Sex differences in how stress affects brain activity during face viewing

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Under stress, men tend to withdraw socially whereas women seek social support. This functional magnetic resonance imaging study indicates that stress also affects brain activity while viewing emotional faces differently for men and women. Fusiform face area response to faces was diminished by acute stress in men but increased by stress in women. Furthermore, among stressed men viewing angry faces, brain regions involved in interpreting and understanding others' emotions (the insula, temporal pole, and inferior frontal gyrus) showed reduced coordination with the fusiform face area and the amygdala, whereas the functional connectivity among these regions increased with stress for women. These findings suggest that stress influences emotional perception differently for men and women. *NeuroReport* 21:933–937 © 2010 Wolters Kluwer Health | Lippincott Williams & Wilkins.

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Introduction

Stress can affect men and women quite differently (for example see [1]). Such differences are particularly evident in social behavior: stress leads men to withdraw socially but leads women to seek social support [2]. Little is known about which brain regions mediate these sex differences in how stress affects behavior, but earlier research suggests that the amygdala plays a role. The amygdala is activated by stress and helps regulate stress responses [3] and is more sexually dimorphic than most other brain regions [4]. Furthermore, animal research shows that the amygdala responds differently to stress in males and females [5–7], and research with humans shows sex differences in whether the right or left amygdala is most responsive to emotionally arousing stimuli [4].

Of particular relevance for social behavior, the amygdala is involved in processing emotional faces, especially angry or fearful faces. For instance, healthy individuals show increased fusiform and occipital cortex activity when viewing fearful faces, whereas patients with amygdala lesions do not show this increased visual processing of emotional faces [8].

This study builds on earlier findings that stress increases affiliative behavior in response to stress for women but decreases it for men [2]. The specific hypothesis is that, for men observing other's emotions, stress will decrease interactions between the amygdala and brain regions such as the insula and temporal pole that help people understand others' state of mind and simulate others' emotions [9,10], whereas for women, stress will increase interactions among these regions. In addition, it is hypothesized that, for men, stress will decrease coordination between a brain region engaged in basic visual processing of faces (the fusiform face area or FFA) [11] and regions engaged in simulating and interpreting facial emotions (the temporal pole and insula), whereas, for women, stress will increase coordinated activities among these regions.

Methods

Participants

Forty-seven right-handed nonsmoker young adults (age range 18–33, mean = 22.2 years) were included in the study (one additional woman participated but did not complete the face scan session). Each of the four groups (men/women × stress/control) had 12 participants except the control group of women, which had 11 participants. To reduce cortisol level variability, all the participants were scanned between 2 and 5 p.m. and refrained from caffeine, eating, and exercising for at least an hour and avoided sleeping for at least 2 h before arriving for the study. None were on hormone birth control, corticosteroid medications, or β-adrenergic agonists. There were no differences by sex or stress group in age, years of education, hours of sleep the night before, or baseline measures of stress, affect, or depression.

Experiment procedure

After participants gave informed consent for the session, they were asked to drink 8 oz. of water. After a delay of at

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least 10 min filled with scan instructions and questionnaires, they provided a 1-ml baseline saliva sample by drooling into a tube. Then, participants assigned to the stress group were asked to immerse their hand in ice water (0–5°C) for as long as possible up to 3 min [control participants immersed their hand in warm water (37–40°C)]. To increase the strength of the stress manipulation, participants were also told that they might need to repeat the hand immersion procedure (with the same temperature water) on nearing the end of the session. For approximately the next 15 min, participants received instructions and practice trials for a decision task and entered the scanner. They first lay quietly during a prescan (2 min), a structural scan (5 min), and then were scanned while doing a 9-min decision task unrelated to this study (without any social or pictorial stimuli). Approximately 35 min ($M = 35.5$ min, standard deviation = 4.6, minimum = 28 min, maximum = 46 min) after the stress manipulation onset, while still in the scanner, they gave a saliva sample using two small sponges placed inside their mouth. There were no significant differences in time from the stress manipulation onset to the pretask saliva sample by condition or sex and no significant interaction of sex and condition. Immediately after this saliva sample, participants were scanned while they viewed eight blocks of 20 faces each. Half of the blocks had neutral faces and half had angry faces and block order was counterbalanced across participants. Face blocks were interspersed with 16-s fixation blocks. Each face appeared for 1.5 ms and participants indicated whether it was man or woman.

Salivary biomarkers

After experimental sessions, the samples were stored in a laboratory freezer at −30°C. At the end of the study, the samples were transported frozen to analytical laboratories (Salimetrics, LLC, State College, Pennsylvania, USA) where duplicate assays for cortisol were conducted for each sample and for testosterone and estrogen for the baseline drool sample (the mean of the duplicate assays was analyzed).

