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Stress-induced reduction in reward-related prefrontal cortex function

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ABSTRACT

Acute psychological stress can trigger normal and abnormal motivated behaviors such as reward seeking, habitual behavior, and drug craving. Animal research suggests that such effects may result from actions of catecholamines and glucocorticoids that converge in brain regions that regulate motivated behaviors and incentive processing. At present, however, little is known about the acute effects of stress on these circuits in humans. During functional magnetic resonance imaging (fMRI), twenty-seven healthy young women performed a modified version of the monetary incentive delay (MID) task, which is known to robustly engage ventral striatal and medial prefrontal regions. To induce psychological stress, strongly aversive movie clips (versus neutral movie clips) were shown with the instruction to imagine being an eyewitness. Physiological (cortisol levels, heart rate frequency, and heart rate variability) and subjective measurements confirmed successful induction of moderate levels of acute psychological stress. Brain imaging data revealed that stress induction resulted in a significant decrease in reward-related responses in the medial prefrontal cortex (PFC) without affecting ventral striatal responses. Our results thus show that acute psychological stress induces regionally specific changes in functioning of incentive processing circuits. This regional specificity is in line with animal data showing inverted U-shaped relations between levels of stress-related neuromodulators and functioning of the PFC, a structure that is believed to be critical for coordinating behavior in accordance with higher order internal goals. Our findings thus suggest that stress-related increases in habitual and reward-seeking behaviors may be triggered primarily by an impairment of such PFC-dependent cognitive control mechanisms.

Introduction

Exposure to acute stress can trigger normal and abnormal motivated behaviors such as reward seeking, habitual behavior, and drug craving. For example, it has been shown that stress enhances compulsive drug use (Sinha, 2001) and gambling (Ledgerwood and Petry, 2006) in addicted patients and habitual behavior in healthy participants (Schwabe and Wolf, 2009, 2010). It has been suggested that stress enhances these motivated behaviors by modulating functioning of neural circuits that process rewards (Koob, 2008). At present, however, little is known about the immediate effects of stress on the neurobiological substrates underlying incentive processing in humans.

Dopaminergic projections, mainly from the ventral tegmental area to the nucleus accumbens and the medial prefrontal cortex (PFC), appear to play a major role in modulating incentive processing and motivated behaviors (Salamone et al., 2007). The related monoamine norepinephrine (NE) has likewise been implicated in motivational processes (Fibiger and Phillips, 1974; Weinshenker and Schroeder, 2007), and the noradrenergic and dopaminergic systems are anatomically highly interconnected (Sara, 2009; Tong et al., 2006). Notably, acute stress increases the release of these catecholamines in the same circuits (Finlay et al., 1995; Kalivas and Duffy, 1995). Catecholaminergic effects on the brain may moreover be amplified by glucocorticoids, which are released peripherally in response to stress (Grundemann et al., 1998; Roozendaal et al., 2002). Thus, stress and reward-related processes involve catecholaminergic action in overlapping target regions like the ventral striatum and the medial PFC.

Effects of tonically elevated levels of stress-related neuromodulators such as catecholamines and glucocorticoids may, however, be heterogeneous and regionally specific (Finlay and Zigmond, 1997; Sara, 2009). Stress-induced increases of catecholamine release in the striatum (Cenci et al., 1992; Kalivas and Duffy, 1995) are accompanied by increases in striatal-dependent behaviors like habit learning and reward seeking (Schwabe and Wolf, 2009, 2010; Shaham and Stewart, 1995), suggesting that stress levels of catecholamines enhance

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functioning of this region. In contrast, both DA and NE have been shown to influence PFC-dependent higher order cognitive control functions in an inverted U-shaped fashion, with impairing effects at both high and low levels (Arnsten, 2009; Arnsten and Goldman-Rakic, 1998; Vijayraghavan et al., 2007). High levels of catecholamines reached under stress may therefore be supraoptimal in this region. Thus, we hypothesized that acute stress would result in a shift in neural processing of incentives away from prefrontal (top–down cognitive control) and towards striatal regions.

To test this hypothesis, twenty-seven healthy female volunteers were randomly assigned to a stress induction or control group and tested using functional Magnetic Resonance Imaging (fMRI). Participants in the stress group were exposed to strongly aversive movie clips. Neutral movies were used in the control group. Participants were instructed to imagine themselves being an eyewitness of the events that occur in the movie clips. In between presentation of these movie clips, participants performed a modified version of the monetary incentive delay (MID) task in which they had to give an instrumental response to obtain a monetary reward. This task is known to robustly activate the medial PFC and the ventral striatum (Knutson et al., 2001a). To assess the effects of stress induction on autonomic nervous system and hypothalamic–pituitary–adrenal (HPA) axis activation, heart rate (HR) was recorded continuously throughout scanning and salivary cortisol was sampled at baseline and at various time delays before and after the task.

