI runs. During the first run, participants were familiarized with 12 items, each repeated five times. The next four runs were test runs, in which participants were presented with six items from the familiarization

phase five times each and 30 novel items, presented once. Thus at the conclusion of the experiment, each participant had viewed 120 novel images once, and 12 familiar items 15 times. Each item was presented for 3.5 s.

During image presentation, participants rated their subjective reaction to each image in terms of arousal on a scale of 1–3 by button press.

Prior to scanning, each participant completed a brief practice run outside the scanner to become familiar with the experimental task. The images used for practice varied in valence and arousal and were not used in the experimental runs. Stimuli were presented using E-Prime experimental software (Psychology Software Tools, Pittsburgh, PA, USA). Participants viewed images via a mirror mounted on the head coil.

### Image acquisition

Images were acquired using a Siemens Magnetom Trio Tim 3T whole-body high-speed imaging device equipped for echo planar imaging (EPI) (Siemens Medical Systems, Iselin, NJ, USA) with a 12-channel gradient head coil. Expandable foam cushions restricted head movement. After an automated scout image was acquired and shimming procedures were performed, high resolution 3D MPRAGE sequences (TR/TE/flip angle = 2.53 s/3.39 ms/7°) with an in-plane resolution of 1.3 × 1.0 mm and 1.3-mm slice thickness were collected for spatial normalization and for positioning the slice prescription of the subsequent sequences. Next, T1-EPI (TR/TE/flip angle = 10 s/39 ms/90°) and T2-weighted (TR/TE/flip angle = 5.21 s/94 ms/150°) sequences were collected to assist in registration of the functional data to the high-resolution anatomical scan. Functional MRI images were acquired using a gradient-echo T2\*-weighted sequence (TR/TE/flip angle = 2 s/30 ms/90°). Prior to each scan, four time points were acquired and discarded to allow longitudinal magnetization to reach equilibrium. The T1, T2 and T2\* images were all collected in the same plane (33 coronal slices angled perpendicular to the AC/PC line), with a slice thickness of 5 mm, for a voxel size of 3.12 × 3.12 × 5 mm, interleaved acquisition order and foot-to-head phase encoding.

### Image preprocessing

Functional and structural MRI data were analyzed in FreeSurfer, using the standard processing stream of the Martinos Center for Biomedical Imaging (<http://surfer.nmr.mgh.harvard.edu>). BOLD data were motion corrected and inspected for gross motion. Slices were discarded if the total motion vector exceeded 5 mm. Data in each functional run were intensity normalized and spatially smoothed (full-width half-maximum = 5 mm) using a 3D Gaussian filter. To remove temporal autocorrelation noise, polynomial drift correction was used, with two nuisance regressors to account for low-frequency drift and whitening based on a single autocorrelation function estimated across all brain voxels (Burock and Dale, 2000).

Following preprocessing, functional images for each participant were registered to an average 3D structural image created from that participant's two high-resolution 3D MPRAGE images.

### Functional analysis

All functional analysis was performed in FS-Fast, the functional analysis package for FreeSurfer (<http://surfer.nmr.mgh.harvard.edu>). All functional data were convolved around a canonical gamma function with a hemodynamic delay of 2.25 s, and dispersion of 1.25 mm. Each combination of valence, arousal and novelty was modeled separately in a general linear model. First-level maps comparing each of six combinations of valence (positive, neutral and negative) and novelty (novel and familiar) to fixation were generated for each participant. These

maps were used in a region of interest (ROI) analysis of the amygdala, where average signal change *vs* fixation was extracted for each of the six valence/novelty combinations. These values were then entered into a mixed model three-way Analysis of Variance, with valence and novelty as within subjects factors, and subject sex as a between-subjects factor.

### Cluster analysis

Potential sex differences in other regions associated with affective processing were assessed using an anatomically restricted cluster analysis. Using FreeSurfer's automated anatomical labeling, a mask containing key regions of the affective network including amygdala, orbitofrontal, insular and cingulate cortices was generated. This mask was then conjoined with the results of a whole-brain analysis comparing all stimulus conditions *vs* fixation, resulting in a volume including all selected regions of the affective network that showed significantly greater activity during image viewing relative to fixation at  $P < 0.05$  (corrected for multiple comparisons by Monte-Carlo simulation). Contrasts measuring the difference between novel and familiar items for each type of valence (i.e. novel positive–familiar negative, novel neutral–familiar neutral, novel negative–familiar negative) were applied to this volume to assess the influence of novelty on the neural response to images of each valence. In this analysis, a large difference between novel and familiar would signify a declining response over multiple repetitions, and thus a high degree of habituation. A small difference would indicate a response that remains persistent through multiple repetitions.

