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Gender differences in reward-related decision processing under stress

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Recent research indicates gender differences in the impact of stress on decision behavior, but little is known about the brain mechanisms involved in these gender-specific stress effects. The current study used functional magnetic resonance imaging (fMRI) to determine whether induced stress resulted in gender-specific patterns of brain activation during a decision task involving monetary reward. Specifically, we manipulated physiological stress levels using a cold pressor task, prior to a risky decision making task. Healthy men ($n = 24$, 12 stressed) and women ($n = 23$, 11 stressed) completed the decision task after either cold pressor stress or a control task during the period of cortisol response to the cold pressor. Gender differences in behavior were present in stressed participants but not controls, such that stress led to greater reward collection and faster decision speed in males but less reward collection and slower decision speed in females. A gender-by-stress interaction was observed for the dorsal striatum and anterior insula. With cold stress, activation in these regions was increased in males but decreased in females. The findings of this study indicate that the impact of stress on reward-related decision processing differs depending on gender.

Keywords: stress; decision making; fMRI; gender differences; cortisol

INTRODUCTION

Recent experimental studies reveal stress-induced alterations to motivated decision making: stress alters reward learning (Cavanagh *et al.*, 2011; Petzold *et al.*, 2010), risk taking (Preston *et al.*, 2007; Starcke *et al.*, 2008; Lighthall *et al.*, 2009; Porcelli and Delgado, 2009; van den Bos *et al.*, 2009), reward responsivity (Bogdan and Pizzagalli, 2006; Ossewaarde *et al.*, 2011) and decision-making speed (Porcelli and Delgado, 2009; van den Bos *et al.*, 2009). Furthermore, several studies have observed gender-dependent effects of stress, including our previous work (Lighthall *et al.*, 2009), which examined the impact of cold pressor stress (Lovallo, 1975) on subsequent decision behavior for the Balloon Analogue Risk Task (BART) (Lejuez *et al.*, 2002). The BART is a risky decision task that involves pumping up a series of computerized balloons in order to earn reward. Balloons may be 'cashed out' to collect earnings at any time, with larger balloons yielding greater earnings. However, each additional pump increases the risk of an explosion that eliminates earnings for that balloon. Thus, earnings on the BART are optimized by balancing some risk taking to earn reward while avoiding too many explosions. Our previous study revealed that men and women had similar BART behavior and earnings under control conditions but diverged with stress (Lighthall *et al.*, 2009). Specifically, stress increased earnings and risk taking under uncertainty in males, but decreased earnings and risk taking for females. Studies using psychological stressors and the Iowa Gambling Task report consistent findings (Preston *et al.*, 2007; van den Bos *et al.*, 2009). In men, psychological stress led to more high-risk disadvantageous choices. In women, increased stress led to more low-risk advantageous choices, with some decline in females' performance at the highest levels of stress response (van den Bos *et al.*, 2009). In a study of men alone, pharmacologically elevated stress hormone levels (cortisol) resulted in increased risk-taking behavior (Putman *et al.*, 2010). Thus, at least in males, activation of the hypothalamic–pituitary–adrenal (HPA) axis appears to influence risk-related decision making. In addition, stress from threat of shock has been found to decrease women's reward responsiveness (Bogdan and Pizzagalli, 2006), presenting the possibility that stress decreases women's risk taking by diminishing the drive for larger rewards. Supporting this proposition, a recent study found that exposure to mild psychological stress (aversive movie clips) resulted in diminished reward-related activation of the medial prefrontal cortex (PFC) in women during a

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monetary incentive task (Ossewaarde *et al.*, 2011). However, as males were not included in this study, it is unclear how gender may modulate stress effects on neural response to reward.

Little is known about the neural underpinnings of these gender-specific stress effects. To our knowledge, the present study is the first functional magnetic resonance imaging (fMRI) study to examine gender differences in response to decision making among individuals exposed to stress. We used the BART as our decision task as we have previously observed gender differences in stress effects with this task (Lighthall *et al.*, 2009). Given the dearth of research on neural mechanisms of gender–stress interactions in decision processing, hypotheses for the brain regions mediating these interactions were derived by identifying brain regions that have been independently associated with (i) gender-related differences in response to stress and (ii) decision making on the BART.

Brain regions involved in decision making are also affected by acute stress (Dedovic *et al.*, 2009 for review) and show gender differences in stress response. For example, Wang *et al.* (2007) exposed males and females to varying levels of a psychological stressor with mental arithmetic during a perfusion fMRI scan. Stress increased cerebral blood flow in the right PFC and decreased blood flow in the left orbitofrontal cortex in men, but increased blood flow responses in limbic structures including the insula, cingulate cortex, ventral striatum and dorsal striatum (putamen) in women. Further, cortisol reactivity predicted neural response to stress more in men than in women. Gender differences in neural response to visceral stress have also been observed, with greater stress responses in the ventromedial PFC, right anterior cingulate and left amygdala in women, but greater activation of the insula and right dorsolateral PFC in men (Naliboff *et al.*, 2003). Presenting negative pictures to elicit stress in men and women revealed stronger amygdala and anterior cingulate responses in males when compared with females, with the magnitude of gender differences depending on menstrual cycle phase (Goldstein *et al.*, 2010). Several brain regions showing gender-specific stress responses have also been associated with decision behavior on an fMRI-adapted BART (Rao *et al.*, 2008). In this study, voluntary risk taking was found to rely on the striatum, anterior insula, midbrain, dorsolateral PFC and anterior cingulate/medial PFC. Thus, the common regions mediating BART behavior and gender–stress interactions appear to include the striatum, anterior insula and PFC, leading us to hypothesize that one or more of these regions would moderate gender differences in stress effects on decision making in our fMRI-adapted BART.

In the current study, healthy males and females were exposed to either the cold pressor stress task or a control task prior to playing an fMRI-adapted version of the BART, which included real monetary outcomes. Salivary cortisol was collected to confirm an elevated HPA axis response during decision processing among stressed participants. Based on our previous behavioral findings and those of others, we predicted different effects of stress on behavior and brain activation for males and females. More specifically, we predicted that stress would enhance risk taking in males but diminish risk taking in females. Further, we hypothesized that, depending on gender, stress would alter neural decision responses to the BART in one or more of our regions of interest. Given the lack of previous studies examining gender–stress interactions in neural response to decision making, we did not make directional hypotheses for effects on brain activation.

METHODS

Participants

Twenty-three females (in the age group of 18–31 years, $M_{age} = 21.8 \pm 3.6$, 11 stressed) and 24 males (in the age group of 18–33 years, $M_{age} = 23.0 \pm 3.6$, 12 stressed) participated in the study. All provided written informed consent approved by the University of Southern California (USC) Institutional Review Board. All were right-handed, nonsmokers free of hormone birth control, corticosteroid medications or β-adrenergic agonists. For further details on the sample, see 'Methods' in Supplementary Data.

Protocol

The study was conducted from 2 to 5 pm to reduce diurnal variations in cortisol levels. Participants completed psycho-social questionnaires and drank 8 oz of water (completed $\geq$10 min before the first saliva sample). Participants received scan- and task-related instructions and practiced two abbreviated trials of each task condition. Baseline saliva samples were then collected followed by either cold pressor stress or a control task outside the scanner. Next, participants entered the scanner and a brief structural scan was conducted. The decision task with fMRI followed, beginning ~24 min after the start of the stress manipulation. To measure HPA axis response to the cold pressor or control task, saliva samples were taken immediately before and after the decision task, while participants were in the scanner. At the end of the session, participants provided postexperiment ratings of stress experienced during the hand immersion task and fMRI scan (7-point Likert scale; 1 = no stress, 7 = a great deal of stress) as well as ratings of effort put into the BART (7-point Likert scale; 1 = no effort, 7 = a great deal of effort).

Stress induction

The cold pressor task (Lovallo, 1975) was used to induce a stress response in one-half of the participants of each gender. The cold pressor involves holding one's hand in ice water for as long as possible up to 3 min; the control task was identical except that the water was approximately body temperature. For more details, see Methods in Supplementary Data.

Salivary biomarkers

Before the manipulation, participants provided 1 ml of saliva (*s*1) for the assessment of baseline cortisol. Immediately before (*s*2) and after (*s*3) the decision task (21 and 35 min after the start of the manipulation, respectively), saliva samples for cortisol assay were collected while participants lay in the scanner bore. Based on prior research (Dickerson and Kemeny, 2004; see also Schwabe *et al.*, 2008), cortisol responses to stress were expected to be at their peak during the decision task. Poststress samples were collected using sorbettes (Salimetrics, LLC, State College, PA, USA). The difference between *s*1 (baseline) cortisol levels and the average of *s*2 and *s*3 levels was used to measure cortisol change. Postexperiment, samples were stored in a laboratory freezer at −30°C and later transported frozen to a CLIA-certified laboratory (Salimetrics, LLC, State College, PA, USA) and stored frozen at −80°C until assayed. Samples were centrifuged on the day of assay at 3000 rpm for 15 min to remove mucins and samples were duplicate tested.

Decision task

The BART (Lejuez *et al.*, 2002) was adapted to allow for a blocked design and programmed using MATLAB software (The Mathworks, Inc., Natick, MA, USA). The task included four 'active' blocks (Figure 1A) and four 'passive' blocks (Figure 1B). For a full description of the decision task, see Methods in Supplementary Data.

Imaging data acquisition

Imaging was done using a 3 T Siemens MAGNETOM Trio scanner with a 12-channel matrix head coil at the USC Dornsife Cognitive Neuroscience Imaging Center. Functional scans were acquired in a single 9.5 min run, with a repetition time of 2000 ms in a T2*-sensitive echo-planar imaging sequence (echo time, 25 ms; flip angle, 90°). Volumes included 31 slices at 3.5-mm thickness (in-plane resolution, 3 × 3 mm; no gap; matrix size = 64 × 64) extended axially from the temporal lobe to the top of the skull. Prior to the functional scan, high-resolution structural scans were acquired using a T1-weighted MPRAGE sequence (resolution, 1 × 1 × 1 mm; repetition time, 1950 ms; echo time, 2.26 ms; flip angle, 7°).

Whole-brain analysis

Whole-brain analyses were conducted with FMRIB's Software Library (FSL; www.fmrib.ox.ac.uk/fsl) using FSL FEAT v. 5.98. Preprocessing included: motion correction with MCFLIRT, spatial smoothing with a Gaussian kernel of full-width half-maximum 5 mm, high-pass temporal filtering equivalent to 140 s and skull stripping of structural images with BET. MELODIC ICA (Beckmann and Smith, 2004) was used to remove noise components (see Methods in Supplementary Data for further details). Registration was performed with FLIRT; each functional image was registered to both the participant's high-resolution brain-extracted structural image and the standard Montreal Neurological Institute (MNI) average of 152 brains (with 2-mm voxel resolution) using an affine transformation with 12 degrees of freedom.