Methods and materials

Participants

Twenty-nine young, healthy, right-handed females (aged 18–25 years) with normal or corrected-to-normal vision participated in this study. Participants reported no history of neurological, psychiatric, or endocrine disease; no current use of any psychoactive drugs or corticosteroids; and no habit of watching violent movies or playing violent video games. None of them had experienced severe physical or emotional trauma. To avoid confounds related to gender differences and menstrual cycle-dependent variance in stress responsiveness (Kirschbaum et al., 1999; Ossewaarde et al., 2010), only women taking standard single-phase oral contraceptives were included. They were tested in the final 2 weeks of their cycle to ensure stable hormone levels. Women were tested in a mixed factorial design with stress induction (stress versus control) as between-subject factor and reward condition (reward versus non-reward) as within-subject factor. They were randomly assigned to either the stress induction ($n=14$; aged 21 ± 2.1 years) or the control group ($n=13$; aged 20 ± 1.8 years). Data of two additional women were excluded because of technical failure or incapability to complete the experiment. The study was approved by the local ethical review board (CMO Region Arnhem-Nijmegen, The Netherlands), and all participants provided written informed consent before the experiment started.

General procedure

The experiment was carried out between 2 and 7 PM to ensure relatively stable and low levels of endogenous cortisol. After arrival, participants had an acclimatization period of 1.5 h, during which baseline measurements of cortisol and subjective affect (Positive And Negative Affect Schedule [PANAS]; Watson et al., 1988) were obtained. After this, participants were told to which of the two experimental groups they were randomly assigned. The full fMRI experiment, embedded in either a continuously stressful or neutral context, started with the first movie clip (2.20 min) in the MRI scanner and was followed by a passive viewing task involving facial expressions (11.5 min; van Marle et al., 2009), a second movie clip (1.30 min), an N-back task (13.6 min; Qin et al., 2009), a third movie clip (1.30 min), the MID task (12.5 min), and a fourth movie clip (1.30 min). The experiment ended with a resting condition (8 min; van Marle et al., 2010) and a structural scan (see Fig. 1).