In a second-level analysis, maps representing between-group differences in all first-level contrasts were generated. Clusters showing significant differences within and between groups were identified using

FS-fast's clustering algorithm at  $P < 0.005$ , uncorrected, with a minimum cluster size threshold of 10 voxels.

### Regression analyses

Potential relationships between affect measures (i.e. STAI, PANAS, CES-D) and regional activity for contrasts of interest were investigated by first extracting average group-level signal change from the amygdala ROI, masked with the all *vs* fixation contrast, as described above. Signal change was then included as the dependent variable in a regression analysis, with score on the affect inventories used as the predictor variable. Sex was included in these analyses as a moderating variable, to test whether it would influence the zero-order correlation between the other two variables in each analysis. This approach assesses whether participant sex affects the direction and/or strength of any potential relationship between signal change and self-reported affect. For more details on this procedure, see Baron and Kenny (1986).

## RESULTS

### ROI analysis of the amygdala

As predicted, women showed a sustained amygdala response to familiar negative items when compared with men. Average amygdala signal change to each valence condition for familiar and novel items is shown in Figure 1. A significant novelty  $\times$  valence  $\times$  sex interaction was found in left amygdala [ $F(2,42) = 3.239$ ,  $P < 0.05$ ], and this interaction approached significance on the right [ $F(2,42) = 2.414$ ,  $P < 0.1$ ]. When familiar and novel items were considered separately, a significant valence  $\times$  sex interaction was found in left [ $F(2,42) = 4.384$ ,  $P < 0.05$ ] and right amygdala [ $F(2,42) = 3.444$ ,  $P < 0.05$ ] for familiar items, but this effect was not found for the response to novel items [left:

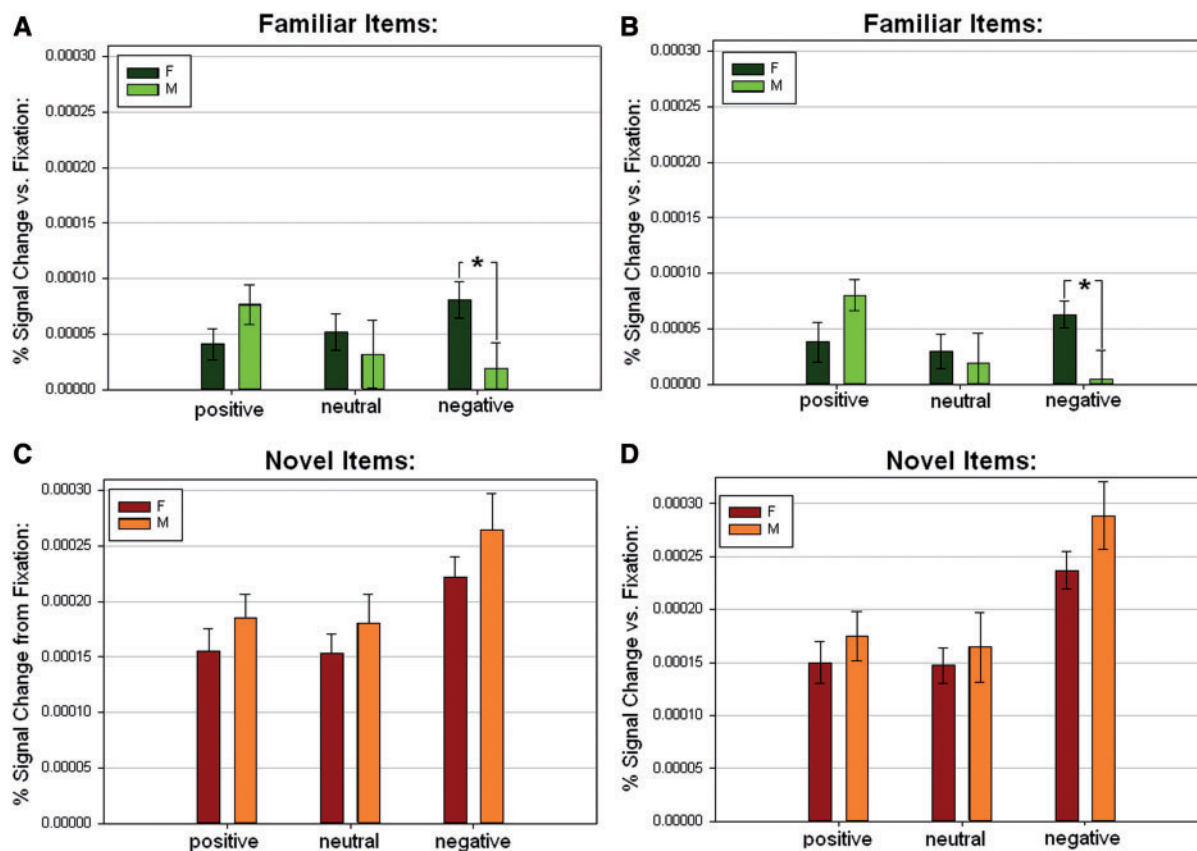


Fig. 1 Average amygdala % signal change from baseline *vs* fixation to familiar (a,b) and novel (c,d) stimuli in the left (a,c) and right (b,d) amygdalae. \* =  $P < 0.05$ .

$F(2,42) = 0.538, P = 0.588$ , right:  $F(2,42) = 0.411, P = 0.665$ ]. *Post hoc* analysis revealed that women showed a significantly greater response to familiar negative items compared with men in left amygdala [ $t(43) = 2.092, P < 0.05$ ], and this comparison closely approached significance on the right [ $t(43) = 2.010, P = 0.051$ ]. No significant sex difference was detected at any other valence/arousal combination, although there was a nonsignificant trend towards a greater response to familiar positive items in men relative to women in left amygdala ( $t(43) = -1.449, P = 0.146$ ).

### Cluster analysis

Clusters where the difference between novel and familiar items differed significantly for men and women are shown in Table 1. Significant sex differences in the novelty response were observed throughout the brain's affective workspace. With a only single exception (right insula in the novel negative–familiar negative contrast), all significant clusters showed a greater difference between novel and familiar items in men, relative to women. Clusters in bilateral amygdalae were detected only for the novel negative–familiar negative contrast, and not neutral or positive material. Significant sex differences in the response of the amygdala were found only in the contrast comparing novel and familiar negative items (Figure 2).

### Amygdala correlations with self-reported negative affect

Average scores by sex on STAI, PANAS and CES-D are shown in Table 2. No significant sex differences were observed on any measure.

As predicted, individuals with a more persistent amygdala response to familiar negative images reported greater anxiety on the STAI ( $r = 0.486, P < 0.01$ , left amygdala;  $r = 0.35, P = 0.063$ , right amygdala). Sex was not found to be a significant moderating factor in either relationship. STAI scores were also positively correlated with the amygdala response to familiar positive images ( $r = 0.496, P < 0.01$ , left;  $r = 0.415, P < 0.05$ , right). However, for these relationships, sex was a moderating factor (left:  $P = 0.005$ , right:  $P = 0.005$ ), such that while the relationship was highly significant in women bilaterally (left:  $r = 0.698, P = 0.001$ , right:  $r = 0.644, P < 0.005$ ), no relationship was present among men ( $P > 0.7$ , bilaterally). No significant correlations with STAI were found for amygdala signal in response to novel items at any valence level. The relationship between persistence in amygdala response and STAI scores is shown in Figure 3.

A similar pattern of results was observed for amygdala response and reports of depressive symptoms on the CES-D. Individuals with a more persistent amygdala response to familiar negative images reported greater depression. This relationship was significant in left amygdala, ( $r = -0.504, P < 0.005$ ), and approached significance on the right ( $r = -0.345, P = 0.062$ ). Sex was not found to be a significant moderating factor in either relationship. No significant correlations with CES-D were found for amygdala signal in response to novel items of any valence.

The relationship between novel negative–familiar negative signal change and scores on the CES-D are shown in Figure 4.