The individual time series statistical analysis was carried out using FILM (Woolrich *et al.*, 2001) with local autocorrelation correction. Both explanatory variable regressors (active, passive), convolved with a double-gamma hemodynamic response function and their temporal derivates

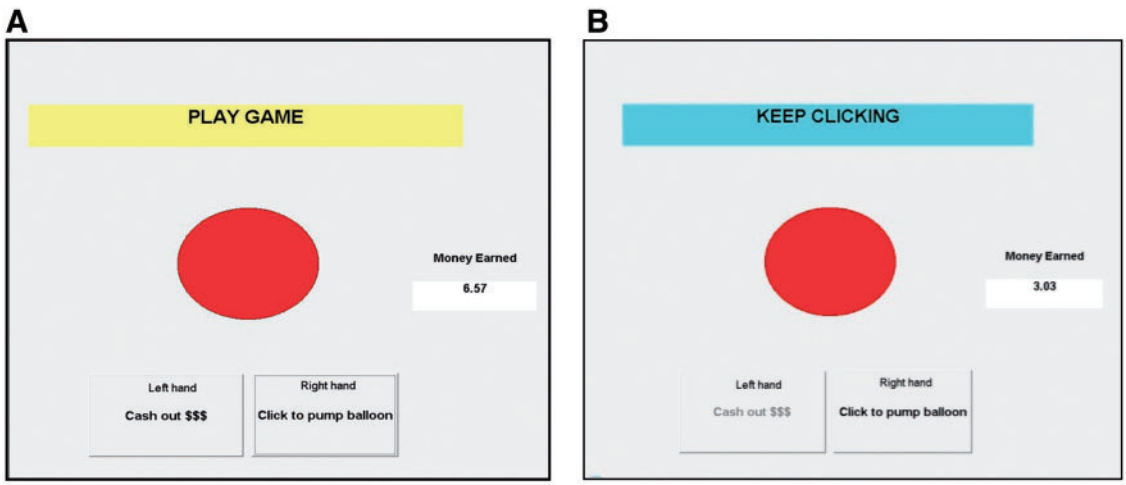


Fig. 1 Two versions of the adapted BART included (**A**) an active task (*PLAY GAME* screen) in which participants decided how large to inflate a series of balloons in order to earn money which accumulated with each 'pump' while trying to avoid 'explosions' which resulted in a loss of earnings for the current balloon and a balloon popping sound effect. At any point, participants could decision to 'cash out' their earnings for the current balloon, which transferred current balloon earnings to the permanent bank and resulted in a cash register sound effect. In (**B**) the passive task (*KEEP CLICKING* screen) participants could not earn or lose money but were instructed to press the pump balloon button throughout the block. In the passive task, the 'Cash out $$$' button was disabled and balloons appeared at random sizes while cash out and explosion sounds occurred randomly. Fixation periods (10 s) appeared in between alternating active and passive task blocks (four blocks per condition).

were used to model data. The primary lower level contrasts were conducted for active–passive and its inverse. Higher level mixed-effects analysis was carried out using FMRIB's local analysis of mixed effects (FLAME 1+2; Beckmann *et al.*, 2003). The general linear model (GLM) included two between-subject conditions, each with two levels: gender (male, female) and stress (cold pressor, control task). Unequal variance among the four gender/stress groups was assumed. The GLM was used to test for main effects of stress and gender and their interaction for the two lower-level contrasts. In these lower level and higher level analyses, Z (Gaussianized T/F) statistic images were corrected for multiple comparisons with clusters determined by $Z > 2.3$ voxel-wise thresholding and a family-wise error-corrected cluster significance threshold of $P < 0.05$ (Worsley, 2001). To facilitate communication of results including clusters spanning several brain regions (revealed by the whole-brain analysis at $Z > 2.3$, cluster threshold $P < 0.05$), more stringent thresholds were applied in some cases (see Supplementary Tables S1 and S2).

Region-of-interest analysis

The whole-brain analyses described above test for gender-by-stress interactions, but do not indicate which group showed more task-related activation. As *post hoc* tests to characterize the direction and relative magnitude of gender-specific stress effects, regions-of-interest (ROIs) were created. These were based on the significant clusters of activation revealed in the whole-brain gender-by-stress interactions that were hypothesized to mediate gender–stress interactions. For significant clusters, spanning multiple brain regions, anatomical borders for ROIs were structurally defined using masks from FSL's MNI structural atlas (based on probabilistic map; $P = 0.5$). Average percent signal change values were determined for each ROI. To determine the relationship between individual differences in ROI activation and other outcome measures, Pearson's correlations were conducted across and within groups.

RESULTS

Salivary cortisol

The cold pressor nearly doubled mean cortisol levels in stress subjects, while cortisol levels did not change in controls, $F_{1,43} = 25.56$, $P = 0.000002$ (Figure 2). Although mean cortisol levels were higher in males, overall, $F_{1,43} = 5.15$, $P = 0.03$, there were no main effects of gender on cortisol change, $F_{1,43} < 1$, nor was there a gender-by-stress condition interaction, $F_{1,43} < 1$. The effect of the stressor on cortisol elevation remained highly significant after excluding participants from the analysis who did not complete the full 3-min cold pressor challenge (see Results in Supplementary Data). These results indicate that the cold pressor reliably elevated cortisol levels without significant gender-specific effects.

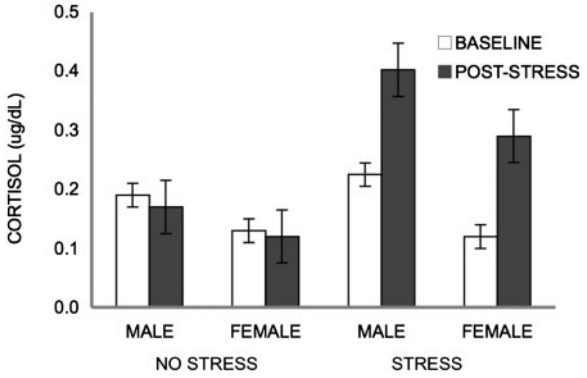


Fig. 2 Cortisol levels increased significantly in the stress group (cold pressor) but not in the control group (warm water). Cortisol responses to stress were not dependent on gender. Poststress cortisol is the average of cortisol at 21 and 35 min after the start of the hand immersion task (s2, s3, respectively); immediately before and just after the decision task. Error bars represent s.e.m.

Subjective stress: hand immersion task

Postexperiment ratings of stress resulting from the hand immersion task indicated that subjective stress experienced by participants in the cold pressor group was greater than that experienced by the control group, $F_{1,43} = 231.75$, $P < 0.000001$ ($M_{stress} = 5.11 \pm 1.41$; $M_{control} = 1.04 \pm 0.21$). Subjective responses to the cold pressor were greater in women than in men, $F_{1,43} = 4.57$, $P = 0.04$ ($M_{women} = 5.73 \pm 0.91$; $M_{men} = 4.50 \pm 1.57$), with no gender differences in the control group ($M_{women} = 1.0 \pm 0.00$; $M_{men} = 1.08 \pm 0.29$), resulting in a gender-by-stress interaction, $F_{1,43} = 6.00$, $P = 0.02$. Additional analyses indicated that gender differences in stress-modulated decision processing were not simply the result of greater subjective stress response in females compared with males (see Results in Supplementary Data).

Behavioral data

Consistent with our previous behavioral findings (Lighthall *et al.*, 2009), BART behavior and earnings were similar for males and females under control conditions, but diverged with stress, leading to a gender-by-stress interaction. As displayed in Figure 3, stress increased gender differences in reward collection rate (mean number of balloons 'cashed out'), $F_{1,43} = 4.82$, $P = 0.03$, decision speed (button pressing intervals), $F_{1,43} = 4.79$, $P = 0.03$ and total earnings, $F_{1,43} = 7.93$, $P = 0.007$. Examination of confidence intervals indicated no gender differences in these outcome measures in the control condition, only in the stress condition. While gender-by-stress interactions were observed for these measures, individual cortisol change values were not correlated with any of the behavioral outcomes across conditions or within any groups (P's > 0.05). Regarding our measure of risk taking (mean number of pumps per balloon for non-exploding balloons), we did not find any differences by stress

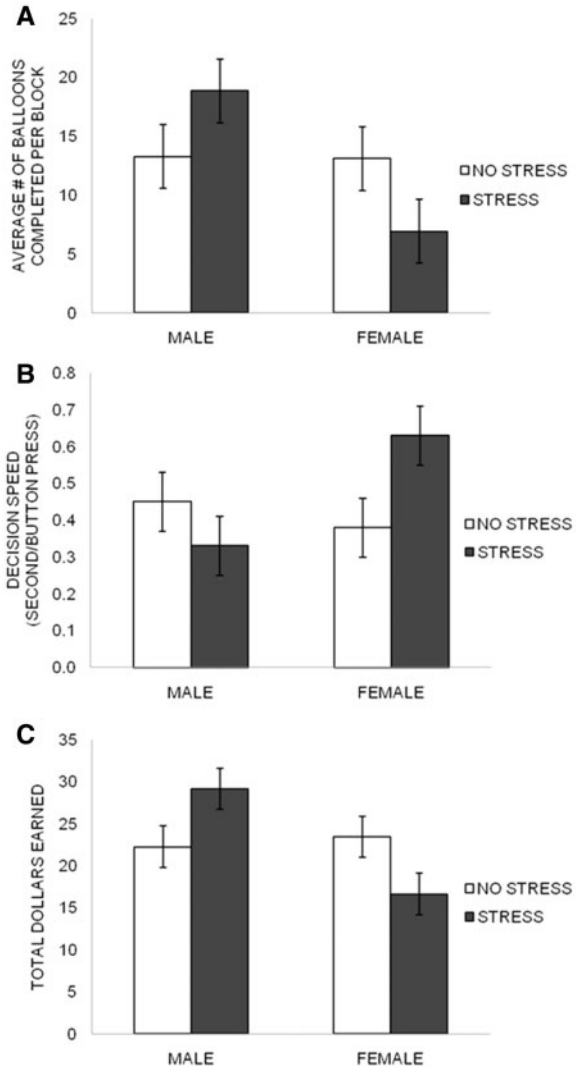


Fig. 3 Gender-by-stress effects on behavior and earnings in the BART. Group means for number of balloons completed per active block (**A**), decision speed (**B**) and total earnings in US dollars across all four active blocks (**C**). Error bars represent s.e.m.

condition, $F_{1,43} < 1$, gender, $F_{1,43} < 1$, nor was there a gender-by-stress interaction, $F_{1,43} < 1$. Relative to the number of pumps possible per balloon (maximum = 90), the average number of pumps was fairly low across groups ($M = 19.39 \pm 2.38$), indicating low risk taking overall. As the likelihood of losses ('explosions') during the BART increased with the number of pumps per balloon, the average number of explosions experienced per block was also low across conditions ($M = 2.59 \pm 0.31$). There were no significant group differences or interactions in the number of explosions per block (P's > 0.05); as may be expected given the low number of pumps per balloon on average.

While risk taking was not modulated by gender or stress in this study, our fMRI-adapted BART differed from the original task (Lejuez *et al.*, 2002) in that the number of balloons played was only limited by the duration of active blocks. This introduced a potentially successful strategy—not present in the original BART—of playing as many balloons as quickly as possible in order to earn more money. Notably, Pearson's correlations confirmed that balloon count and decision speed were related to earnings ($R_{47} = 0.33$, $P = 0.03$; $R_{47} = -0.76$, $P < 0.000001$, respectively). Direction of stress effects by gender indicated that, from an earnings standpoint, stress led to more profitable decision behavior in males but less profitable behavior in females

See Supplementary Data in the Results section for **'Subjective stress: Scan session and BART effort'**.

Table 1 Regions with activation differences by gender and stress conditions (for lower level active– passive contrast).