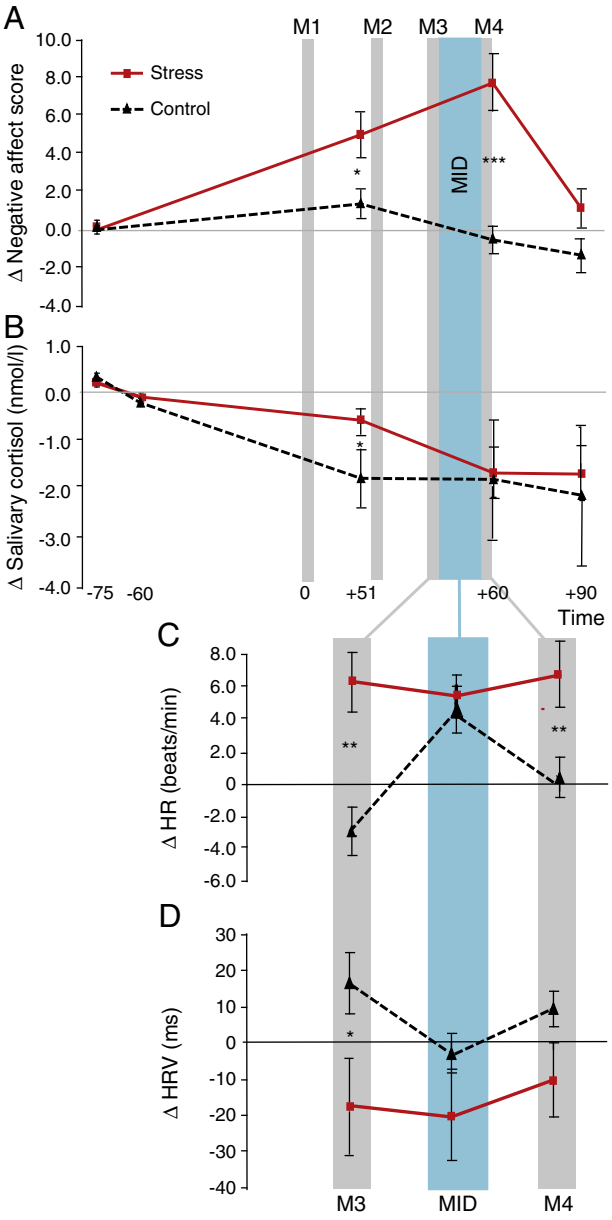

Fig. 1. Experimental design and subjective, endocrine, and autonomic measurements of stress. The experiment (either stressful or neutral) started with the first movie clip (M1: 2.20 min) at time point 0 in the magnetic resonance imaging (MRI) scanner and was followed by a passive viewing task involving facial expressions (11.5 min), a second movie clip (M2: 1.30 min), an N-back task (14 min), a third movie clip (M3: 1.30 min), the MID task (12.5 min), a fourth movie clip (1.30 min), a resting state scan (8 min), and a T1-weighted scan (5 min); subjective (positive and negative affect schedule [PANAS]), endocrine (cortisol), and autonomic (heart rate frequency [HRF] and HR variability [HRV]) measurements of stress were acquired throughout the experiment. (A and B) Averaged and baseline-corrected negative affect ratings and free salivary cortisol levels at different time points for the stress and control group: four negative affect measurements coinciding with five saliva samples were acquired (i.e., two baseline salivary samples at −75 min and −60 min, and three additional ones at +15, +60, and +90 min relative to the start of MRI scanning). (C and D) Averaged and baseline-corrected HRF and HRV during the MID task and its surrounding movie clips (M3 and M4) for the stress and the control groups (i.e., M3 starts at +30 and M4 at +50 relative to the start of MR scanning). Error bars indicate standard error of the mean. Control, control group; Stress, stress group; $^{*}p<0.05$; $^{**}p<0.01$; $^{***}p<0.001$.

Stress induction

To induce a stressful state, highly aversive movie clips were shown immediately before the actual task (Henckens et al., 2009; Qin et al., 2009; van Marle et al., 2009). These clips consisted of scenes of a movie [Irréversible (2002), Gaspar Noé] containing maximally aggressive behavior and violence against men and women. For the control condition, neutral scenes of another movie were shown [Comment j'ai tué mon père (2001), Anne Fontaine]. The stressful and the neutral movie clips were similar in the amount of speech, human (face) presence, luminance, and language. Relative human/face presence during the movie clips was similar in both conditions (93% in neutral and 96% in stressful movie clips). Participants were asked to constantly and attentively view the movie clips (2.20 and 1.30 min, respectively) after short introductory scripts were presented that instructed participants to imagine experiencing the events in the movie as an eyewitness, thereby attempting to involve them maximally in the scenes. This method of stress induction closely corresponds to the determinants of the human stress response as described by Mason (1968), that is, unpredictability, novelty, and uncontrollability. Previous studies have shown that similar methods elicit measurable physiological stress responses (Cousijn et al., 2010; Henckens et al., 2009; Nejtek, 2002; Wittling and Pfluger, 1990).

Monetary incentive delay task (MID)

This task was based on the MID task developed by Knutson et al. (2001a, 2001b) and consisted of 25 potentially rewarding trials, 25 non-rewarding trials, and 25 periods of low-level fixation with an overall mean duration equal to trials. In total, trials lasted between 8.5 and 11.5 s (mean 10 s). Thus, the total duration of the task was 12.5 min. At the beginning of each trial, a cue (cue duration: 3.5–8.5 s; mean 6 s) was presented signaling a potentially rewarding (red square) or non-rewarding (green square) trial. Following this cue, a target was presented to which subjects had to respond as fast as possible (by pressing a button) irrespective of the cue type. When the button was pushed within the presentation time of the circle, the target remained on the screen, thus providing the participant with feedback that the target was hit. Otherwise, it disappeared. When the target was hit in a rewarding trial, participants earned one euro. After disappearance of the target (duration: 1.2–5.3 s; mean 3.25 s), short feedback was provided (500 ms) of the current cumulative gain. To ascertain that reward outcome was similar across participants and sessions, the target duration was variable (150–500 ms) and shortened with 20 ms for the subsequent trial when the previous target was hit. The target duration was increased with 10 ms in the subsequent trial when the previous target was missed. This procedure results in a hit rate of about 33% on average, ensuring that all participants won approximately the same amount of money (between eight and eleven euros). Prior to the experiment, practice trials were presented outside and inside the scanner to familiarize the participants with the task, in which they were required to hit the target in five and three potentially rewarding trials, respectively, before procedures continued.