Face localizer

After the angry/neutral face scan, a separate functional localizer scan identified the FFA for each participant by alternating four 18-s blocks of neutral faces with four 18-s blocks of intermixed nonface objects and scenes. Sixteen images were shown in each block and participants were asked to indicate whether each image was repeated. Contrasts of the face and nonface blocks during the localizer scan showed the most significantly activated voxel in response to faces for each participant within a structurally defined mask of the right fusiform gyrus. Significantly activated voxels within an 8-mm radius sphere around this voxel were used as the FFA region of interest (ROI) for each participant.

Recognition memory

At the end of the experimental session, after exiting the scanner, participants completed a yes/no recognition test with 80 faces from the main face task and 40 new faces (half of each type were angry and half were neutral; old and new faces were counterbalanced across participants).

Scan parameters

Data were acquired on a 3T scanner (Siemens, Munich, Germany) using a T2*-sensitive echo-planar imaging sequence (slice thickness = 3.5 mm, repetition = 2 s, echo time = 25 ms, and field of view = 192 mm). T1-weighted anatomical images were acquired using a 3D-MPRAGE sequence [12].

Functional MRI analyses

FEAT Version 5.98, part of FSL (FMRIB's Software Library, *www.fmrib.ox.ac.uk/fsl*) was used. Data were skull stripped with BET [13], motion corrected with MCFLIRT [14], smoothed with a Gaussian kernel (5 mm full-width half-maximum), and registered with FLIRT [14]. In the general linear model, the models included the regressors of the angry and neutral face blocks and the temporal derivates. Temporal filtering was also applied [15]. Noise components were identified using MELODIC ICA [16] and removed.

Featquery (*http://www.fmrib.ox.ac.uk/fsl/feat5/featquery.html*) was used to extract mean percent signal change values for the FFA during the main face task. In addition, to assess functional connectivity during emotional face viewing, three psychophysiological interaction (PPI) analyses [17] were conducted. The first used the functionally defined FFA for each participant as the seed region and the other two used the left and right amygdala (structurally defined using the FSL Harvard–Oxford cortical atlas) as seed regions. For each PPI analysis, a regressor was created that convolved: (i) hemodynamic-response-function-convolved task regressor for the angry–neutral contrast and (ii) the time-course of the seed ROI. This regressor was entered in a lower-level FEAT analysis. On the higher-level analysis, a 2×2 analysis of variance design tested the effects of sex and stress in a mixed effects analysis. Both on the lower-level and higher-level analyses, Z statistic images were thresholded at the whole-brain level using clusters determined with $Z > 2.3$ voxelwise thresholding and a familywise error-corrected cluster significance threshold of $P = 0.05$ [18].

Results

Cold pressor stress increased cortisol levels

The stress manipulation increased salivary cortisol levels [cortisol change in micrograms per decilitre from baseline to just before the angry vs. neutral faces task approximately 35 min later: $M_{\text{stress}} = 0.15$, standard error = 0.03, $M_{\text{control}} = -0.01$, standard error = 0.03, $t(45) = 3.95$, $P < 0.001$]. There were no significant sex differences in baseline cortisol or cortisol change; the stress effect on cortisol change was significant for both men ($P < 0.01$) and women ($P = 0.01$).

Encoding task and memory test accuracy were not significantly affected by stress

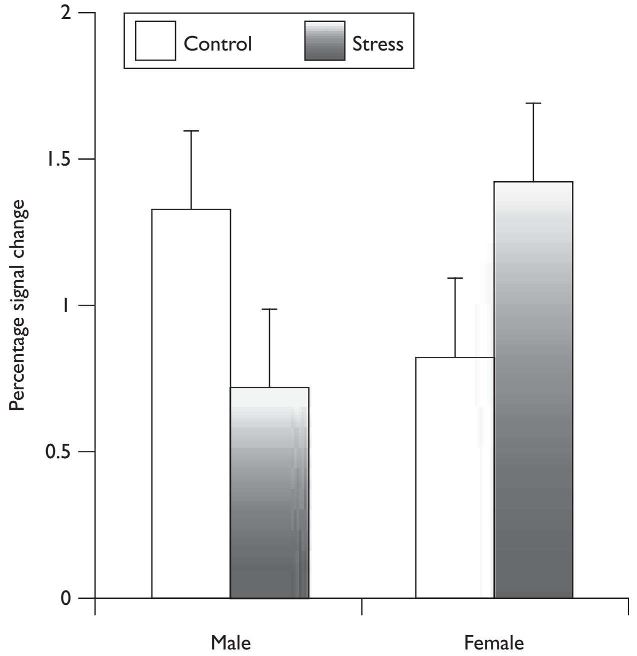
Sex judgments were highly accurate ($M = 96\%$ correct) with no significant differences because of stress condition or sex group. Likewise, there were no significant effects for recognition memory accuracy (Table, Supplemental digital content 1, *http://links.lww.com/WNR/A78*).

Stress had opposite effects on fusiform face area response for men and women

A 2 (stress vs. control condition) × 2 (male vs. female) × 2 (neutral vs. angry facial expression) analysis of variance on the mean percent signal change in the FFA during face viewing showed a significant interaction of participant sex and stress, $F(1,43) = 5.84$, $P < 0.05$, $\eta_p^2 = 0.12$. Stress increased FFA activity in response to faces for women but decreased it for men (Fig. 1). There were no other significant effects (all $P > 0.2$).