Brain Region	BA	H	MNI Peak Coordinates			Z_{max} value	Voxels
			x	*y*	*z*		
Precuneus	7	L	−28	−52	56	4.6	3276
Inferior parietal lobule	40	L	−48	−30	40	4.5	
Postcentral gyrus	40	L	−62	−28	24	4.5	
Precentral gyrus	6	L	−56	−4	32	4.4	
Inferior frontal gyrus	47	L	−38	28	−4	4.2	1247
Putamen		L	−22	20	−2	4.1	
Superior temporal gyrus	22	L	−48	0	−6	3.7	
Middle occipital gyrus	37	R	52	−70	−6	3.7	611
Inferior occipital gyrus	18	R	38	−86	0	3.6	
Middle occipital gyrus	18	R	40	−82	−8	3.6	
Inferior temporal gyrus	37	R	48	−70	2	3.5	

Threshold set to $Z = 2.3$ and a FWE-corrected cluster significance threshold of $P = 0.05$.
Clusters > 50 voxels displayed here.
BA: Brodmann area; H: hemisphere.

Whole-brain analyses

As expected, decision-related activation (active–passive contrast) across groups was observed in regions associated with motivation and decision making. In particular, the decision task resulted in robust activation of the thalamus, putamen, caudate, anterior cingulate, dorsolateral and ventrolateral PFC, insula, inferior parietal lobe and inferior frontal gyrus. Significant clusters were also apparent in sensorimotor and visual structures (Supplementary Table S1). Further details on passive task-related activation and group differences by gender and stress can be found in Results in Supplementary Data. Of primary interest, group level analysis of decision-related activation revealed gender-by-stress interactions in motivation and decision regions; most notably in the left dorsal striatum (putamen) and left anterior insula (Figure 4 and Table 1). Gender–stress interactions were also apparent in sensorimotor and visual regions.

ROI analyses

We anticipated gender–stress interactions for brain activation response to reward-related decision processing in the insula, PFC and striatum. The whole-brain analysis revealed

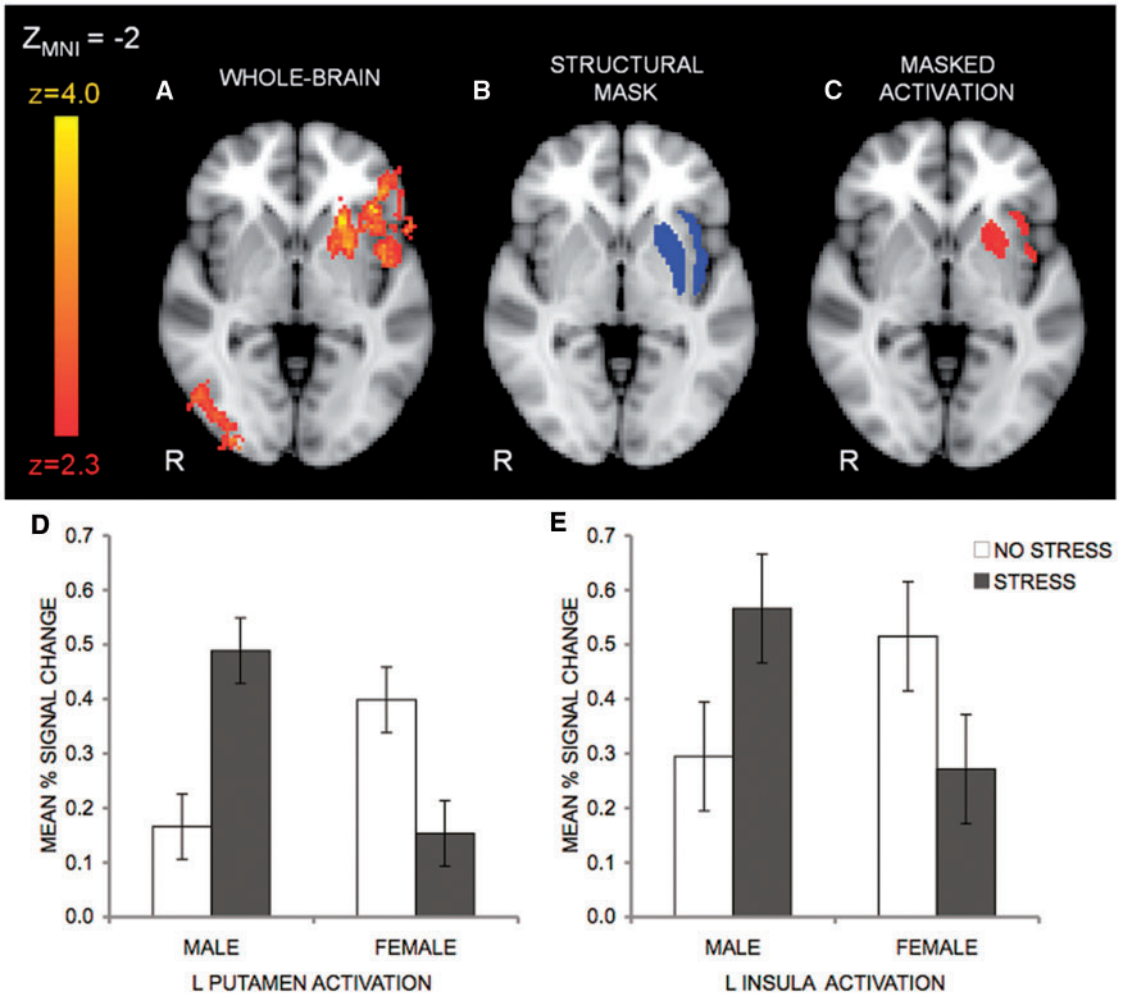


Fig. 4 Whole-brain analysis revealed significant gender–stress interactions for the active *vs* passive contrast in the left putamen and left anterior insula (**A**) with participant as a random factor ($Z > 2.3$; FWE-corrected cluster significance threshold of $P < 0.05$) in the mixed-effects analysis. To ensure we extracted signal change values separately for the putamen and insula, we used structurally defined regions of the putamen and insula from FSL's MNI structural atlas (**B**) to mask these significant clusters from the mixed-effects analysis (**C**). Mean percent signal change was greater in the stress condition for males and diminished in the stress condition in females in the left putamen (**D**) and left anterior insula (**E**).

gender-by-stress interactions in the dorsal striatum (putamen) and anterior insula (Figure 4A–C). We examined the direction of effects in these ROIs by extracting mean percent signal change values by group for the lower level contrast of active–passive. An ANOVA was performed on signal change values with gender and stress condition as between-subject factors and significant interactions were found for both the left dorsal striatum, $F_{1,43} = 22.51$, $P < 0.0001$ and the left anterior insula, $F_{1,43} = 6.88$, $P < 0.05$. Examination of group means revealed that stress increased activation in the dorsal striatum and anterior insula for males during decision making but decreased activation in these regions for females (Figure 4D and E). Dorsal striatum activation did not appear to be the result of differences in motor movements alone between the active and passive conditions (see Results in Supplementary Data). Further, an Independent Component Analysis (ICA) (Calhoun *et al.*, 2001) was conducted to identify functional networks in the brain that were differentially involved in the active BART depending on one's gender and stress status (see Methods and Results in Supplementary Data). The ICA results largely confirm results from the whole-brain GLM and ROI analyses, suggesting that males and females generally relied on the same network of brain regions to complete the BART; but under stress, there were gender differences in the involvement of the putamen and insula in this network.

Correlations were determined for cortisol change and activation in dorsal striatum and insula ROIs across and within conditions. For males only, change in cortisol predicted activation in the dorsal striatum ROI during decision processing ($R_{24} = 0.55$, $P = 0.005$; all other P's > 0.05); change in cortisol did not predict insula activation for any group (Ps > 0.05). Thus, in males, higher levels of physiological stress response were associated with

enhanced dorsal striatum response to reward-related decision making.

Behavior and ROI correlations

A full description of correlation analysis for behavior and ROI activation can be found in the Results in Supplementary Data. Of particular interest, there was a relationship between anterior insula ROI activation and number of balloons cashed ($R_{23} = 0.60$, $P = 0.002$) for the stress group. In addition, for stress males alone, analyses revealed a positive correlation for dorsal striatum ROI activation and number of balloons cashed ($R_{12} = 0.90$, $P < 0.000001$) and a negative correlation between dorsal striatum ROI activation and risk taking ($R_{12} = -0.75$, $P = 0.005$). No other significant relationships were observed within gender–stress groups.

DISCUSSION

Exposure to cold pressor stress resulted in differential reward-related decision processing on a risky decision task in males and females. Specifically, stress exposure affected behavior and brain activity during the decision task in opposite ways for men and women. Across conditions the risky decision task elicited robust responses in reward- and decision-associated regions including the thalamus, striatum, anterior cingulate, insula, as well as prefrontal and parietal regions (for reviews, see Ernst and Paulus, 2005; Taylor *et al.*, 2007; Clark, 2010; Haber and Knutson, 2010). The decision task was timed to occur during HPA axis response to cold stress (~24 min poststress). Salivary hormone measures confirmed a significant elevation in cortisol for the stress group during decision making with no gender differences in cortisol response. We also observed no gender differences in decision behavior or neural response to decision making under control conditions. With stress, however, decision behavior diverged for males and females for several outcome measures; but not risk taking, which was low across groups. This finding runs counter to our prediction that risk taking would increase in males and decrease in females with stress, but task design limitations may explain this finding as discussed below.

We did observe gender-dependent stress effects for number of balloons 'cashed out' (reward collection rate), decision speed and total money earned. Relative to controls, males exposed to cold stress exhibited more profitable decision behavior which included faster decision responses and more cashed balloons, while stressed females had slower decision responses and fewer cashed balloons resulting in diminished earnings. Notably, these behavioral differences were associated with group and individual differences in brain activation. The fMRI results presented here are the first we know of to demonstrate that exposure to an acute stressor affects brain activity during motivated decision making differently for healthy men and women. Consistent with our predictions, the striatum and insula were associated with gender-dependent stress effects on decision processing. Specifically, exposure to cold stress increased neural response to the risky decision task in the dorsal striatum (putamen) and anterior insula among men, but decreased response in these regions among women.

Differences in correlations between activation of these ROIs and behavior by group shed light on the underlying mechanisms of gender-dependent stress effects in this decision task. For participants exposed to cold stress, activation of the anterior insula ROI was associated with reward collection rate. Relevant to this finding, the anterior insula has been associated with riskless choices and behavioral switching from risky to safe choices (Kuhnen and Knutson, 2005). Risk taking was low overall but with each additional pump of the balloon, the chance of losses ('explosions') increased. Thus, making the decision to stop inflating a balloon and collect its earnings, reflects a switch from taking risk to making a 'safe' decision. The relationship between insula ROI activation and reward collection rate was similar across stressed males and females, suggesting that the anterior insula mediated cash-out choices under stress for both genders.

Stress did not alter risk taking in men or women as previously observed (Preston *et al.*, 2007; Lighthall *et al.*, 2009; van den Bos *et al.*, 2009). In fact, participants displayed low risk-taking behavior (number of pumps per balloon) across groups. The absence of group differences in risk taking is likely due to changes made to the BART for compatibility with fMRI analysis. In particular, the original BART (Lejuez *et al.*, 2002) limited the number of balloons, while our version of this risky decision task did not limit the balloon number but instead limited the total time available to play the game. Thus, in our task, participants could increase earnings by increasing decision speed and keeping balloons relatively small to reduce risk of losses. While this design choice may have limited our ability to observe differences in risk processing, a notable strength of our design was that participants could respond flexibly in a way that captured the impact of stress on motivated decision processes.