Subjective and physiological measurements of stress

Subjective mood was assessed using the positive and negative affect schedule (PANAS; Watson et al., 1988) at baseline and three additional time points coinciding with collection of saliva samples. To monitor the HPA axis response, saliva samples were collected using salivette collection devices (Sarstedt, Rommelsdorf, Germany). Participants were requested to abstain from eating, drinking, or smoking for 1 h before arrival. Salivary sampling consisted of two baseline measurements (before MRI scanning) and three additional ones (15, 60, and 90 min after the start of movie clip 1; see Fig. 1B). Taking the subject out of the scanner may affect registration and anatomical localization. Therefore, head position was kept as constant as possible by collecting the samples while subjects were lying in the scanner. The cotton swap of the salivette was carefully placed into the mouth of the subject, who remained static in scan position. After approximately 2 min, the swap was collected carefully. In addition, EPI angulation parameters were adjusted automatically for potential between-scan session movement. All samples were stored at −20 °C until analysis. Samples were prepared for biochemical analysis by centrifuging at 3000 rpm for 5 min, which resulted in a clear supernatant of low viscosity. Salivary free cortisol concentrations were determined employing a chemiluminescence assay (CLIA) with high sensitivity of 0.16 ng/ml (IBL, Hamburg, Germany). HR was recorded continuously throughout MRI scanning using an MR compatible pulse oximeter attached to the left index finger. Offline analysis included calculation of both HR frequency (HRF) and HR variability (HRV). HRV was calculated as the root mean square of successive differences (rMSSD), which indexes respiratory sinus arrhythmia. The HRF and HRV were averaged for the duration of each movie clip and the task and baseline-corrected by subtracting the corresponding values measured during a resting condition, which ended the fMRI session. For all stress measures, statistical analyses were performed with repeated measures analyses of variance (ANOVAs) over all time points of measurement with stress induction (stress versus control) as between subject factor. Whenever necessary, further testing was done with simple *t*-tests. Alpha was set at 0.05 throughout.

MR data acquisition

MRI scans were collected using a Siemens (Erlangen, Germany) TIM Trio 3.0-T MRI scanner equipped with an 8 channel-phased array head coil. We acquired 402 T2*-weighted BOLD images during the task (gradient echo EPI, TE/TR: 25/1890 ms, flip angle 80°, FOV: 212*212 mm, matrix 64*64, 3-mm slice thickness, 0.3-mm slice gap, 37 ascending slices). To reduce signal drop-out and geometric distortions, we used a short TE, an oblique axial angulation (de Zwart et al., 2006), and reduced echo-train length by means of factor 2 accelerated GRAPPA (Griswold et al., 2002). Structural scans were obtained using an MP-RAGE sequence (TE/TR: 2.96/2300 ms, flip angle: 8°, FOV: 256*256*192 mm, voxel size: 1-mm isotropic, GRAPPA acceleration factor 2).

Data analysis

Functional MRI data were analyzed using Statistical Parametric Mapping software (SPM5; Wellcome Department of Imaging Neuroscience, London). To allow for T1 equilibration, the first five EPI volumes of each run were discarded. The remaining images were realigned to the first volume, slice timing corrected, coregistered to the structural MR image, spatially normalized to standard Montreal Neurological Institute (MNI) 152 coordinate space, resampled into $2\times2\times2$ mm^3 voxels, and smoothed with an isotropic 8-mm full-width half maximum Gaussian kernel.

Statistical analysis was performed within the framework of the general linear model. For each subject, the rewarding and non-rewarding trials were modeled as separate regressors in an event-related manner for the duration of the anticipation cue (i.e., the duration of the red and the green square, which was between 3.5 and 8.5 s for both conditions). Subsequently, these regressors were convolved with the canonical hemodynamic response function implemented in SPM5. The six parameters corresponding with movements (3 translations and 3 rotations) obtained from the realignment procedure were also included in the model. We used a high-pass filter with a cut-off frequency of 1/128 Hz. We applied proportional global signal scaling to reduce effects due to global signal variations between scans. The single subject parameter estimates of each condition obtained from the first-level analysis were included in subsequent second-level analyses treating subjects as a random

variable. A repeated measures ANOVA was used including stress induction (stress versus control) as between-subject factor and reward condition (reward versus non-reward) as within-subject factor, with non-sphericity corrections for repeated measures.