Across men and women participants, higher baseline testosterone levels predicted higher FFA activity in response to faces in the control condition, $r(23) = 0.60$, $P < 0.01$, but predicted lower FFA activity in the stress condition, $r(23) = -0.49$, P value of < 0.05 (for the FFA–testosterone correlations, one outlier with testosterone more than three standard deviations above the mean was excluded). Baseline estrogen did not correlate significantly with FFA face activation in either condition.

Fig. 1



Percent signal change in the fusiform face area defined functionally for each participant. Error bars indicate standard error of the mean.

There were no sex differences in the overall amygdala activity

Analyses of the mean percent signal change within the right and left amygdala structural ROIs showed no significant sex effects or interactions.

For men versus women, stress had opposite effects on functional connectivity of regions involved in processing facial emotion

All three PPI analyses showed that stress increased the functional connectivity with clusters overlapping the right temporal pole, insula, and inferior frontal gyrus for women but decreased functional connectivity with these regions for men (Fig. 2, Table Supplemental digital content 2, *http://links.lww.com/WNR/A79* and ROIs and color clusters in Supplemental digital content 3, *http://links.lww.com/WNR/A80*). In addition, similar sex-by-stress functional connectivity interactions were seen in posterior visual regions.

Across stress and control, functional connectivity during viewing angry faces was greater for women than for men

Although the main purpose of this study was to examine sex-by-stress interactions, in all three PPI analyses, women showed an overall greater functional connectivity with the insula and adjacent brain regions than men did (Table in Supplemental digital content 4, *http://links.lww.com/WNR/A81* and Figure in Supplemental digital content 5, *http://links.lww.com/WNR/A82*). There were no regions for which men showed greater functional connectivity to the amygdala and FFA than women did. Furthermore, the only main effect of stress was that, for the right amygdala, the control group showed greater functional connectivity with the middle frontal gyrus on viewing the angry faces than the stress group. Thus, most effects of stress on functional connectivity with the amygdala were sex-specific.

Discussion

This study shows that acute stress affects face perception in opposite ways for men and women. Activity in a visual region specialized for face processing (FFA) showed an interaction effect such that FFA activity was greater under stress for women but diminished under stress for men, a relationship that was correlated with baseline testosterone but not estrogen levels.

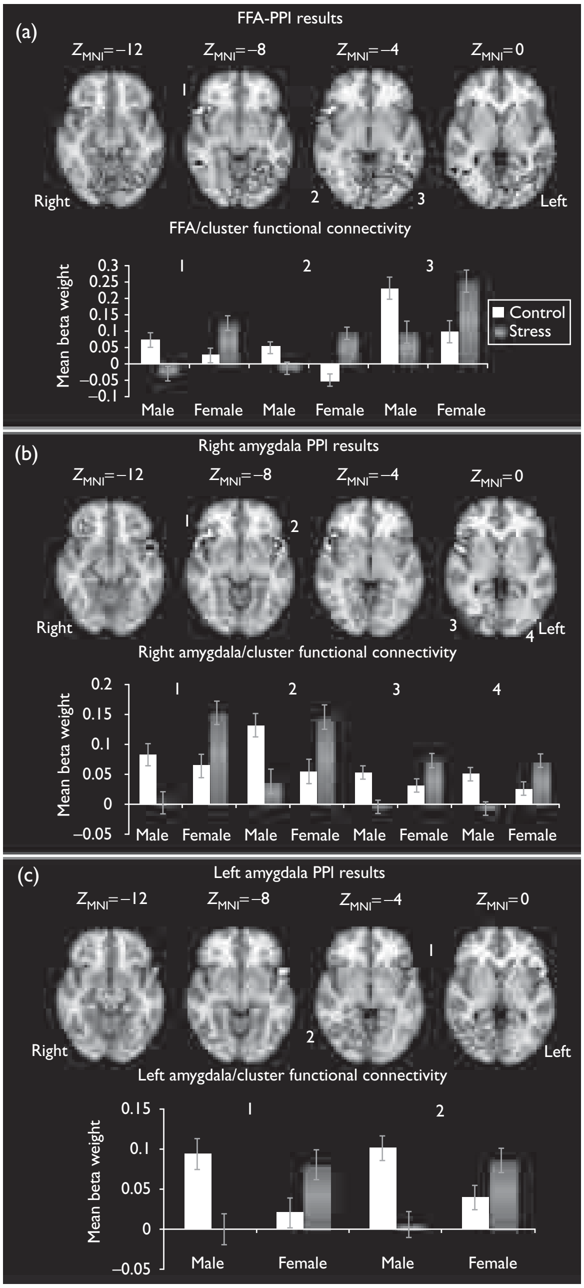
In addition, there were sex differences in how stress affected functional connectivity among brain regions involved in socioemotional processing of faces. To interpret emotional expressions, people recruit a broader network of brain regions than just the FFA [19]. For instance, the temporal pole is important for face processing and understanding others' state of mind and emotions [9]. The insula contributes to empathy and social understanding because it helps simulate the experiences of others [10]. Together, the temporal pole, insula, and nearby inferior frontal regions – along with the amygdalae – are part of an action representation circuit that helps people to internally simulate others' emotions [20].