Indeed, because multiple strategies could be used to increase profits in our decision task, the present study provides new insight into the conditions under which men and women may become more risk seeking or risk averse. That is, this version of the BART presented two potentially profitable strategies: (i) fast decision speed with greater risk taking and longer reward delays (large balloons, cashed intermittently) or (ii) fast decision speed with less risk taking and shorter reward delays (small balloons, cashed frequently). Our results revealed that when an alternative low-risk option was present that provided rapid delivery of small rewards during the entire active block, males were biased toward this option under stress. This stress-related shift in behavior appeared to be related to activation of the dorsal striatum as, in stressed males alone, activation in this ROI was significantly associated with an increased reward

collection rate and less risk taking. Further, stress-related effects in males included increased decision speed, consistent with more automatic processing (Porcelli and Delgado, 2009). In addition, among males only, cortisol change from baseline to the decision task was positively correlated with decision-related activation in the dorsal striatum. This finding is consistent with previous reports of stronger relationships between cortisol and neural response to stress in males (Wang *et al.*, 2007) and further suggests that males and females differ in the degree to which acute fluctuations in cortisol predict neural response to motivated decision making. Relatedly, some recent evidence suggests that male traders' cortisol responses to volatile financial markets may result in exaggerated market movements (Coates and Herbert, 2008). An important avenue for future research will be to determine whether real-life financial decisions, including stock trading, are differentially affected by physiological stress responses in men and women.

Compared with female controls, stressed females in our study exhibited decreased dorsal striatum activation, slower decision speeds and fewer reward collections. Our findings are consistent with other reports of decreased reward responsiveness in stress-exposed females (Bogdan and Pizzagalli, 2006; Ossewaarde *et al.*, 2011); as, in our study, stressed females tended to collect their earnings less frequently (i.e. decreased drive for small rewards) while stress did not affect risk taking. Furthermore, in contrast to males, exposure to cold stress led to slower decision speed in females, perhaps indicative of more deliberative processing under stress in females. These stress effects in women are in line with a previously observed trend toward greater explicit knowledge about game contingencies in females with increasing stress response, but opposite patterns in males (Preston *et al.*, 2007). Together, with stress effects, we observed in males, these findings support the conclusion that the dorsal striatum mediated gender–stress interactions in level of automatic and reward-driven processing for the BART. The dorsal striatum is thought to integrate sensorimotor, cognitive and motivational, as well as emotional signals (Balleine *et al.*, 2007). In decision making, this region appears to play a role in obtaining predictable rewards (Doya, 2008). For example, single-cell recordings with monkeys show activation of the dorsal striatum during execution of well-learned behaviors resulting in a juice reward (Miyachi *et al.*, 2002). In our study, dorsal striatum activation was associated with reward-motivated behavior that carried little risk. That is, cashing out many smaller balloons quickly to accumulate small—but predictable—rewards. This behavior is also consistent with the proposed role of the dorsal striatum as the 'instrumental actor' that maintains information action–reward associations (O'Doherty *et al.*, 2004).

While this study provides new information about gender–stress interactions in motivated decision processing, further research is needed to better understand interaction mechanisms. In particular, future studies may use more controlled fMRI tasks to examine stress effects on specific decision components (e.g. Bolla *et al.*, 2004; Rao *et al.*, 2008; Xue *et al.*, 2010). For example, studies may test stress effects on level of automatic processing or reward responsiveness among men and women. Implementation of different stressors may also help to determine the precise mechanisms of gender differences in decision making under stress. We chose to use the cold pressor stress task, which resulted in equivalent and sustained cortisol responses in men and women. Some gender differences in subjective stress response to the cold pressor were observed, which may have reflected real differences in psychological stress and/or other factors, such as gender-related social norms about expressing pain-related stress. With respect to social factors, our study included a female experimenter at each session, which has been related to under-rerported pain, unpleasantness and arousal in males exposed to a thermal stressors; even when their physiological response is similar to female subjects (Levine and De Simone, 1991; Aslaksen *et al.*, 2007). Although our behavioral and fMRI findings were largely unaffected after we controlled for gender differences in subjective stress response, important insights can be gained from studies that specifically examine the relationship between levels of psychological distress and decision processing. In particular, we did not find gender–stress interactions in PFC response to decision making as hypothesized, but it is possible that our choice of stressor impacted our ability to observe group differences in this region. This proposal is supported by research indicating that exposure to a psychological stressor (aversive movie clips) altered PFC response to reward processing among females (Ossewaarde *et al.*, 2011). Finally, from an earnings perspective, more deliberative processing among stressed females was not beneficial in our risky decision task due to time constraints. A full understanding of gender–stress interactions in decision making requires consideration of decision tasks in which optimal behavior is associated with thoughtful and rational processing. It may be in these situations that women perform best under stress.

In sum, the current study found that cold pressor stress altered motivated decision making on a risky decision-making task and did so in a gender-specific manner. Behavioral results indicated that risk taking was not altered by stress when an alternative option was present that offered rapid delivery of small rewards under a time constraint. In addition, neural substrates of reward-motivated decision making for this task, including the dorsal striatum and anterior insula, were differentially altered by stress exposure in males and females. The present study also found differences in decision speed between men and women only after stress exposure, which raises the possibility that stress leads to gender differences in levels of processing. While the current study contributes to our understanding of the neural mechanisms of these

gender–stress interactions, it also begs the larger question about why such interactions exist. Addressing this question is likely to require consideration of individual effects of social environment, genetics, sex hormones, development and their interactions.

SUPPLEMENTARY DATA

Supplementary Data are available at *SCAN* online.

Conflict of Interest

None declared.

REFERENCES

Aslaksen, P.M., Myrbakk, I.N., Høifødt, R.S., Flaten, M.A. (2007). The effect of experimenter gender on autonomic and subjective responses to pain stimuli. *Pain*, *129*, 260–8.

Balleine, B.W., Delgado, M.R., Hikosaka, O. (2007). The role of the dorsal striatum in reward and decision-making. *The Journal of Neuroscience*, *27*, 8161–5.

Beckmann, C.F., Jenkinson, M., Smith, S.M. (2003). General multilevel linear modeling for group analysis in FMRI. *Neuroimage*, *20*, 1052–63.

Beckmann, C.F., Smith, S.M. (2004). Probabilistic independent component analysis for functional magnetic resonance imaging. *IEEE Transactions on Medical Imaging*, *23*, 137–52.

Bogdan, R., Pizzagalli, D.A. (2006). Acute stress reduces reward responsiveness: implications for depression. *Biological Psychiatry*, *60*, 1147–54.

Bolla, K.I., Eldreth, D.A., Matochik, J.A., Cadet, J.L. (2004). Sex-related differences in a gambling task and its neurological correlates. *Cerebral Cortex*, *14*, 1226–32.

Calhoun, V.D., Adali, T., Pearlson, G.D., Peker, J.J. (2001). A method for making group inferences from functional MRI data using independent component analysis. *Human Brain Mapping*, *14*, 140–51.

Cavanagh, J.F., Frank, M.J., Allen, J.J. (2011). Social stress reactivity alters reward and punishment learning. *Social Cognitive and Affective Neuroscience*, *6*, 311–20.

Clark, L. (2010). Decision-making during gambling: an integration of cognitive and psychobiological approaches. *Philosophical Transactions of the Royal Society of London. Series B, Biological Sciences*, *365*, 319–30.

Coates, J.M., Herbert, J. (2008). Endogenous steroids and financial risk taking on a London, trading floor. *Proceedings of the National Academy of Sciences of the United States of America*, *105*, 6167–72.

Dedovic, K., D'Aguiar, C., Pruessner, J.C. (2009). What stress does to your brain: a review of neuroimaging studies. *Canadian Journal of Psychiatry*, *54*, 6–15.

Dickerson, S.S., Kemeny, M.E. (2004). Acute stressors and cortisol responses: a theoretical integration and synthesis of laboratory research. *Psychological Bulletin*, *130*, 355–91.

Doya, K. (2008). Modulators of decision making. *Nature Neuroscience*, *11*, 410–6.

Ernst, M., Paulus, M.P. (2005). Neurobiology of decision making: a selective review from a neurocognitive and clinical perspective. *Biological Psychiatry*, *58*, 597–604.

Goldstein, J.M., Jerram, M., Abbs, B., Whitfield-Gabrieli, S., Makris, N. (2010). Sex differences in stress response circuitry activation dependent on female hormonal cycle. *Journal of Neuroscience*, *30*, 431–8.

Haber, S.N., Knutson, B. (2010). The reward circuit: linking primate anatomy and human imaging. *Neuropsychopharmacology*, *35*, 4–26.

Kuhnen, C.M., Knutson, B. (2005). The neural basis of financial risk taking. *Neuron*, *47*, 763–70.

Lejuez, C.W., Read, J.P., Kahler, C.W., et al. (2002). Evaluation of a behavioral measure of risk taking: The Balloon Analogue Risk Task (BART). *Journal of Experimental Psychology. Applied*, *8*, 75–84.

Levine, F.M., De Simone, L.L. (1991). The effects of experimenter gender on pain report in male and female subjects. *Pain*, *44*, 69–72.

Lighthall, N.R., Mather, M., Gorlick, M.A. (2009). Acute stress increases sex differences in risk seeking in the Balloon Analogue Risk Task. *PLoS ONE*, *4*, e6002. doi:10.1371/journal.pone.0006002.

Lovallo, W. (1975). The cold pressor test and autonomic function: a review and integration. *Psychophysiology*, *12*, 268–82.

Miyachi, S., Hikosaka, O., Lu, X. (2002). Differential activation of monkey striatal neurons in the early and late stages of procedural learning. *Experimental Brain Research*, *146*, 122–6.

Naliboff, B.D., Berman, S., Chang, L., et al. (2003). Sex-related differences in IBS patients: Central processing of visceral stimuli. *Gastroenterology*, *124*, 1738–47.

O'Doherty, J., Dayan, P., Schultz, J., Deichmann, R., Friston, K., Dolan, R.J. (2004). Dissociable roles of ventral and dorsal striatum in instrumental conditioning. *Science*, *304*, 452–4.

Ossewaarde, L., Qin, S., Van Marle, H.J., van Wingen, G.A., Fernández, G., Hermans, E.J. (2011). Stress-induced reduction in reward-related prefrontal cortex function. *Neuroimage*, *55*, 345–52.

Petzold, A., Plessow, F., Goschke, T., Kirschbaum, C. (2010). Stress reduces use of negative feedback in a feedback-based learning task. *Behavioral Neuroscience*, *124*, 248–55.

Porcelli, A.J., Delgado, M.R. (2009). Acute stress modulates risk taking in financial decision making. *Psychological Science*, *20*, 278–83.

Preston, S.D., Buchanan, T.W., Stansfield, R.B., Bechara, A. (2007). Effects of anticipatory stress on decision making in a gambling task. *Behavioral Neuroscience*, *121*, 257–63.

Putman, P., Antypa, N., Crysovergi, P., van der Does, W.A. (2010). Exogenous cortisol acutely influences motivated decision making in healthy young men. *Psychopharmacology*, *208*, 257–63.