We applied an alpha of 0.05, corrected for multiple non-independent comparisons using Gaussian random field theory (Worsley et al., 1996) and suprathreshold cluster size statistics (Friston et al., 1996; Friston et al., 1994). The initial voxel-level threshold for all analyses was set at $p<0.001$, uncorrected, which was also used for visualization of different contrasts in Fig. 2. Small volume corrections (SVC) were used to test regionally specific hypotheses regarding the stress induction by reward condition interaction. For nucleus accumbens, the SVC was based on an anatomical mask of this region. This mask was created as follows: bilateral nucleus accumbens was delineated in T1-weighted scans of 60 separate individuals (21 males, 39 females; mean age: 21.9, age range: 18–38) using an automated segmentation procedure as implemented in FSL FIRST (see http://www.fmrib.ox.ac.uk/fsl/first/index.html). Subsequently, all T1-weighted images were normalized into MNI152 space using SPM5 as described above, and the same transformation was applied to all segmented images. After visual inspection, all segmented images (boolean maps) were averaged, resulting in a probability mask. This mask was thresholded at a probability of 0.75 (total volume: 2179 mm^3). Given the uncertainties in exact localization of a small area such as the nucleus accumbens, we refer to the region covered by this ROI mask with the more cautious term ventral striatum. For medial PFC, planned SVC procedures were not applied because the interaction effects reached significance even after more conservative whole-brain correction. Outside of these ROIs, and for main effects of reward condition across all participants, only statistical differences exceeding a whole-brain FWE correction were considered significant.

Analysis of behavioral performance

Reaction time (RT) data of responses during the MID were analyzed by first removing any outliers below 150 and over 1000 ms. Subsequently, all RTs outside the range of three standard deviations higher or lower than the participant and reward condition-specific means were removed from the analysis. Resulting RTs were subjected to a repeated measures ANOVA with stress induction (stress versus control) as between-subject factor and reward condition (reward versus non-reward) as within subject factor. As a result of the adaptive procedure adjusting the target presentation time (see above), the total amount of monetary gain in the MID task does not reflect performance.

Results

Subjective and physiological measurements of stress

We first assessed whether stress induction increased negative affect ratings as intended. A 2-by-3 ANOVA with stress induction as between-subject factor and time as within-subject factor (three post-baseline time points) revealed main effects of group ($F(1,25)=18.56$, $p<0.001$) and time ($F(2,24)=12.31$, $p<0.001$), and an interaction effect ($F(2,24)=7.56$, $p<0.003$), indicating that stress induction resulted in an increase in negative affect. Separate independent t-tests showed no significant difference in negative affect between the two groups at baseline ($t(25)=-0.179$, $p>0.05$) but did show higher negative affect ratings in the stress group 60 min after the start of movie clip 1 ($t(25)=4.8$; $p<0.001$; see Fig. 1A). No effects of stress were found for positive affect ratings.

Second, we tested whether cortisol levels were elevated due to the stress induction procedures. An ANOVA with time as within-subject factor and stress induction as between subject factor revealed a downward pattern in baseline-corrected cortisol levels for both groups over time ($F(1,25)=9.59$, $p<0.005$), most likely due to diurnal rhythm and stress anticipation, and a significant interaction effect of group and time ($F(2,24)=3.43$, $p<0.05$). Further testing revealed significantly higher cortisol levels for the stress as compared to the control group at the time point directly preceding the second movie clip ($t(15.8)=1.91$, $p<0.05$, one-tailed) (see Fig. 1B), indicating mild increases in HPA axis activity in the stress group.

Third, we averaged baseline-corrected HRF and HRV separately for the MID task and surrounding movie clips (see Fig. 1C and D). A 2 (stress induction) by 3 (time: pre-, during-, and post-MID task) ANOVA revealed a main effect of stress induction ($F(1,23)=7.89$, $p<0.05$) and a