Across the stress and control conditions in this study, women showed greater functional connectivity between the insula and the FFA and amygdala when viewing angry faces than men did, which is consistent with the findings of greater emotion empathy among women than men [21,22]. Furthermore, stress had opposite effects on men and women, reducing functional connectivity between regions involved in understanding and simulating others' facial emotions (the temporal pole, insula, and inferior frontal cortex) and the FFA in men but increasing functional connectivity in those same networks in women. These findings cannot be explained by a failure to look at the faces among the stressed men, as they later remembered the faces as well as did the other participants and rated the face sex as effectively. Instead, it seems that coordination of basic face processing by the FFA and interpretation and simulation of emotional expressions by the extended temporal pole region increased under stress for women but decreased for men. This pattern is consistent with behavioral findings that stress promotes social affiliation for women but disrupts it for men [2]. However, these are the first findings to indicate that sex differences in how stress affects social behavior extend to one of the most basic social transactions, that is, processing someone else's facial expression.

Earlier studies examining amygdala activity during rest show sex differences in whether the right or left amygdala shows greater functional connectivity with other brain regions [23–26]. Unlike these earlier resting-state studies, this study examined how functional connectivity increased while viewing angry faces rather than neutral faces. There were some main effects of sex, such that, in general, women showed greater functional connectivity between the amygdala and other regions during viewing of angry faces, with this sex difference being strongest for the right amygdala.

However, these findings indicate that such sex differences can reverse under stress, with consistent effects in the right and left amygdala. For women, stress increased connectivity between the amygdala and clusters overlapping the temporal pole, insula, and inferior frontal cortex, whereas, for men, stress decreased connectivity between the amygdala and this extended temporal pole region during viewing of angry faces. Furthermore, stress affected

Fig. 2



(a) A psychophysiological interaction (PPI) analysis with functionally defined fusiform face area (FFA) as the seed region and face expression (angry vs. neutral) as a modulatory variable, showed a sex by stress interaction in functional connectivity of the FFA with a cluster spanning portions of the temporal pole, inferior frontal cortex, and insula (cluster 1) and with occipital cortex regions (clusters 2 and 3). (b) The same PPI analysis substituting the structurally defined right amygdala as the seed region showed a sex by stress interaction in functional connectivity of the right amygdala with extended temporal pole clusters on both the right (cluster 1) and left (cluster 2) and with occipital fusiform cortex and other extrastriate regions (clusters 3 and 4). (c) Repeating the PPI analysis with the left amygdala as a seed region showed a sex by stress interaction in functional connectivity of the left amygdala and a cluster overlapping left temporal pole, inferior frontal cortex, and insula (cluster 1) and with occipital fusiform cortex and other extrastriate regions (cluster 2). MNI, Montreal Neurological Institute coordinates.

amygdala functional connectivity with the right fusiform cortex and other extrastriate visual regions, suggesting that stress reduces the influence of the amygdala on men's visual processing of angry faces, whereas stress increases the influence of the amygdala on women's visual processing of angry faces.

Conclusion

This study indicates that experiencing an acute stressor affects subsequent activity and interactions in brain regions involved in decoding and interpreting others' facial expressions in opposite ways for men and women. These findings contribute to a growing literature showing that stress affects men and women differently [1,4–7].

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References

1 Lighthall NR, Mather M, Gorlick MA. Acute stress increases sex differences in risk seeking in the balloon analogue risk task. *PLoS ONE* 2009; **4**:e6002.

2 Taylor SE. Social support. In: Friedman HS, Siliver RC, editors. *Foundations of health psychology*. New York: Oxford University Press; 2007. pp. 145–171.

3 Ulrich-Lai YM, Herman JP. Neural regulation of endocrine and autonomic stress responses. *Nat Rev Neurosci* 2009; **10**:397–409.

4 Cahill L. Why sex matters for neuroscience? *Nat Rev Neurosci* 2006; **7**:477–484.

5 Iwasaki-Sekino A, Mano-Otagiri A, Ohata H, Yamauchi N, Shibasaki T. Gender differences in corticotropin and corticosterone secretion and corticotropin-releasing factor mRNA expression in the paraventricular nucleus of the hypothalamus and the central nucleus of the amygdala in response to footshock stress or psychological stress in rats. *Psychoneuroendocrinology* 2009; **34**:226–237.

6 Mitsushima D, Yamada K, Takase K, Funabashi T, Kimura F. Sex differences in the basolateral amygdala: the extracellular levels of serotonin and dopamine, and their responses to restraint stress in rats. *Eur J Neurosci* 2006; **24**:3245–3254.