Rao, H., Korczykowski, M., Pluta, J., Hoang, A., Detre, J.A. (2008). Neural correlates of voluntary and involuntary risk taking in the human brain: An fMRI Study of the Balloon Analog Risk Task (BART). *NeuroImage*, *42*, 902–10.

Schwabe, L., Bohringer, A., Chatterjee, M., Schachinger, H. (2008). Effects of pre-learning stress on memory for neutral, positive and negative words: different roles of cortisol and autonomic arousal. *Neurobiology of Learning and Memory*, *90*, 44–53.

Starcke, K., Wolf, O.T., Markowitsch, H.J., Brand, M. (2008). Anticipatory stress influences decision making under explicit risk conditions. *Behavioral Neuroscience*, *122*, 1352–60.

Taylor, S.F., Stern, E.R., Gehring, W.J. (2007). Neural systems for error monitoring: recent findings and theoretical perspectives. *The Neuroscientist*, *13*, 160–72.

van den Bos, R., Harteveld, M., Stoop, H. (2009). Stress and decision-making in humans: performance is related to cortisol reactivity, albeit differently in men and women. *Psychoneuroendocrinology*, *34*, 1449–58.

Wang, J., Korczykowski, M., Rao, H., et al. (2007). Gender difference in neural response to psychological stress. *Social Cognitive and Affective Neuroscience*, *2*, 227–39.

Woolrich, M.W., Ripley, B.D., Brady, M., Smith, S.M. (2001). Temporal autocorrelation in univariate linear modeling of FMRI data. *NeuroImage*, *14*, 1370–86.

Worsley, K.J. (2001). Statistical analysis of activation images. In: Jezzard, P., Matthews, P.M., Smith, S.M., editors. *Functional MRI: an Introduction to Methods*, 1st edn. Oxford: Oxford University Press, pp. 251–70.

Xue, G., Lu, Z., Levin, I.P., Bechara, A. (2010). The impact of prior risk experiences on subsequent risky decision-making: the role of the insula. *Neuroimage*, *50*, 709–16.

SUPPLEMENTARY MATERIALS
Gender differences in reward-related decision processing under stress

SUPPLEMENTARY METHODS

Participants

Twenty-three females (age 18-31, M_{age} = 21.8 ± 3.6, 11 stressed) and 24 males (age 18-33, M_{age} = 23.0 ± 3.6, 12 stressed) participated in the study after providing written informed consent approved by the University of Southern California Institutional Review Board. One stressed female was excluded from the original group of 12 due to protocol inconsistency. All were right-handed, non-smokers who did not use hormone birth control, corticosteroid medications or beta-adrenergic agonists. Participants did not have any chronic illnesses, history of head trauma or neurological disorders, were not pregnant, and did not have any MRI contraindications. In order to observe stable cortisol levels, all participants avoided eating and exercising within 1 hr of the study and avoided sleeping within 2 hrs of the study. There were no differences by gender or stress group in self-reported education, hours of sleep the previous night, or baseline measures of stress (Daily Inventory of Stressful Events; Almeida et al., 2002), affect (Positive and Negative Affect Scale; Watson et al., 1988), or depression (The Center for Epidemiologic Studies-Depression Scale; Radloff, 1977). Participants were paid $15 in addition to their earnings from the decision task.

Stress induction

The cold pressor task was used to induce a stress response in half of the participants of each gender. For the stress task, participants held their non-dominant hand in a pitcher of ice water at 0-5° C for as long as they could up to three minutes. No participants quit the cold pressor before 60 s passed. For the control task, participants held their non-dominant hand in a pitcher of warm water at 37-40° C for three minutes. Stress conditions were randomly assigned and participants did not know their stress condition until administration of the hand immersion task. To increase the strength of the stress manipulation, participants were told they might be asked to repeat their assigned hand immersion task at the end of the session. Four female and two male stress subjects quit the cold pressor task before three minutes elapsed (range: 60-120 s); however, there were no significant gender differences in duration of hand immersion in the cold pressor group, $F_{1,21}$ = 1.78, P = .20.

Decision task

The Balloon Analogue Risk Task (BART; Lejuez et al., 2002) was adapted to allow for a blocked design and programmed using MATLAB software (The Mathworks, Inc., Natick, MA). The task included four "active" blocks and four "passive" blocks. During active blocks, the words *PLAY GAME* appeared at the top of the screen. Also on the screen was a red balloon, a *Money Earned* box, a *Cash out $$$* button, and a *Click to pump balloon* button (**Figure 1A**). Passive blocks included the same visual and auditory stimuli except that the words *KEEP CLICKING* appeared at the top of the screen and the *Cash out $$$* button was disabled (**Figure 1B**).

In active blocks, participants used the pump button (right hand) to increase the size of balloons presented one at a time, accumulating money in a temporary bank for each pump. To encourage participants to pump balloons to larger sizes, they were told that the amount they could earn per pump was larger for bigger balloons. Pumps 1-20 earned $.03 each while pumps over 20 earned $.07 each; however, the payout values and cutoffs were not disclosed to participants. Participants collected earnings for individual balloons by pressing the cash out button (left hand), which transferred earnings from their temporary bank to their permanent bank (the Money Earned box). Cash outs triggered a slot machine payout sound and explosions involved a balloon popping sound. Subsequently participants received a new, uninflated balloon. Every balloon was set to explode at a random point from pump 1-90; with each pump, the likelihood of a balloon explosion increased. Explosions resulted in a loss of earnings in the temporary bank but not the permanent bank. As participants did not know the probability of balloon explosions on any given pump, active blocks involved making reward-related decisions under uncertainty. Participants received their full earnings at the end of the experiment (actual earnings ranged from $3.94 to $45.15).

In passive blocks, participants pressed the pump button as balloons appeared at random sizes; however, they could not cash out or earn money. Passive blocks also included cash out and explosion sounds played at random, at the approximate frequency experienced in active blocks. In this way, sensory experiences were similar in the passive and active blocks, but in passive blocks no rewards were gained or lost.

The length of active blocks was ≥ 60 s (range 60-82 s) such that participants were allowed to complete the balloon currently on the screen 60 s after the start of an active block. Active block time exceeding 60 s was subtracted from the subsequent passive block, which also had a base time of 60 s (i.e., passive blocks ≤ 60 s, range 38-60 s). For example, if a participant spent an additional 4 s to finish their last balloon in an active block (total block time = 64 s), the following passive block would be 56 s (60 s – 4 s). This allowed for observation of each balloon's outcome in active blocks (explosion or cash out). Fixation periods lasting 10 s occurred before and after each active or passive block.

Noise removal for fMRI data
MELODIC ICA (Beckmann and Smith, 2004) was used to remove noise components. Components with normalized time-courses that contained a spike in the component-related activity during one TR for which the absolute value of the peak of that spike minus the peak of the next largest spike during the whole scan was three standard deviations or larger were removed from the data. In addition, components that visually encompassed whole slices or formed rings around the brain were also removed.

Independent component analysis
Independent component analyses (ICA; Calhoun et al., 2001) were conducted using Brain Voyager QX (Brain Innovation BV) to identify task-related functional networks in the brain and determine which brain regions are differentially involved in the "task-related network" depending on one's gender and stress status. Each participant's data was individually preprocessed in Brain Voyager (including slice-timing correction, motion correction, realignment with T1-volumes, and transformation into the Talairach template (Talairach and Tournoux, 1988).

Individual and self-organizing group-level ICA were applied to the functional time-series. The single-subject ICA was conducted with a C++ implementation of the fastICA algorithm (Hyvarinen, 1999). Using principal component analysis, first, the initial dimensions of the functional dataset were reduced from number of time-points to 30. Then, 30 spatially independent components were estimated for each individual. The resulting ICA decompositions from each subject were submitted to the self-organizing group ICA (sogICA) for each of the four groups (i.e., by gender/stress group individually). SogICA was implemented according to the procedure and the clustering algorithm (Esposito et al., 2005). This permits clustering of components from each individual based on the components' mutual similarity measures. The similarity measures were based on linear spatial correlations in a common whole-brain mask. Group-level component maps were generated as random effects maps. The random effects statistic for each voxel was calculated as the mean ICA Z-value of that voxel across the individual maps divided by its standard error, resulting in a *T*-statistic. The resulting maps of *T*-values were visualized using a threshold of $P < .005$ (uncorrected; $T = 3.58$ for stress female and $T = 3.50$ for other three groups). Clusters that involved less than 20 contiguous voxels were discarded.

To define the task-related network in each group, temporal correlations between each component activity and the active BART were obtained for each individual. Then, for each group-level component obtained from the sogICA clustering, a group average correlation between component activity and BART was calculated. The group-level component that had the highest correlation with BART was defined as the "task-related network" for each group. To determine whether the "task-related networks" showed similar group differences as those observed in the whole brain GLM analysis, functional masks were created from regions where stress effects were gender-specific in the whole brain analysis (i.e., where gender by stress effects were present). Mean component activity signals for these regions were extracted from each participant's task-related network and tested for group differences.

SUPPLEMENTARY RESULTS

Control for individual differences in stressor exposure: Cortisol response
The effect of the stressor on cortisol elevation remained highly significant after excluding participants from the analysis who did not complete the full 3-min cold pressor challenge (4 females, 2 males), $F_{1,37} = 22.73$, $P = .000003$, and cortisol change in response to the stress condition did not differ for males and females after excluding these participants, $F_{1,37} < 1$. These results indicate that the cold pressor reliably elevated cortisol levels without significant gender-specific effects.

Subjective stress ratings
Excluding who completed less than 3 min of the cold pressor challenge did not alter observed group differences. Consistent with whole sample results, ratings were higher in the stress group, $F_{1,37} = 212.28$, $P < .000001$($M_{stress} = 4.81 \pm .40$; $M_{control} = 1.04 \pm .33$), in females versus males,$F_{1,37} = 4.89$, $P = .03$ ($M_{female} = 3.21 \pm .39$; $M_{male} = 2.64 \pm .35$), and stressed females compared to stressed males (gender by stress effect), $F_{1,37} = 6.42$, $P = .02$ ($M_{stress\_female} = 5.43 \pm .62$; $M_{stress\_male} = 4.20 \pm .52$; $M_{control\_female} = 1.00 \pm .47$; $M_{control\_male} = 1.08 \pm .47$).

Consistent with previous reports (Dickerson and Kemeny, 2004), however, subjective distress ratings did not correlate with cortisol responses to the stressor. That is, higher subjective stress ratings for the cold pressor did not predict cortisol response to the stressor across gender groups, $R_{23} = .11$, $P = .64$, or within stressed male and female groups individually ($R_{12} = .42$, $P = .18$ and $R_{11} = -.40$, $P = .23$, respectively).

To address the possibility that gender differences in behavioral and neural outcomes were the result of differential stress in males and females, additional analyses for primary outcome measures were conducted in which males and females did not differ significantly in their subjective stress ratings of the cold pressor. These analyses excluded the three females with the highest subjective stress ratings for the cold pressor (7 out of 7) and the two male subjects with the lowest rating for the cold pressor (2 out of 7). Within the remaining sample, there was still a strong main effect of the stress condition on subjective stress ratings, $F_{1,38} = 448.84$, $P < .000001$ ($M_{stress} = 5.13 \pm .30$; $M_{control} = 1.04 \pm .31$), but ratings no longer differed for males and females in the stress condition, $F_{1,38} < 1$($M_{stress\_male} = 5.00 \pm .39$; $M_{stress\_female} = 5.25 \pm .44$). Importantly, differences in cortisol response due to the stress condition also remained highly significant after excluding subjects to control for gender differences in subjective stress, $F_{1,38} = 26.43$, $P = .000009$ ($M_{stress} = .19 \pm .06$; $M_{control} = -.01 \pm .05$). And, as in the full sample, there was no gender by condition interaction for cortisol change when subjective ratings were similar in stressed males and females, $F_{1,38} < 1$.