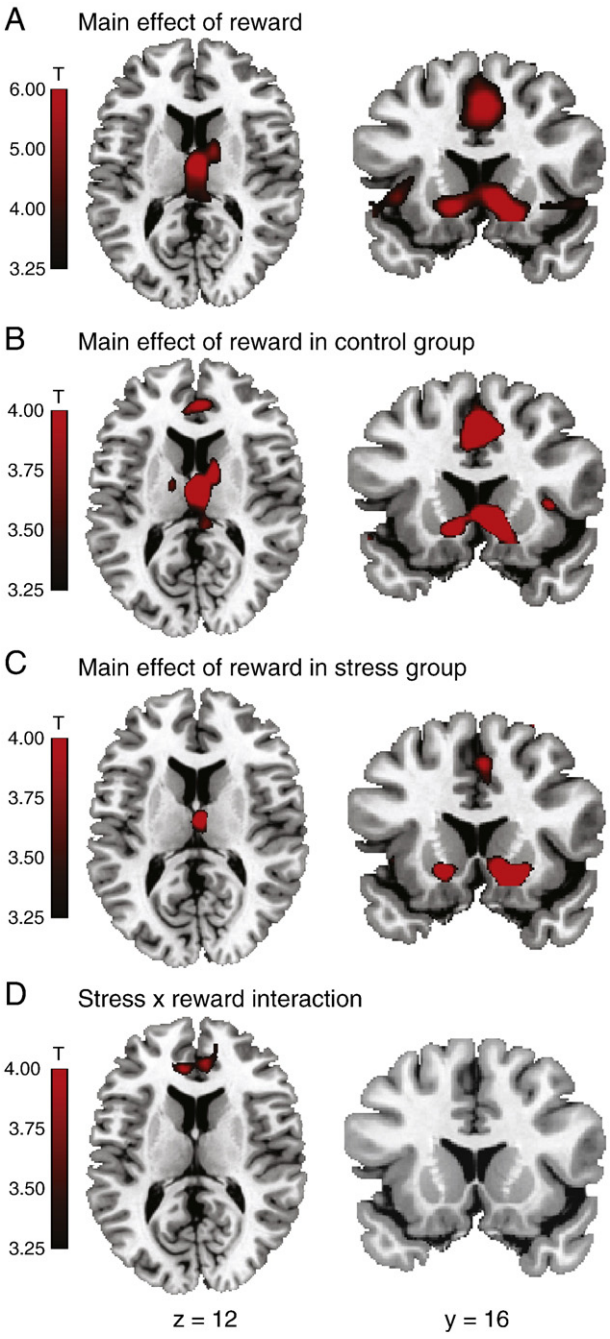

Fig. 2. Statistical parametric maps showing effects of reward and stress. (A) Main effect of reward condition (reward versus non-reward) for both groups). (B) Main effect of reward condition in the control group. (C) Main effect of reward condition in the stress group. (D) Reward condition by stress induction interaction. Statistical parametric maps are thresholded at $p<0.001$, uncorrected, for visualization purposes (see Table 1 for cluster-level inferential statistics), and overlaid onto a canonical T1-weighted scan. Right, right hemisphere.

stress induction by time interaction ($F(2,22) = 4.55$, $p<0.05$) for HRF. Separate independent *T*-tests revealed increased HRF for the two movie clips only (movie 3: $t(24) = 3.57$, $p<0.01$; movie 4: $t(23) = 2.81$; $p<0.05$). A similar analysis for HRV showed a main effect of stress induction ($F(1,23) = 5.12$, $p<0.05$) with decreased HRV in the stress group as compared to the control group. The two groups did not differ significantly in either HRF ($t(24) = 0.85$, ns) or HRV ($t(24) = -1.15$, ns) at baseline.

Taken together, the results from subjective and physiological measurements of stress consistently confirm that the monetary incentive delay task was embedded in a moderately stressful context for the stress group.

Monetary incentive delay task, reaction times

A 2-by-2 repeated measures ANOVA with reward condition (reward versus non-reward) as within-subject factor and group (stress versus control) as between-subject factor revealed a main effect of reward condition ($F(1,25) = 99.71$, $p<0.001$), indicating that responses to the target during potentially rewarding trials were significantly faster than to non-rewarding trials (mean ± SD in ms, stress: reward 233 ± 16; non-reward 266 ± 27; control: reward 235 ± 21; non-reward 262 ± 30). There was neither a significant main effect of stress induction ($F(1,25) < 1$, ns), nor a stress induction by reward condition interaction ($F(1,25) < 1$, *ns*). The adaptive reinforcement schedule indeed resulted in a rewarding outcome in approximately 33% of potentially rewarding trials: observed mean percentages of hits (and SD) were 39.7% (3.3%) and 36.1% (4.1%) for potentially rewarding and non-rewarding conditions, respectively.

Imaging results

fMRI data were analyzed with a second-level repeated measures ANOVA with reward condition (anticipation of potential reward versus non-reward) as within-subject factor and stress induction (stress versus control) as between-subject factor. The main effect of reward condition showed widespread activations in the dorsal and ventral striatum, midbrain, parietal regions, insula, and anterior cingulate gyrus (all $p<0.05$, whole brain corrected), which is in line with previous observations (Knutson et al., 2001a,b; see Table 1).

Subsequently, we investigated the effects of stress induction. No suprathreshold clusters were found for the contrast testing the main effect of stress induction (i.e., testing between-group differences in neural responses to the task regardless of incentive value). In line with our hypotheses, an interaction effect between the factors stress induction and reward condition was observed in a cluster in the medial PFC ($p<0.05$, whole brain corrected at cluster level, see Fig. 2D), with reduced reward-related activity in this region in the stress group as compared to the control group. However, no significant differences in reward-related ventral striatal activity were observed between the two groups (stress induction by reward condition interaction: $p>0.05$, SVC). Further analyses on the effects of stress on potentially rewarding and non-rewarding trials separately also did not show significant differences in ventral striatal activity ($p>0.05$, SVC corrected). Thus, we found a specific effect of stress induction on reward-related activity in the medial PFC.