7 Wang Z, Guo YM, Bradesi S, Labus JS, Maarek JMI, *et al.* Sex differences in functional brain activation during noxious visceral stimulation in rats. *Pain* 2009; **145**:120–128.

8 Vuilleumier P, Richardson MP, Armony JL, Driver J, Dolan RJ. Distant influences of amygdala lesion on visual cortical activation during emotional face processing. *Nat Neurosci* 2004; **7**:1271–1278.

9 Olson IR, Ploaker A, Ezzyat Y. The enigmatic temporal pole: a review of findings on social and emotional processing. *Brain* 2007; **130**:1718–1731.

10 Singer T, Lamm C. The social neuroscience of empathy, in year in cognitive neuroscience 2009. *Ann N Y Acad Sci* 2009;**1156**:81–96.

11 Kanwisher N, McDermott J, Chun MM. The fusiform face area: a module in human extrastriate cortex specialized for face perception. *J Neurosci* 1997; **17**:4302–4311.

12 Mugler J. P. III, Brookeman JR. Three-dimensional magnetization-prepared rapid gradient-echo imaging (3D MP RAGE). *Magn Reson Med* 1990; **15**:152–157.

13 Smith SM. Fast robust automated brain extraction. *Hum Brain Mapp* 2002; **17**:143–155.

14 Jenkinson M, Bannister P, Brady M, Smith S. Improved optimization for the robust and accurate linear registration and motion correction of brain images. *Neuroimage* 2002; **17**:825–841.

15 Woolrich MW, Ripley BD, Brady JM, Smith SM. Temporal autocorrelation in univariate linear modelling of fMRI data. *Neuroimage* 2001; **14**: 1370–1386.

16 Beckmann CF, Smith SM. Probabilistic independent component analysis for functional magnetic resonance imaging. *IEEE Trans Med Imaging* 2004; **23**:137–152.

17 Friston KJ, Buechel C, Fink GR, Morris J, Rolls E, Dolan RJ. Psychophysiological and modulatory interactions in neuroimaging. *Neuroimage* 1997; **6**:218–229.

18 Worsley KJ. Statistical analysis of activation images. In: Jezzard P, Matthews PM, Smith SM, editors. *Functional MRI: an introduction to methods*. New York: Oxford University Press; 2001.

19 Adolphs R. The social brain: neural basis of social knowledge. *Annu Rev Psychol* 2009; **60**:693–716.

20 Carr L, Iacoboni M, Dubeau MC, Mazziotta JC, Lenzi GL. Neural mechanisms of empathy in humans: a relay from neural systems for imitation to limbic areas. *Proc Natl Acad Sci U S A* 2003; **100**: 5497–5502.

21 Derntl B, Finkelmeyer A, Eickhoff S, KellerMann T, Falkenberg DI, Schneider S, Habel U. Multidimensional assessment of empathic abilities: neural correlates and gender differences. *Psychoneuroendocrinology* 2010; **35**:67–82.

22 Schulte-Ruther M, Markowitsch HJ, Shah NJ, Fink GR, Piefke M. Gender differences in brain networks supporting empathy. *Neuroimage* 2008; **42**:393–403.

23 Ciumas C, Hirschberg AL, Savic I. High fetal testosterone and sexually dimorphic cerebral networks in females. *Cereb Cortex* 2009; **19**: 1167–1174.

24 Kilpatrick LA, Zald DH, Pardo JV, Cahill LF. Sex-related differences in amygdala functional connectivity during resting conditions. *Neuroimage* 2006; **30**:452–461.

25 Savic I, Lindstrom P. PET and MRI show differences in cerebral asymmetry and functional connectivity between homo- and heterosexual subjects. *Proc Natl Acad Sci U S A* 2008; **105**:9403–9408.

26 Wang L, Zhu CZ, He Y, Zhong QH, Zang YF. Gender effect on functional networks in resting brain. In: Gao XH, Müller H, Loomes M, Comley R, Luo SQ, editors. *Medical imaging and informatics*. Berlin, Germany: Springer-Verlag; 2008. pp. 160–168

Table (Supplemental Digital Content 1)

Corrected recognition (proportion of old faces correctly identified as old – proportion of new faces incorrectly identified as old) of angry and neutral faces by stress and control males and females. Standard errors of the means are in parentheses.

Participant Group	Angry	Neutral
Control Female	.42 (.05)	.43 (.04)
Control Male	.37 (.05)	.42 (.04)
Stress Female	.47 (.05)	.49 (.04)
Stress Male	.49 (.05)	.44 (.04)

Supplemental Digitial Content 2. Number of voxels, p values, and MNI coordinates and brain regions for local maxima associated with the PPI clusters shown in Figures 2A-C. All significant clusters for the sex by stress interaction PPI analyses are listed in this table (including those not visible in the slices shown in the figure).