## DISCUSSION

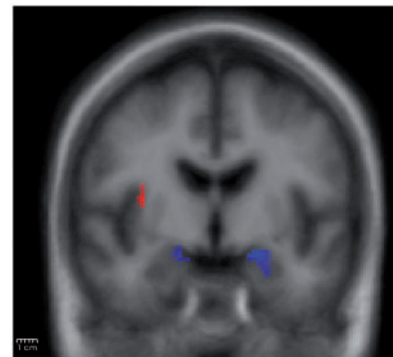
### Sex differences in the persistence of the amygdala response to negative information

We found support for the hypothesis that women showed persistent amygdala responses to negative images, whereas this was not true of men. Women showed a larger amygdala response to familiar negative images relative to men, while the response to novel negative images was equivalent. Similarly, significant clusters in bilateral amygdalae were found where the difference in response between novel and

**Table 1** Clusters showing significant sex differences on novelty  $\times$  valence contrasts

Size (in voxels)	X	Y	Z	t		Location
<b>Novel negative–familiar negative</b>						
107	-30	29	-1	-5.69	m>f	l anterior insula
114	22	15	-25	-5.6	m>f	r medial OFC
64	34	23	1	-5.1	m>f	r anterior insula
238	40	39	-15	-4.57	m>f	l lateral OFC
14	32	-37	-11	-4.2	m>f	r hippocampus
17	36	-9	7	3.45	f>m	r central insula
69	30	33	-7	-3.35	m>f	r lateral OFC
10	18	-1	-19	-2.96	m>f	r amygdala
24	-28	19	-19	-2.81	m>f	l lateral OFC
43	-20	-5	-15	-2.81	m>f	L amygdala
14	10	23	29	-2.31	m>f	r pregenual cingulate
<b>Novel Neutral–Familiar Neutral</b>						
348	28	-37	-11	-5.91	m>f	r white matter
118	-42	39	-15	-4.24	m>f	l lateral OFC
62	-26	13	-23	-3.34	m>f	l lateral OFC
196	-24	-15	-28	-2.89	m>f	l hippocampus
11	-30	31	-1	-2.81	m>f	l anterior insula
14	26	15	-23	-2.42	m>f	r medial OFC
<b>Novel Positive–Familiar Positive</b>						
527	-22	-29	-11	-7.68	m>f	l hippocampus
669	28	-37	-11	-7.42	m>f	r hipp
250	-8	13	49	-6.67	m>f	l dorsal midcingulate
478	-42	35	-15	-6.27	m>f	l lateral OFC
42	26	15	-25	-4.24	m>f	r medial OFC
23	2	3	33	-4.19	m>f	r midcingulate
109	34	23	1	-4.13	m>f	r anterior insula
23	-16	39	-21	-4	m>f	l medial OFC
66	34	23	1.43	-3.98	m>f	r anterior insula
115	10	15	53	-3.4	m>f	frontal superior gyrus
27	38	27	-7	-3.06	m>f	r anterior insula

All clusters are significant at  $P < 0.005$ , uncorrected, with a minimum cluster size of 10 voxels. All coordinates are reported in MNI space.

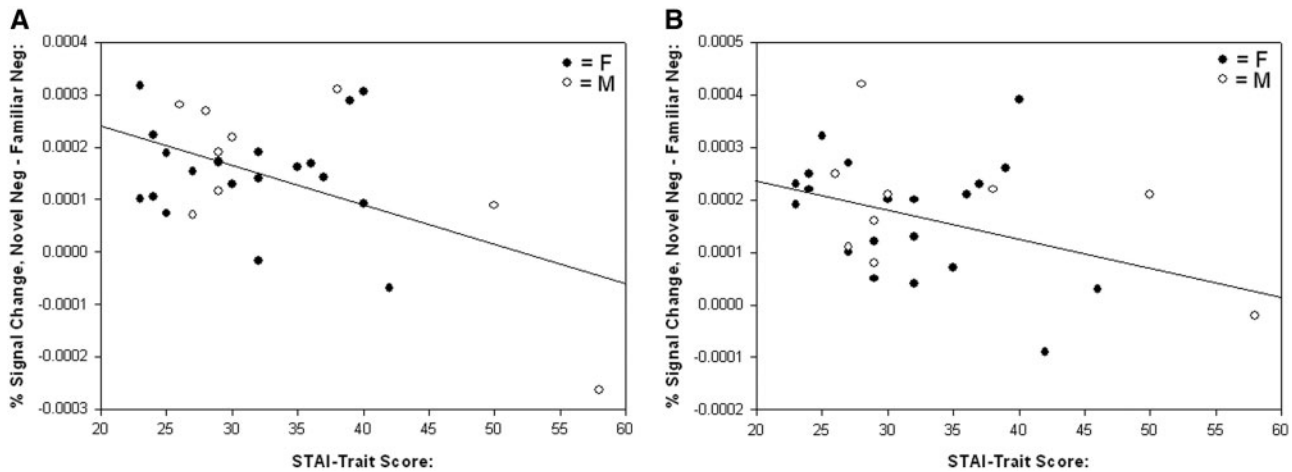


**Fig. 2** Clusters in bilateral amygdalae showing significantly greater signal change between novel negative and familiar negative items for men relative to women (blue). The only region where novel-familiar signal difference is greater in women, right insula, is also visible (red).