Control for gender differences in subjective stress ratings: Behavioral and ROI activation
Gender differences in the impact of stress on behavior and brain activation during decision making were largely unchanged after paring down the stress group to make males and females similar in their subjective ratings of the cold pressor in the manner described above. Specifically, after removing stress subjects from the analyses as described above, significant gender by stress interactions were still observed for number of balloons ($F_{1,38} = 5.35$, $P = .03$), speed ($F_{1,38} = 4.47$, $P = .04$), and money earned ($F_{1,38} = 6.58$, $P = .01$); as well as for decision-related brain activation (active – passive contrast) in the left putamen ($F_{1,38} = 20.46$, $P = .00006$) and left insula ($F_{1,38} = 4.37$, $P = .04$) regions of interest. Means are presented in **Supplementary Figure 1**.

Subjective stress: Scan session
Post-experiment ratings of stress experienced during the brain scan (with concurrent decision task) were similar across stress conditions, $F_{1,43} < 1$, gender groups $F_{1,43} < 1$, and these two factors did not interact to affect stress ratings, $F_{1,43} < 1$. Based on the 7-point rating scale, ratings of stress experienced during this period appeared to be moderately low ($M = 2.49 \pm .31$). Thus, despite apparent differences in task performance and strategy by males and females in the stress condition, participants in these groups, as well as those in the control condition, rated their level of effort similarly.

BART effort
Post-experiment ratings of the amount of effort participants put into playing the decision game did not differ by stress condition $F_{1,43} < 1$, gender $F_{1,43} < 1$, nor was there an interaction between these factors, $F_{1,43} < 1$ (**Supplementary Fig. 2**). Based on the 7-point rating scale, ratings of expended effort across participants were moderately high ($M = 4.98 \pm .42$). Thus, despite gender differences in task performance and strategy in the stress condition, males and females in these groups, as well as those in the control condition, rated their level of effort similarly.

Whole brain analysis
Greater activation during the passive task (passive – active contrast) was only observed in the cerebellum, and posterior cingulate, parietal, and some occipital regions (**Supplementary Table 2**). These results indicate that,

compared to the passive condition, our fMRI-adapted BART elicited activation of mesocorticolimbic structures in the PFC and subcortical limbic system that are involved in decision processing.

Across gender groups, there was greater activation of the occipital regions in the control group compared to the stress group during active decision making across males and females (**Supplementary Table 3**). No regions showed significantly greater activation under stress compared to control. Across the stress conditions, greater activation of sensorimotor regions was observed for males compared to females (**Supplementary Table 4**), while females did not exhibit significantly greater activation in any brain region compared to males. Tests examining gender differences in response to the BART under control conditions revealed no significant differences between males and females. When analyzed separately, however, both male and female control groups exhibited enhanced activation in reward processing regions including bilateral striatum for the active – passive contrast (**Supplementary Fig. 3**). These results provide evidence that the BART elicited similar brain activation responses in men and women under control conditions.

Active versus passive task motor movement and dorsal striatum activation

To address the possibility that dorsal striatum activation differences merely reflected differences in motor movements, Z-scores were calculated for button pressing in both active and passive tasks (standardized across all participants). The difference between active button pressing and passive button pressing ($Z_{active} - Z_{passive}$) was calculated for each participant representing motor activity for the contrast of interest in our fMRI analysis (active – passive). Including button pressing difference from active to passive tasks as a covariate did not alter the interaction of gender and stress for activation in the putamen ($F_{1,42} = 22.16$, $P = .0001$).

Behavior and ROI Correlations

Across participants, dorsal striatum ROI activation was positively correlated with number of balloons cashed (i.e., reward collection; $R_{47} = .64$, $P = .000001$) and total money earned ($R_{47} = .38$, $P = .008$), and negatively with risk taking as measured by number of pumps per balloon ($R_{47} = -.40$, $P = .005$). We also observed a correlation between anterior insula ROI activation and number of balloons cashed ($R_{47} = .30$, $P = .04$).

Analyses conducted separately for the stress and control groups revealed a significant positive relationship between dorsal striatum ROI activation and number of balloons cashed ($R_{23} = .87$, $P < .000001$) and a negative relationship with activation in this region and risk taking ($R_{23} = -.60$, $P = .002$) in the stress group. A positive correlation was also observed in the stress group for anterior insula ROI activation and number of balloons cashed ($R_{23} = .60$, $P = .002$). In control participants, the only significant correlation observed was between decision speed and activation of the dorsal striatum ROI ($R_{24} = -.43$, $P = .03$).

Breaking groups into gender-stress cells revealed that significant relationships between dorsal striatum ROI activation and behavioral outcome measures were primarily driven by stressed males. Specifically, a significant positive correlation was observed for dorsal striatum ROI activation and number of balloons cashed ($R_{12} = .90$, $P < .000001$) and a negative correlations between dorsal striatum ROI activation and risk taking ($R_{12} = -.75$, $P = .005$). No other significant relationships were observed within gender-stress groups. However, as a relationship between anterior insula activation ROI activation and reward collection was observed for the stress group as a whole, but not for stressed males and females alone, we tested for a statistical difference in non-significant correlations for these two groups (Blalock, 1972), but found that there was none ($P > .05$). This indicated that the relationship between anterior insula ROI activation and reward collection was similar in stressed males and females despite group differences in activation of this region.

SUPPLEMENTARY REFERENCES

Almeida, D. M., Wethington, E., & Kessler, R. C. (2002) The daily inventory of stressful events: an interview-based approach for measuring daily stressors. Assessment, 9, 41-55.

Beckmann, C. F., & Smith, S. M. (2004) Probabilistic independent component analysis for functional magnetic resonance imaging. IEEE Transactions on Medical Imaging, 23, 137-52.

Blalock, H. (1972) Social Statistics. New York, NY: McGraw-Hill.

Calhoun, V. D., Adali, T., Pearlson, G. D., & Peker, J. J. (2001) A method for making group inferences from functional MRI data using independent component analysis. Human Brain Mapping, 14, 140-51.

Dickerson, S. S., & Kemeny, M. E. (2004) Acute stressors and cortisol responses: A theoretical integration and synthesis of laboratory research. Psychological Bulletin, 130, 355-91.

Esposito, F., Scarabino, T., Hyvarinen, A., Himberg, J., Formisano, E., Comani, S., et al. (2005) Independent component analysis of fMRI group studies by self-organizing clustering. NeuroImage, 25, 193-205.

Hyvarinen, A. (1999) Fast and robust fixed-point algorithms for independent component analysis. IEEE Transactions on Neural Networks, 10, 626-34.

Lejuez, C. W., Read, J. P., Kahler, C. W., Richards, J. B., Ramsey, S. E., Stuart, G. L, et al. (2002) Evaluation of a behavioral measure of risk taking: The Balloon Analogue Risk Task (BART). Journal of Experimental Psychology. Applied, 8, 75-84.

Radloff, L. S. (1977) The CES-D scale: A self-report depression scale for research in the general population. Applied Psychological Measurement,1, 385-401.

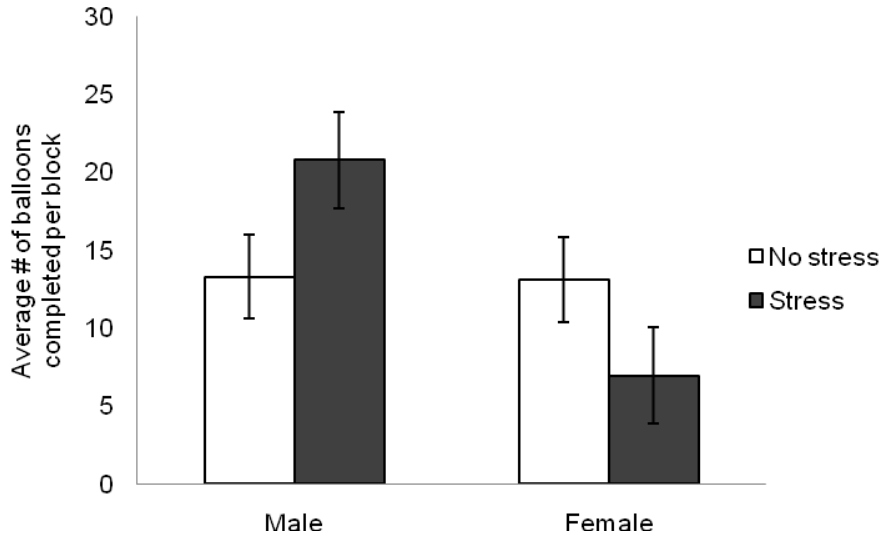
Talairach, J., & Tournoux, P. (1988) Co-planar stereotaxic atlas of the human brain: 3-dimensional proportional system: An approach to cerebral imaging. New York: Thieme.

Watson, D., Clark, L. A., & Tellegen, A. (1988) Development and validation of brief measures of positive and negative affect: the PANAS scales. Journal of Personality and Social Psychology, 54, 1063-70.

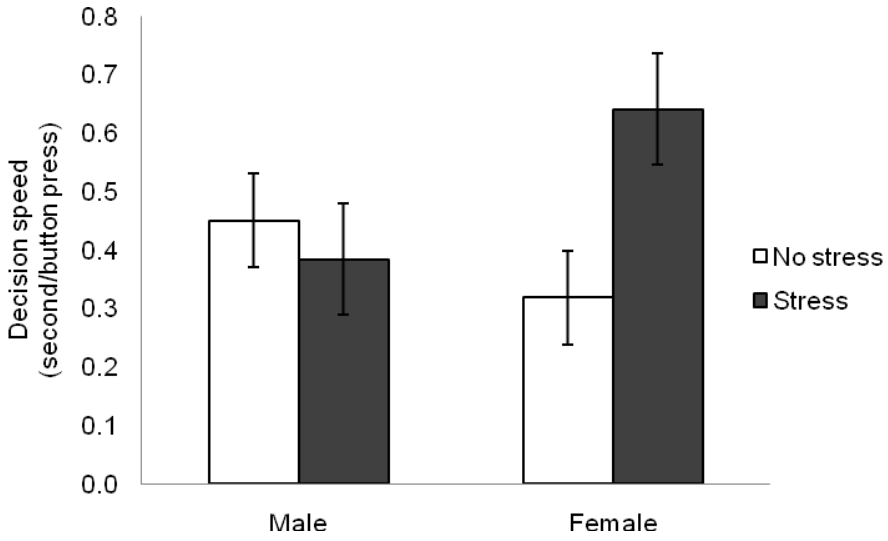
SUPPLEMENTARY FIGURES

Supplementary Figure 1 Gender x stress effects on behavior and earnings in the BART after excluding 3 female stress subjects and 2 male subjects to eliminate significant gender differences in subjective stress responses to the cold pressor. Group means for (**A**) number of balloons completed per active block, (**B**) decision speed, (**C**) total earnings in US dollars across all four active blocks, (**D**) mean percent signal change in the left putamen (**D**) and left anterior insula (**E**) for the active – passive contrast. Error bars represent s.e.m.