FFA (Figure 2A)							
Cluster # in figure	Voxels	p	X MNI	Y MNI	Z MNI	Region	Brodmann Area
1	339	0.037	48	24	-4	Inferior Frontal Gyrus	47
			42	22	-6	Insula	13
			30	24	-16	Sub-Gyral	47
			50	16	-8	Inferior Frontal Gyrus	47
			32	18	-14	Extra-Nuclear	13
			62	8	-4	Superior Temporal Gyrus	22
2	503	0.004	52	-46	-8	Sub-Gyral	37
			64	-60	8	Middle Temporal Gyrus	21
			56	-48	-10	Sub-Gyral	37
			66	-54	-2	Middle Temporal Gyrus	37
			66	-52	10	Superior Temporal Gyrus	22
			50	-62	4	Middle Temporal Gyrus	37
3	3106	0.000	-50	-78	-2	Middle Occipital Gyrus	19
			6	-86	6	Lingual Gyrus	18
			-50	-62	2	Middle Temporal Gyrus	37
			-10	-90	26	Cuneus	18
			-52	-64	-2	Inferior Temporal Gyrus	19
			12	-70	-10	Culmen	
4*	351	0.031	-36	-46	44	Inferior Parietal Lobule	40
			-48	-40	62	Inferior Parietal Lobule	40
			-44	-52	56	Inferior Parietal Lobule	40
			-54	-36	52	Inferior Parietal Lobule	40
			-50	-38	50	Inferior Parietal Lobule	40
			-48	-54	62	Inferior Parietal Lobule	40
5*	336	0.039	-48	26	42	Middle Frontal Gyrus	8
			-34	40	44	Middle Frontal Gyrus	8
			-28	38	44	Middle Frontal Gyrus	8
			-24	42	44	Superior Frontal Gyrus	8
			-44	32	38	Middle Frontal Gyrus	8
			-44	30	42	Middle Frontal Gyrus	8

*cluster not in figure

R Amygdala (Figure 2B)							
Cluster # in figure	Voxels	p	X MNI	Y MNI	Z MNI	Region	Brodmann Area
1	311	0.038	56	12	-2	Superior Temporal Gyrus	22
			54	8	-2	Superior Temporal Gyrus	22
			50	6	-2	Insula	13
			52	22	-8	Inferior Frontal Gyrus	47

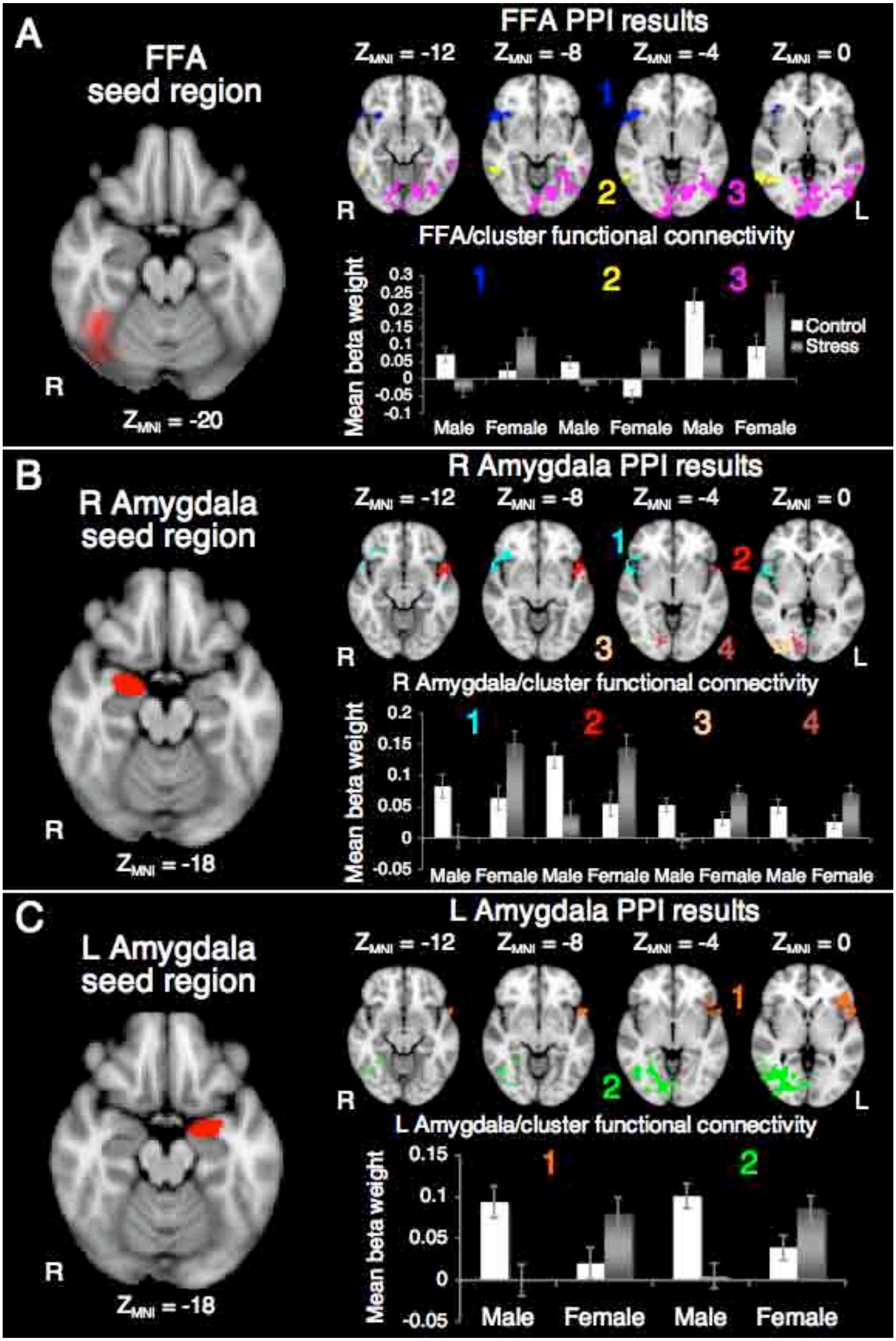
			44	24	-6	Inferior Frontal Gyrus	47
			38	30	-8	Inferior Frontal Gyrus	47
2	305	0.042	-50	16	-8	Inferior Frontal Gyrus	47
			-44	6	-8	Insula	13
			-56	12	-14	Superior Temporal Gyrus	22
			-50	8	-6	Superior Temporal Gyrus	22
			-38	2	-18	Superior Temporal Gyrus	38
			-48	8	-12	Superior Temporal Gyrus	38
3	532	0.001	32	-90	12	Middle Occipital Gyrus	19
			40	-72	12	Middle Occipital Gyrus	19
			30	-82	0	Middle Occipital Gyrus	18
			40	-96	10	Middle Occipital Gyrus	19
			42	-92	14	Middle Occipital Gyrus	18
			40	-88	2	Middle Occipital Gyrus	18
4	1054	0.000	26	-74	48	Precuneus	7
			20	-76	54	Precuneus	7
			14	-82	-2	Lingual Gyrus	18
			32	-80	48	Precuneus	19
			14	-80	28	Cuneus	18
			12	-90	0	Lingual Gyrus	18
5*	475	0.003	-38	-48	54	Inferior Parietal Lobule	40
			-32	-54	62	Superior Parietal Lobule	7
			-32	-54	56	Superior Parietal Lobule	7
			-36	-76	42	Precuneus	19
			-20	-68	56	Precuneus	7
			-30	-78	50	Precuneus	19