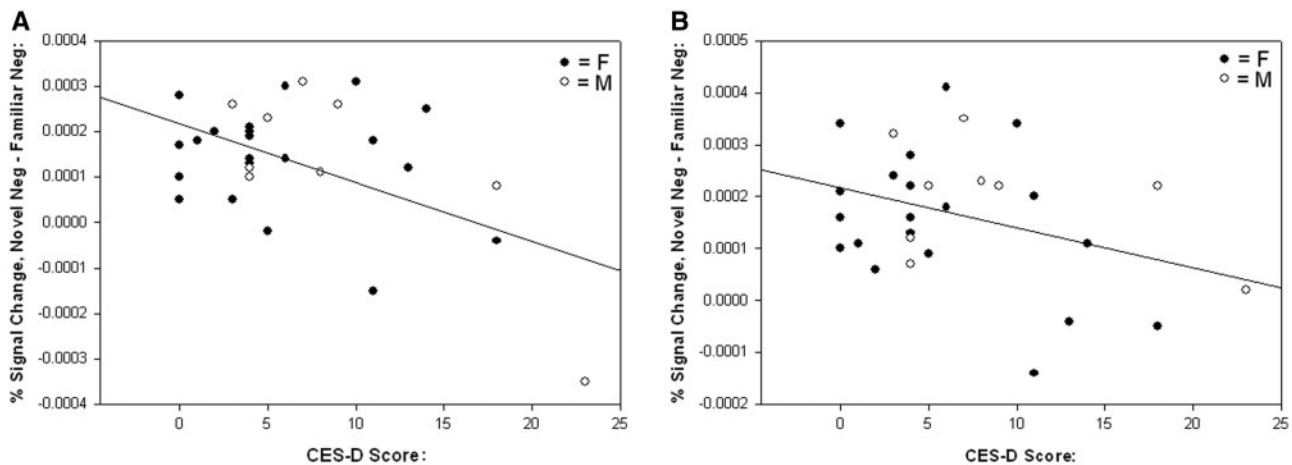
**Table 2** Means and standard deviations for scores on STAI, PANAS negative affect subscore, PANAS positive affect subscore and CES-D, by sex

	STAI	PANAS neg	PANAS pos	CES-D
Female	31.4 (6.95)	15.4 (4.39)	38.8 (5.04)	5.71 (5.2)
Male	35 (11.47)	15.5 (7.43)	36.9 (4.90)	9 (6.92)

familiar negative images was significantly greater in men, relative to women, while contrasts comparing novel and familiar neutral or positive images showed no significant differences in the amygdala. These findings indicate that the response of the amygdala to negative stimuli



**Fig. 3** Relationship between STAI scores and the signal change difference between novel and familiar negative items in (a) left and (b) right amygdalae. A smaller signal change difference represents a more persistent amygdala response.



**Fig. 4** Relationship between CES-D scores and the signal change difference between novel and familiar negative items in (a) left and (b) right amygdalae. A smaller signal change difference represents a more persistent amygdala response.

is significantly more persistent over multiple repetitions in women than it is in men.

These results are consistent with previous studies showing a resistance to habituation to negative material in both female adults (Williams *et al.*, 2005) and children (Thomas *et al.*, 2001). The present data extend previous findings in showing that the persistence effect in the amygdala is valence specific. For familiar positive items, there was a nonsignificant trend towards a greater response in men.

These findings build on previous research showing a greater response to negativity in women, and a greater response to positivity in men (Stevens and Hamann, 2012). However, the present data suggest that this effect is importantly mediated by novelty, as sex differences were found only for familiar images. The majority of studies used in Stevens and Hamann's meta-analysis used only novel stimuli, while in our study novel and familiar images were intermixed. It is possible that the inclusion of familiarized material heightens the amygdala's response to novelty, making valence differences more difficult to detect.