Discussion

The current study investigated the effects of acute stress on reward-related activity in incentive processing circuits in humans. Physiological and psychological measures of stress confirmed that our procedure yielded moderate stress responses. Our hypothesis of a shift from prefrontal to striatal processing of rewards under stress was partially confirmed: neuroimaging data revealed reduced reward-related medial PFC activation after exposure to acute stress but did not show stress-induced changes in ventral striatal activity.

Our stress induction procedure resulted in salivary cortisol levels that were slightly elevated in the stress group as compared to the non-stress group. Although activation of the HPA axis and peripheral release

Table 1
Cluster sizes and local maxima for significant areas of activation for the main effect and stress induction × reward anticipation interaction.

Contrast						
Cluster location	Side	*x*	*y*	*z*	Cluster size	Local maximum
						t Value
Local maximum location						
Main effect of reward condition (reward ≥ non-reward)						
Ventral stiatum/midbrain	**R/L**				**4650****	
Ventral striatum	R	12	14	−8		8.93
Ventral striatum	L	−10	4	−4		8.75
Midbrain	R	6	−14	−16		8.16
Mid-cingulate/precentral gyrus	**R/L**				**3693****	
Mid-cingulate gyrus	R	4	14	46		7.37
Supplementary motor area	R	4	0	72		6.89
Primary motor cortex	L	−44	−16	66		6.16
Cerebellum	**R/L**				**1670****	
Cerebellum (lobule VI)	R	30	−46	−26		6.36
Cerebellum (lobule VIIb)	R/L	2	−76	−24		5.64
Cerebellar vermis	R/L	2	−46	−16		5.70
Cerebellum (lobule VIIa)	**L**				**611****	
Cerebellum (lobule VIIa)	L	−38	−56	−32		5.81
Cerebellum (lobule VIIa)	L	−48	−60	−32		5.22
Cerebellum (lobule VI)	L	−26	−62	−30		4.96
Stress induction × reward anticipation interaction: stress ≤ control						
Medial PFC	**R/L**				**228***	
Medial PFC (BA 10)	R	10	54	18		4.03
Medial PFC (BA 32)	L	−6	38	12		4.00
Medial PFC (BA 32)	R	6	42	12		3.94

Local maxima for significant areas of activation for the main and simple effects, and stress induction × reward interaction. Initial statistical threshold is set at p = 0.001, uncorrected. Only significant clusters surviving whole brain FWE correction are reported.
*$p<0.05$, FWE whole brain corrected at cluster level; **$p<0.001$, FWE whole brain corrected at cluster level; R, right; L, left; PFC, prefrontal cortex; BA, Brodmann area.

of glucocorticoids is often seen as the hallmark of the stress response, rapid central catecholaminergic mechanisms may play a more central role in facilitating cognitive flexibility and vigilance in the early phases of the stress response (Valentino and Van Bockstaele, 2008). It is well established that acute stress results in tonic elevation of catecholamines through the pontine locus coeruleus–norepinephrine (LC-NE) system and midbrain dopaminergic neurons in the ventral tegmental area (VTA) and the substantia nigra (SN) (Arnsten, 2009; Aston-Jones and Cohen, 2005). Through the hypothalamus, such changes are accompanied by activation of preganglionic neurons of the sympathetic nervous system, which lead to autonomic changes that are characteristic of the fight-or-flight response (Ulrich-Lai and Herman, 2009). The observed sympathetic dominance (reflected in elevated HRF and decreased HRV; see Lang et al., 1998) in response to the stressor in the current study therefore indicates that it is plausible that in addition to a mild elevation of glucocorticoids, catecholaminergic activity was tonically elevated in the stress induction group.

Our finding of decreased stress-induced medial PFC responses during reward-related processing is in line with a number of previous findings. Animal studies have shown detrimental effects of stress on the PFC and its higher order cognitive functions and have associated these effects with changes in catecholamine and glucocorticoid levels (Arnsten, 2009; Clinton et al., 2006; Finlay et al., 1995; Radley et al., 2008; Roozendaal et al., 2004). In line with these animal studies, human neuroimaging studies have shown decreases in PFC activity during stress (Qin et al., 2009; Sinha et al., 2005) or emotional distraction (Dolcos and McCarthy, 2006). Likewise, another study showed a negative correlation between cortisol levels and neural activity in the medial PFC after stress induction in patients with social anxiety disorder (Åhs et al., 2006). Glucocorticoids increase NE and DA levels in the brain (McEwen, 1987; Piazza and Le Moal, 1996), and noradrenergic activity, mainly in the basolateral amygdala, mediates glucocorticoid effects on higher order PFC-dependent functions such as working memory (Roozendaal et al., 2004, 1999). Thus, stress-induced impairments of PFC function are likely caused by a combination of elevated levels of both catecholamines and glucocorticoids.