*cluster not in figure

L Amygdala (Figure 2C)

Cluster # in figure	Voxels	p	X MNI	Y MNI	Z MNI	Region	Brodmann Area
1	404	0.011	-40	26	0	Inferior Frontal Gyrus	18
			-60	2	4	Superior Temporal Gyrus	19
			-54	14	-8	Superior Temporal Gyrus	19
			-60	14	-12	Superior Temporal Gyrus	37
			-44	32	0	Inferior Frontal Gyrus	18
			-48	28	0	Inferior Frontal Gyrus	37
2	1295	0.000	16	-80	-2	Lingual Gyrus	45
			28	-60	-2	Parahippocampal Gyrus	22
			42	-80	6	Middle Occipital Gyrus	22
			52	-70	2	Inferior Temporal Gyrus	38
			28	-80	2	Lingual Gyrus	13
			40	-68	0	Middle Occipital Gyrus	45

Supplemental Digital Content 3. This figure is a color version of Fig. 2 that also displays the seed regions used for each psychophysiological interaction (PPI) analysis. See Fig. 2 caption for details.



Supplemental Digital Content 4. Number of voxels, p values, and MNI coordinates and brain regions for local maxima associated with significant group main effects for the PPI analyses. All significant clusters are listed in this table (including those not visible in the slices shown in the figure).

FFA (See Images in Supplemental Digital Content 5A)

Effect	Voxels	p	X MNI	Y MNI	Z MNI	Region	Brodmann Area
F > M	326	0.045	44	-8	14	Insula	13
			56	2	2	Superior Temporal Gyrus	22
			60	10	4	Precentral Gyrus	44
			62	8	-2	Superior Temporal Gyrus	22
			58	-2	0	Superior Temporal Gyrus	22
			60	14	2	Precentral Gyrus	44
	401	0.015	6	-38	6	Parahippocampal Gyrus	30
			4	-24	6	Thalamus	
			10	-48	18	Posterior Cingulate	29
			14	-48	20	Posterior Cingulate	29
			0	-36	8		
			0	-32	8	Thalamus: Pulvinar	
	931	0.000	-70	-46	-10	Middle Temporal Gyrus	21
			-66	-36	16	Superior Temporal Gyrus	22
			-54	-28	-18	Inferior Temporal Gyrus	20
			-62	-36	16	Superior Temporal Gyrus	22
			-72	-36	-10	Middle Temporal Gyrus	21
			-64	-38	-10	Middle Temporal Gyrus	21
	1119	0.000	8	-4	10	Thalamus: Anterior Nucleus	
			42	22	0	Insula	13
			4	-4	14	Thalamus	
			32	8	4	Lentiform Nucleus: Putamen	
			32	12	2	Claustrum	
			20	-2	14	Thalamus: Ventral Anterior Nucleus	
M > F	No significant clusters						
Stress > Control	No significant clusters						
Control > Stress	No significant clusters						