Although the effect was present bilaterally, the sex difference in the persistence of amygdala response observed in this study was notably stronger in the left hemisphere than it was on the right. Meta-analysis

indicates that the responses to affective material are generally larger and more sustained in left amygdala, (Sergerie *et al.*, 2008), thus sex differences in these more robust amygdala responses may be easier to detect. Additionally, a sex/laterality interaction has been previously reported in the relationship between amygdala activity at encoding and subsequent memory success, such that left amygdala activity is more predictive of successful encoding in women (Cahill *et al.*, 2004). In the present study, however, women showed a greater resistance to habituation, a basic form of memory, in left amygdala than was evident on the right.

#### Relationship with negative affect and affective disorder

A persistent response to negativity of the sort observed here in women has also been reported in several studies of negative affect and affective disorder. Individuals with inhibited temperament (a group at increased risk for both depression and anxiety disorders) exhibit amygdala activity in response to both novel and familiar faces, while controls respond only to novel faces (Blackford *et al.*, 2011, Schwartz, 2003a), and continue to show increased amygdala response to faces even after extended habituation (Blackford *et al.*, 2012). Similarly, individuals high in trait anxiety fail to habituate to previously threat-associated stimuli,

as these stimuli continue to evoke amygdala activity after extinction training (Barrett and Armony, 2009; Sehlmeier *et al.*, 2011). There is also some evidence that individuals with posttraumatic stress disorder show decreased habituation in amygdala signal to repeated fearful faces (Shin *et al.*, 2005).

Consistent with these findings, our results showed that the difference in amygdala signal between novel and familiar negative items was negatively related with both self-reported trait anxiety and depressive symptoms. Thus those individuals with a more persistent amygdala response to negativity (and therefore a smaller difference in response novel and familiar negative images) also reported more anxiety and depressive symptoms. Considering that women as a group showed a smaller novel vs familiar difference and a larger response to familiar negative items, these findings may have implications for sex differences in the incidence of affective disorder. Studies of the incidence of psychiatric disorders have consistently indicated that disorders of affect appear at significantly higher rates in women than in men. Women are twice as likely to experience clinical depression (Kessler *et al.*, 1994; Altemus, 2006; Solomon and Herman, 2009) or generalized anxiety disorder (Wittchen *et al.*, 1994) in their lifetimes. Women who have experienced trauma are also significantly more likely to develop posttraumatic stress disorder than are men (Breslau, 2009), even when the type of trauma experienced is equivalent (Luxton *et al.*, 2010).

If, as our findings suggest, women are more resistant to habituation in their affective responses to negative information, then chronic stressors could have more pronounced effects on mood in women than in men. Additionally, given that amygdala activity at encoding has been shown to predict subsequent memory (Cahill *et al.*, 2004; LaBar and Cabeza, 2006), increased engagement of the amygdala in response to repeated stressors could lead to relatively improved consolidation of memory for negative events in women. Such a selective consolidation enhancement could contribute to the distortions of memory characteristic of affective disorders such as clinical depression and PTSD, as both spontaneous intrusive memories (Brohawn *et al.* 2010), and mood-congruent recall (Ramel *et al.*, 2007) have been related to increased amygdala activity.

### Potential limitations and future studies

A significant limitation of these analyses is that no information on the hormonal status of women was obtained. Previous studies have shown significant differences in the amygdala response to affective stimuli between women in different menstrual phases (Goldstein *et al.*, 2005; Andreano and Cahill, 2010), or between naturally cycling women and those treated with exogenous hormones (van Wingen *et al.*, 2008, 2011). It is likely that these cyclic variations in amygdala activity contribute to sex differences (Goldstein *et al.*, 2010). Furthermore, while some evidence suggests that women are slower to acquire extinction learning for aversive stimuli, as our findings would predict, this difference has been reported only during high-estrogen periods (Milad *et al.*, 2010).

Additionally, while inferences can be drawn about the habituation of affective responses from this data by comparing novel and familiar stimuli sets, the present analysis does not directly compare habituation curves between the sexes. Instead, the response to familiar items was averaged across repetitions. Future studies should use sufficient familiar stimuli to estimate the response at each stimulus presentation, while considering the influence of ovarian hormones.

### CONCLUSIONS

In conclusion, these data indicate that women's amygdalae respond more to negative material that is familiar than do the amygdalae of

men. This suggests that the response to negativity in women is more resistant to habituation than in men. The persistence of this amygdala response predicts self-reported anxiety and depression. Thus a resistance to habituation to negative material in women may represent a potential vulnerability contributing to women's higher rate of affective disorder.

### Conflict of Interest

None declared.

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