The medial PFC plays an important role in modulating HPA and autonomic responses to emotional stress and is involved in the regulation of cognitive and emotional processing (Radley et al., 2006, 2008; Sullivan and Gratton, 1999). In addition to this role in stress regulation, a meta-analysis of human neuroimaging studies shows the involvement of this region in tracking reward value and exerting inhibitory control (Kringelbach, 2005; Kringelbach and Rolls, 2004). Although functions related to anticipation of rewards have mostly been ascribed to the ventral striatum (Knutson et al., 2001a,b), a recent study demonstrated that the medial PFC codes potential reward value already during reward anticipation (Kahnt et al., 2010). The PFC innervates motivational pathways including the nucleus accumbens, likely by glutamatergic input, and therefore may directly or indirectly affect DA neurons (Moghaddam and Jackson, 2004). It has been suggested that without appropriate reward monitoring and inhibitory cognitive control mechanisms regulated by the medial PFC, motivational pathways would function in an uncontrolled manner and behavior would become inadequate. Such impulsive or disorganized behavior is indeed characteristic of PFC dysfunction in humans (Li and Sinha, 2008; Miller and Cohen, 2001). Thus, it is well possible that stress-induced down regulation of the medial PFC may primarily impair regulatory cognitive control functions.

The present data provide no evidence for stress-induced increases in ventral striatal activity, which would complement the hypothesized shift from prefrontal to striatal function. One possible reason for this is that the mPFC may be more sensitive to stress than the ventral striatum. In line with this notion, animal data show that stress-induced extracellular DA levels increase most in the PFC and to a lesser extent in the nucleus accumbens and neostriatum (Abercrombie et al., 1989). This would imply that the medial PFC is especially vulnerable to acute stress. Another possibility is that DA neurons respond to stress and novelty by changing their tonic firing rates (Grace, 1991; Pruessner et al., 2004; Serrano et al., 1989), while the BOLD signal in the ventral striatum is probably more related to phasic firing of neurons (Knutson and Gibbs, 2007). It has indeed been argued that stress induces a prolonged, tonic change in brain activation (Wang et al., 2005). Note that an inherent limitation of conventional task-based BOLD-fMRI as used in this study is its insensitivity to such slowly modulated changes, because one only models and estimates phasic task-related responses. Finally, although robust autonomic changes in response to our stressor indicate that catecholamine levels were likely elevated, the stressor used in this study may have been too mild to achieve an increase of corticosteroid levels sufficient to affect the ventral striatum. Corticosteroids have been shown to facilitate stress-induced DA release in the nucleus accumbens and appear to specifically determine the higher dopaminergic response to stress observed in some individuals (Piazza and Le Moal, 1996; Rouge-Pont et al., 1998). Therefore, future studies using pharmacological fMRI with cortisol administration in combination with a monetary incentive delay task may shed more light on the potential effects of stress-related neuromodulators on striatal function.

Finally, it is interesting to consider differences between effects of acute and chronic types of stress. Whereas acute stress can trigger normal and abnormal motivated behaviors such as reward seeking and craving, prolonged stress often leads to anhedonia and a reduction in reward-related behavior (Knoll and Carlezon, 2010; Nestler and Carlezon, 2006; Pizzagalli et al., 2008). In agreement, a large number of neuroimaging studies have shown ventral striatal hyporesponsiveness in major depressive disorder (MDD) and post-traumatic stress disorder (PTSD) patients (Elman et al., 2009; Keedwell et al., 2005; Pizzagalli et al., 2009; Sailer et al., 2008), although null findings have also been reported (Knutson et al., 2008). As discussed in previous paragraphs, acute stress likely results in a rapid increase in NE and DA levels in mesocortical regions and to a lesser extent in the mesolimbic system (Abercrombie et al., 1989; Finlay et al., 1995; Kalivas and Duffy, 1995). In contrast, however, chronic stress has been shown to lead to lower NE and DA concentrations in target regions of the mesolimbic system such as the nucleus accumbens (Flügge et al., 1997; Imperato et al., 1993). Thus, effects of chronic and acute stress may differ due to opposite effects on catecholaminergic availability.

In conclusion, we found partial evidence for the hypothesized shift from prefrontal to striatal processing of potential rewards. The present study is the first to demonstrate a reduction in reward-related medial PFC activity under stress in healthy volunteers. The decrease in medial PFC activity suggests that acute stress primarily induces an impairment of PFC-dependent regulatory and cognitive control mechanisms.

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