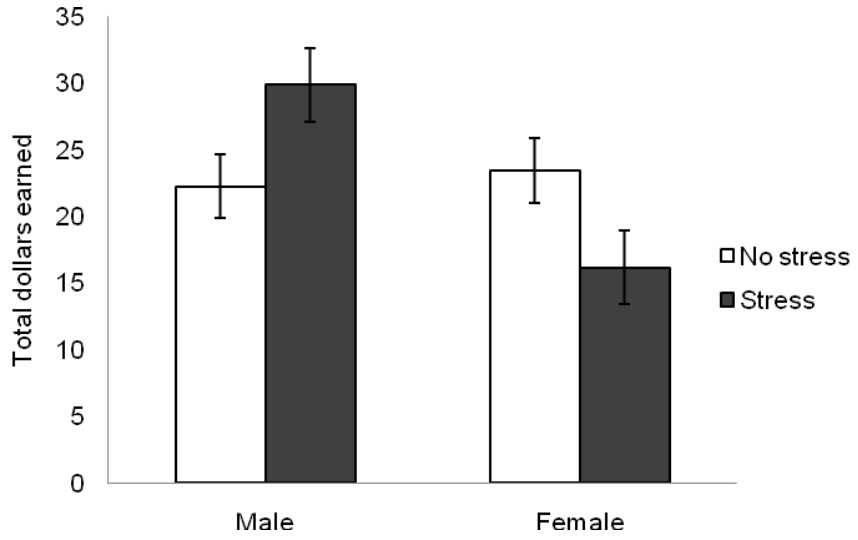
1A



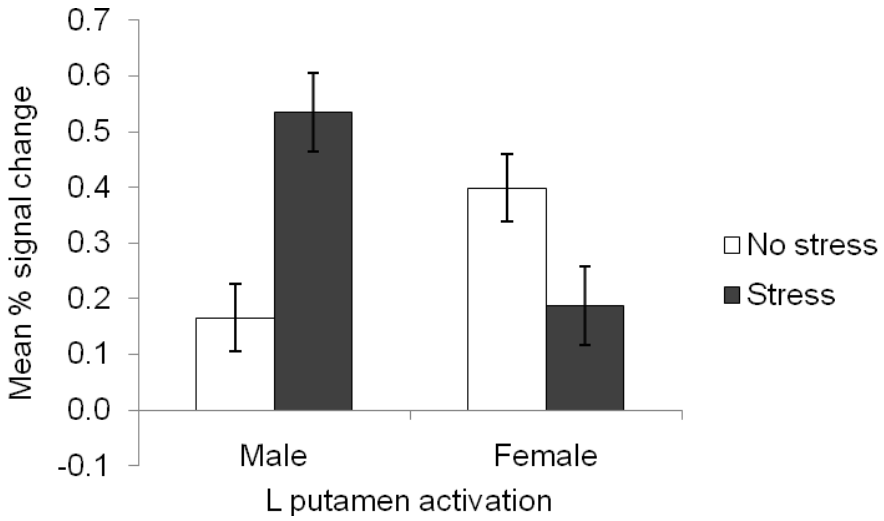
1B



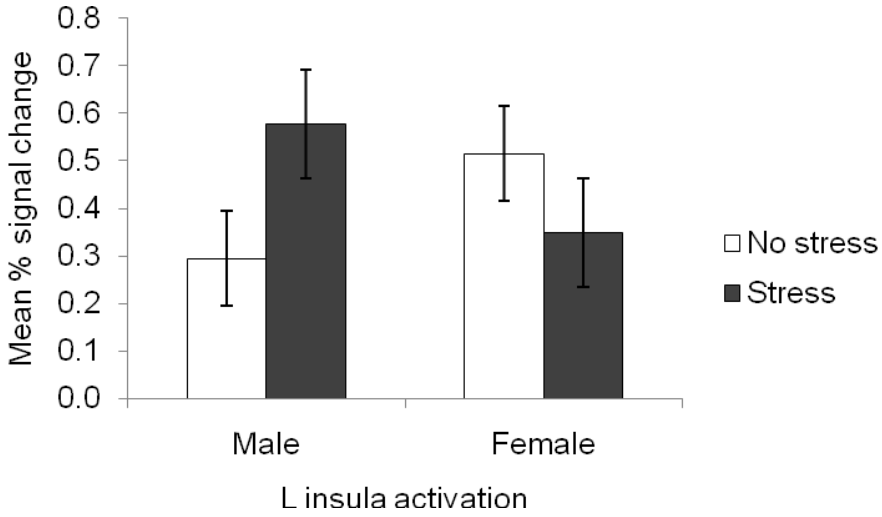
1C


35
30
25
20
15
10
5
0
Total dollars earned
No stress
Stress
Male
Female

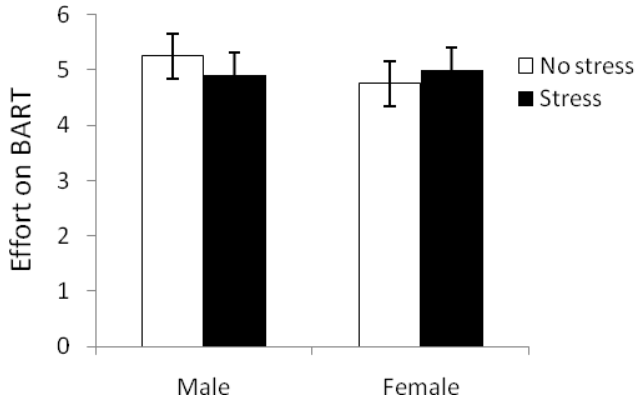
1D


0.7
0.6
0.5
0.4
0.3
0.2
0.1
0.0
-0.1
Mean % signal change
No stress
Stress
Male
Female
L putamen activation

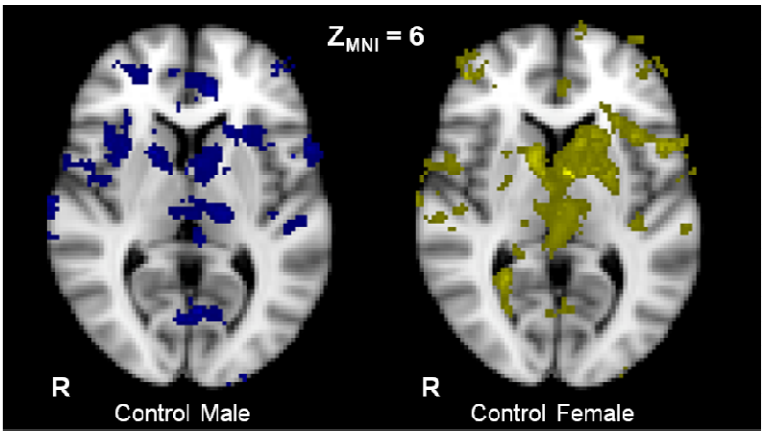
1E



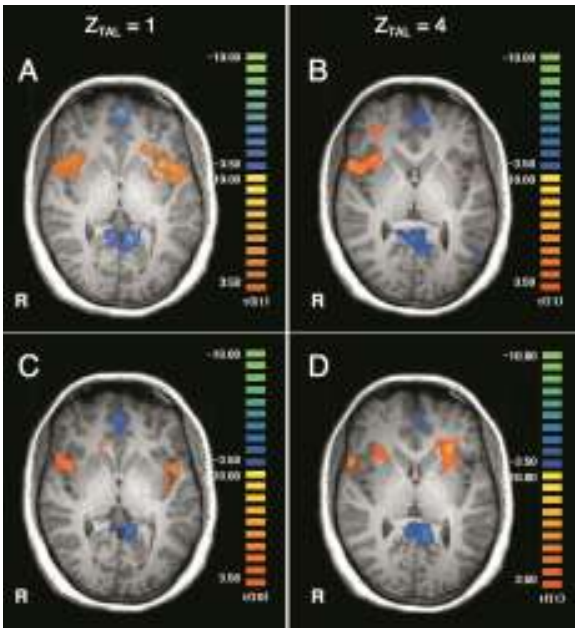
Supplementary Figure 2 Analysis of post-experiment ratings (on a 7-point Likert scale) of the amount of effort participants put into playing the decision game indicated that there were no differences in effort exerted by gender, stress nor was there an interaction of these factors (s > .05).



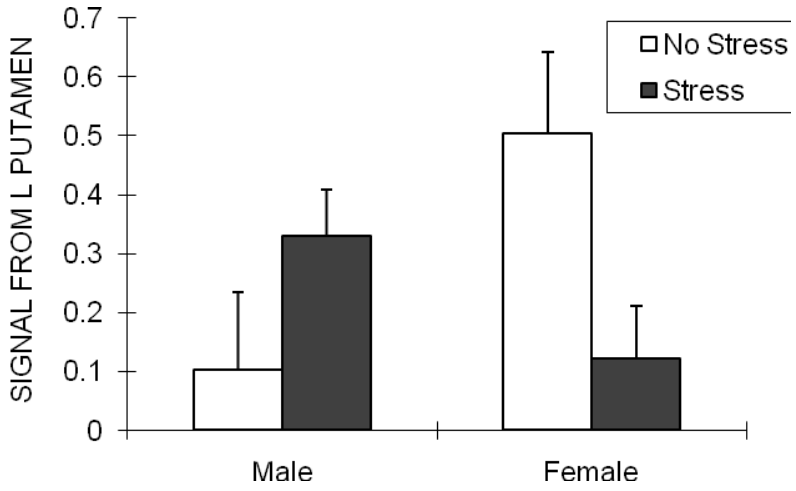
Supplementary Figure 3 Reward processing regions including bilateral striatum activation were observed in both males and females during reward-related processing (active – passive contrast) under control conditions – with no significant sex differences (Z > 3.0; FWE-corrected cluster significance threshold of P = 0.001).



Supplementary Figure 4 The left putamen and insula were differently involved in the task-related network depending on gender and stress condition. Control females (**A**) had greater activity in left putamen and insula than stressed females (**C**), while stressed males (**D**) had greater activity in left insula than control males (**B**).



Supplementary Figure 5 The left putamen cluster was differentially involved in the task-related network revealed by the independent component analysis depending on sex and stress condition.



SUPPLEMENTARY TABLES

Supplementary Table 1 Regions responding to the fMRI-adapted Balloon Analogue Risk Task across sex and stress groups (active – passive contrast).