R Amygdala (See Images in Supplemental Digital Content 5B)

Effect	Voxels	p	X MNI	Y MNI	Z MNI	Region	Brodmann Area
F > M	336	0.025	0	68	-12	Medial Frontal Gyrus	10
			2	64	-12	Medial Frontal Gyrus	10
			0	44	-10	Anterior Cingulate	32
			-12	46	2	Anterior Cingulate	32
			2	48	-10	Anterior Cingulate	32
			4	44	-10	Anterior Cingulate	32
	363	0.016	60	-58	30	Superior Temporal Gyrus	39
			58	-54	34	Supramarginal Gyrus	40
			52	-58	40	Inferior Parietal Lobule	40
			48	-54	42	Inferior Parietal Lobule	40
			58	-46	28	Inferior Parietal Lobule	40
			54	-46	28	Inferior Parietal Lobule	40
	441	0.005	-44	-42	4		
			-54	-62	26	Middle Temporal Gyrus	39
			-42	-46	14		
			-52	-66	48	Inferior Parietal Lobule	39
			-46	-48	30	Inferior Parietal Lobule	40
			-60	-62	32	Superior Temporal Gyrus	39
	497	0.002	2	-34	28	Cingulate Gyrus	23
			-6	-8	44	Cingulate Gyrus	24
			-6	-8	40	Cingulate Gyrus	24

			-6	-22	28	Cingulate Gyrus	23
			0	-28	34	Cingulate Gyrus	31
			-4	-12	48	Paracentral Lobule	31
	505	0.002	-66	-52	4	Middle Temporal Gyrus	21
			-66	-52	10	Middle Temporal Gyrus	21
			-70	-38	14	Superior Temporal Gyrus	22
			-54	-28	12	Superior Temporal Gyrus	41
			-64	-20	12	Superior Temporal Gyrus	42
			-56	-36	12	Superior Temporal Gyrus	42
	669	0.000	20	-82	42	Cuneus	19
			28	-64	46	Superior Parietal Lobule	7
			40	-72	42	Precuneus	19
			36	-80	40	Precuneus	19
			40	-76	42	Precuneus	19
			10	-84	34	Cuneus	19
	888	0.000	28	-86	10	Middle Occipital Gyrus	18
			28	-90	10	Middle Occipital Gyrus	19
			16	-68	-10	Culmen	
			34	-82	-2	Middle Occipital Gyrus	18
			16	-54	-14	Culmen	
			40	-70	-8	Fusiform Gyrus	19
	1097	0.000	48	32	6	Inferior Frontal Gyrus	46
			52	32	2	Inferior Frontal Gyrus	45
			26	24	-8	Lentiform Nucleus: Putamen	
			54	12	-2	Superior Temporal Gyrus	22
			44	34	4	Inferior Frontal Gyrus	13
			70	-14	6	Superior Temporal Gyrus	42
	1875	0.000	-50	16	-10	Inferior Frontal Gyrus	47
			-40	22	4	Insula	13
			-32	26	-6	Insula	13
			-46	50	-8	Inferior Frontal Gyrus	10
			-46	32	-14	Inferior Frontal Gyrus	47
			-46	54	-10	Middle Frontal Gyrus	10
Control > Stress	354	0.019	-34	40	-10	Middle Frontal Gyrus	47
			-30	48	-12	Middle Frontal Gyrus	10
			-46	44	-12	Middle Frontal Gyrus	47
			-34	60	-16	Middle Frontal Gyrus	10
			-38	44	-14	Middle Frontal Gyrus	47
			-38	60	-16	Middle Frontal Gyrus	10
M > F	No significant clusters						
Stress > Control	No significant clusters						

L Amygdala (See Images in Supplemental Digital Content 5C)

Effect	Voxels	p	X MNI	Y MNI	Z MNI	Region	Brodmann Area
F > M	410	0.010	46	20	6	Inferior Frontal Gyrus	44
			36	20	10	Insula	13
			50	18	8	Inferior Frontal Gyrus	44
			44	34	-2	Inferior Frontal Gyrus	13
			40	30	-2	Inferior Frontal Gyrus	47
			40	20	-8	Extra-Nuclear	47
M > F	No significant clusters						
Stress > Control	No significant clusters						
Control > Stress	No significant clusters						

Supplemental Digital Content 5. Psychophysiological interaction (PPI) analyses with face expression (angry versus neutral) as a modulatory variable and A) functionally defined fusiform face area (FFA) as the seed region, B) the right amygdala as the seed region, or C) the left amygdala as the seed region revealed main effects of sex, with females consistently showing greater functional connectivity with the insula than males. The right amygdala PPI also revealed a main effect of stress, with greater functional connectivity for the middle frontal gyrus for the control group than the stress group.