			Peak MNI Coordinates				
Brain Region	**BA**	**H**	**x**	**y**	**z**	**Z-max Value**	**Voxels**
Thalamus	*	L	-12	-12	14	8.2	7798
Putamen	*	L	-18	20	-6	7.9	
Claustrum	*	L	-28	24	-8	7.4	
Cingulate Gyrus	32	L	-4	18	32	7.0	3335
Cingulate Gyrus	24	R	8	0	46	7.0	
Medial Frontal Gyrus	9	L	-4	36	30	6.9	
Medial Frontal Gyrus	8	L	2	32	38	6.7	
Cingulate Gyrus	24	L	2	2	40	6.7	
Inferior Parietal Lobule	40	L	-48	-30	40	7.5	2923
Middle Frontal Gyrus	10	L	-40	46	16	6.8	1647
	11	L	-34	52	-18	6.5	
	9	L	-48	40	26	6.5	
Inferior Frontal Gyrus	44	R	62	10	16	7.4	1182
Insula	13	R	38	22	2	6.8	
Inferior Frontal Gyrus	9	R	62	12	24	6.5	
Precentral Gyrus	44	R	50	4	6	6.4	
Middle Frontal Gyrus	10	R	42	40	20	7.2	1114
	9	R	34	34	28	6.8	
Inferior Parietal Lobule	40	R	52	-30	46	6.7	451
Supramarginal Gyrus	40	R	50	-36	40	6.4	
Inferior Occipital Gyrus	18	L	-32	-98	-2	7.3	419
Cuneus	18	L	-26	-98	0	6.6	
Fusiform Gyrus	18	L	-22	-100	-10	6.5	
Lingual Gyrus	18	L	-20	-102	-4	5.9	
Transverse Temporal Gyrus	41	R	50	-30	12	6.9	362
Postcentral Gyrus	40	R	58	-22	18	5.8	
Insula	13	R	60	-36	20	5.7	
Postcentral Gyrus	2	R	62	-22	38	5.1	
Inferior Occipital Gyrus	18	R	30	-96	-2	7.0	350
Fusiform Gyrus	18	R	30	-96	-14	6.6	
Lingual Gyrus	17	R	22	-102	-8	6.5	
Posterior Cingulate	23	L	-4	-30	28	6.5	274
Cingulate Gyrus	23	L	0	-24	32	5.6	
Cingulate Gyrus	31	L	0	-24	42	5.4	
Precuneus	7	L	-12	-68	48	5.6	241
Superior Parietal Lobule	7	L	-8	-60	62	5.2	
Sub-Gyral	6	L	-26	4	58	5.2	165
Precentral Gyrus	4	L	-36	-12	56	5.2	
Middle Frontal Gyrus	6	L	-24	-6	60	5.1	
Superior Temporal Gyrus	41	L	-52	-22	10	6.4	144
Transverse Temporal Gyrus	41	L	-56	-20	10	6.3	
Postcentral Gyrus	43	L	-56	-16	16	4.8	
Superior Frontal Gyrus	10	R	30	54	-8	6.0	112
Superior Frontal Gyrus	10	R	36	60	-12	4.9	
Middle Frontal Gyrus	11	R	36	52	-18	4.9	
Inferior Temporal Gyrus	20	L	-66	-30	-18	5.4	79
Middle Temporal Gyrus	21	L	-58	-32	-14	5.2	
Superior Temporal Gyrus	42	L	-68	-28	10	6.5	60
Superior Temporal Gyrus	22	L	-64	-24	0	5.1	
Mammilary Body	*	R	2	-14	-18	6.5	53

Threshold set to Z=4.26,and a FWE-corrected cluster significance threshold of P = 0.01. Clusters > 50 voxels displayed here.

Supplementary Table 2 Regions responding to the passive version of the fMRI-adapted Balloon Analogue Risk Task across sex and stress groups (passive – active contrast).

			MNI Peak Coordinates				
Brain Region	**BA**	**H**	**x**	**y**	**z**	**Z-max Value**	**Voxels**
Lingual Gyrus	18	L	-16	-82	-10	6.8	694
Fusiform Gyrus	19	L	-26	-60	-8	6.8	
Declive	*	L	-20	-80	-12	6.8	
Cingulate Gyrus	31	L	-4	-58	32	6.7	504
Precuneus	7	L	-2	-56	36	6.1	
Posterior Cingulate	23	L	-2	-52	26	5.7	
Middle Temporal Gyrus	19	R	56	-66	18	6.3	192
Middle Temporal Gyrus	39	R	54	-64	22	6.3	
Superior Temporal Gyrus	22	R	50	-58	20	5.1	
Precuneus	39	R	46	-70	36	5.0	
Cuneus	18	R	18	-102	8	5.6	67
Cuneus	17	R	12	-102	8	5.4	
Middle Occipital Gyrus	18	R	20	-94	16	4.9	

Threshold set to Z=4.26,and a FWE-corrected cluster significance threshold of P = 0.01.
Clusters > 50 voxels displayed here.

Supplementary Table 3 Regions activated more strongly in control subjects compared to stressed subjects across genders (for lower level active – passive contrast).

			MNI Peak Coordinates				
Brain Region	**BA**	**H**	**x**	**y**	**z**	**Z-max Value**	**Voxels**
Fusiform Gyrus	19	L	-22	-60	-10	4.3	1189
Lingual Gyrus	18	L	-20	-78	-4	4.2	
Lingual Gyrus	18	R	14	-64	8	4.0	
Cuneus	30	L	-2	-70	8	4.0	
Lingual Gyrus	*	L	-20	-76	2	3.9	

Threshold set to Z=2.3,and a FWE-corrected cluster significance threshold of P = 0.05.
Clusters > 50 voxels displayed here.

Supplementary Table 4 Regions activated more strongly in males compared to females across stress conditions (for lower level active – passive contrast).

			MNI Peak Coordinates				
Brain Region	**BA**	**H**	**x**	**y**	**z**	**Z-max Value**	**Voxels**
Postcentral Gyrus	2	L	-52	-18	48	3.7	476
Inferior Parietal Lobule	40	L	-50	-32	26	3.6	
Precentral Gyrus	6	L	-62	-4	30	3.5	
Postcentral Gyrus	3	L	-62	-18	40	3.4	

Threshold set to Z=2.3,and a FWE-corrected cluster significance threshold of P = 0.05.
Clusters > 50 voxels displayed here.

Supplementary Table 5 Regions involved in the task-related network (correlated with BART) by sex and stress group based on Independent Component Analysis.

				Talairach				
Group	**Brain Region**	**BA**	**H**	**x**	**y**	**z**	**T-Value**	**VOL (mm^3)**
Control Female	*Task-related activation*							
	Superior/Middle Frontal Gyrus; Cingulate Gyrus	6;24;32	R/L	3	8	49	11.20	34905
	Middle Frontal Gyrus	9	L	-33	32	34	6.60	2067
	Insula/Claustrum;Putamen	13	R	36	20	10	10.09	14038
	Inferior Parietal Lobule/ Postcentral Gyrus	40;41	L	-36	-31	37	8.47	12331
	Inferior Parietal Lobule/Supramarginal Gyrus	2;40	R	30	-34	40	7.55	4354
	Fusiform Gyrus	19	L	-45	-67	-14	6.38	1312
	Cerebellum		R/L	-9	-52	-14	7.37	2903
	Task-related deactivation							
	Precuneus/Posterior Cingulate	31;23	R/L	-6	-49	28	-13.82	25810
	Medial Frontal Gyrus	10	R/L	-6	59	19	-9.94	8681
	Superior Frontal Gyrus	8	L	-21	29	46	-5.23	592
	Middle Temporal Gyrus	21	R	57	-13	-11	-9.05	2801
	Middle/Inferior Temporal Gyrus	21	L	-57	-7	-11	-5.21	3269
	Middle/Superior Temporal Gyrus	22;19	R	36	-55	13	-6.68	4290
	Middle/Superior Temporal Gyrus	39	L	-42	-73	31	-8.01	5192
Stress Female	*Task-related activation*							
	Medial Frontal Gyrus/Cingulate Gyrus	6;24	**R/L**	-12	-4	46	8.12	6644
	Medial/ Superior Frontal Gyrus	9	R	24	32	28	5.65	1641
	Insula	13	L	-45	2	13	8.10	2909
	Insula/Precentral Gyrus	13;44	R	54	8	10	7.13	3216
	Inferior Parietal Lobule/Postcentral Gyrus	40	L	-54	-25	22	8.39	2026
	Inferior Parietal Lobule	40	R	36	-43	40	8.08	3335
	Cerebellum		L	-18	-61	-23	7.66	3900
			R	9	-61	-23	7.53	702
	Task-related deactivation							
	Precuneus/Posterior Cingulate	31;23	R/L	-3	-58	16	-13.37	21481
	Medial Frontal Gyrus	10	R/L	0	35	-5	-7.76	3511
			R/L	-3	47	34	-8.34	2952
	Middle/Superior Frontal Gyrus	6;8	L	-24	23	46	-10.83	3575
	Middle Temporal Gyrus	39;19	L	-48	-64	22	-7.11	4889
		21	R	54	-1	-14	-7.24	834
		21	L	-57	-10	-8	-8.51	2023
		39;19	R	45	-61	19	-8.54	2964
	Hippocampus		R	27	-19	-14	-8.86	708
	Parahippocampal gyrus	36	L	-24	-34	-11	-6.66	716
	Caudate		L	-3	14	-2	-6.93	675
Control male	*Task-related activation*							
	Middle/Superior Frontal Gyrus; Cingulate Gyrus	46;32;10	R	27	26	22	11.29	5918
	Medial Frontal Gyrus	6	R/L	-3	-4	49	6.52	7676
	Middle Frontal Gyrus	10	R	24	44	-2	5.59	1129
	Insula	13	R	51	11	1	8.96	4342
	Inferior Frontal Gyrus	9	L	-39	5	28	5.08	794
	Inferior/Superior Parietal Lobule	7;40	R	30	-52	43	7.51	6833
	Inferior Parietal Lobule	40	L	-48	-31	37	8.42	7305
		40	L	-9	-67	40	8.22	1606
	Precentral Gyrus	6	R	30	-10	49	6.18	1687
	Task-related deactivation							
	Precuneus/Posterior Cingulate	31;23	R/L	-15	-52	16	-10.19	20984

	Medial Frontal Gyrus	10	R/L	-9	50	10	-5.37	2739
	Superior Frontal Gyrus	8	L	-12	44	43	-5.27	809
	Middle Temporal Gyrus	19	R	51	-61	16	-5.37	913
		39	L	-51	-67	22	-6.67	5295
	Hippocampus/Parahipocampal gyrus		R	27	-13	-11	-6.58	1388
Stress male	*Task-related activation*							
	Middle/Superior Frontal Gyrus	10	R	36	38	22	9.16	4022
	Insula/Claustrum;Putamen	13;45	L	-27	26	4	8.87	3843
	Insula	13	R	30	20	10	6.58	1607
	Inferior Frontal Gyrus	9	L	-42	2	19	6.18	563
	Superior Parietal Lobule	7	L	-15	-64	46	5.56	690
	Inferior Parietal Lobule	40	L	-51	-34	46	5.82	1283
	Middle/Inferior Occipital Gyrus	18	R	27	-85	-2	6.32	1620
		18	L	-27	-85	-5	7.01	1419
	Fusiform gyrus	37	L	-39	-61	-8	7.49	1859
	Precentral Gyrus	44	R	15	-61	43	10.08	29968
	Cerebellum		L	-3	-58	-20	4.60	690
	Task-related deactivation							
	Precuneus/Posterior Cingulate	31;23	R/L	-3	-52	22	-14.87	21746
	Medial Frontal Gyrus	10	R/L	0	56	-8	-7.18	7738
	Superior Frontal Gyrus	8	L	-18	29	46	-6.54	2769
	Middle Temporal Gyrus	21	R	57	-7	-5	-6.80	1038
	Middle/Inferior Temporal Gyrus	21	L	-51	-10	-11	-11.71	3865
	Middle/Superior Temporal Gyrus	22	R	42	-52	19	-5.57	1809
		39;19	L	-54	-55	22	-7.77	6346
	Parahippocampal gyrus	36	L	-24	-34	-11	-5.57	677