DIFFERENTIAL EFFECTS OF ACUTE STRESS ON ANTICIPATORY AND CONSUMMATORY PHASES OF REWARD PROCESSING

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Abstract—Anhedonia is one of the core symptoms of depression and has been linked to blunted responses to rewarding stimuli in striatal regions. Stress, a key vulnerability factor for depression, has been shown to induce anhedonic behavior, including reduced reward responsiveness in both animals and humans, but the brain processes associated with these effects remain largely unknown in humans. Emerging evidence suggests that stress has dissociable effects on distinct components of reward processing, as it has been found to potentiate motivation/‘wanting’ during the anticipatory phase but reduce reward responsiveness/‘liking’ during the consummatory phase. To examine the impact of stress on reward processing, we used a monetary incentive delay (MID) task and an acute stress manipulation (negative performance feedback) in conjunction with functional magnetic resonance imaging (fMRI). Fifteen healthy participants performed the MID task under no-stress and stress conditions. We hypothesized that stress would have dissociable effects on the anticipatory and consummatory phases in reward-related brain regions. Specifically, we expected reduced striatal responsiveness during reward consumption (mirroring patterns previously observed in clinical depression) and increased striatal activation during anticipation consistent with non-human findings. Supporting our hypotheses, significant Phase (Anticipation/Consumption) × Stress (Stress/No-stress) interactions emerged in the putamen, nucleus accumbens, caudate and amygdala. Post hoc tests revealed that stress increased striatal and amygdalar activation during anticipation but decreased striatal activation during consumption. Importantly, stress-induced striatal blunting was similar to the profile observed in clinical depression under baseline (no-stress) conditions in prior studies. Given that stress is a pivotal vulnerability factor for depression, these results offer insight to better understand the etiology of this prevalent disorder. © 2014 IBRO. Published by Elsevier Ltd. All rights reserved.

Key words: stress, basal ganglia, reward, anticipation, consumption, monetary incentive delay.

INTRODUCTION

Several vulnerability factors exist for depression, but stress is one of the most reliable predictors of this prevalent disorder. In humans, depressive episodes are often preceded by stressful life events (Kendler et al., 1999; Gold and Chrousos, 2002; Hammen, 2005), and stress has been associated with poorer treatment prognosis and more frequent relapse (Tennant, 2002). Animal and human studies have shown that both acute and chronic stress affects reward mechanisms and induce depression-like phenotypes. However, reward processing is not a homogenous phenomenon and can be parsed, among other subcomponents, into anticipatory (cue-triggered ‘wanting’) and consummatory (‘liking’) phases (Berridge et al., 2009). ‘Wanting’ refers to the attribution of incentive salience to rewards and reward-predicting cues, and is associated with motivational engagement and sustained attention to positive stimuli, whereas ‘liking’ refers to the hedonic value of reward associated with in-the-moment experiences of rewards (Berridge et al., 2009). Animal studies suggest that these phases recruit distinct anatomical and neurochemical substrates (Berridge and Robinson, 1998). Similarly, electrophysiological and human neuroimaging studies indicate that subcortical mesolimbic dopaminergic regions, such as the striatum and amygdala, respond during both reward anticipation and consumption, while other cortical regions, such as the medial prefrontal cortex (mPFC, including the orbitofrontal cortex), are more frequently associated with reward consumption (Knutson et al., 2001; Dillon et al., 2008; Schott et al., 2008; Berridge et al., 2009).

Directly relevant to the current research, stress is thought to affect the anticipatory and consummatory...
phases of reward processing in unique ways given its
differential effect on dopamine (DA). Specifically, both
acute and chronic stress have been found to decrease
sensitivity to reward in both animals (Anisman and
Matheson, 2005; Cabib and Puglisi-Allegra, 2012; Tye
et al., 2013; Wiborg, 2013) and humans (Berenbaum
and Connelly, 1993; Bogdan and Pizzagalli, 2006;
Berghorst et al., 2013). However, acute stress is linked
to increase in “incentive-triggered motivation”, but
severe or chronic stress abolishes this (Lemos et al.,
2012), a phenomenon that might contribute to the
development of depression. Neurobiologically, the
corticostriatal-releasing factor (CRF), a neuropeptide
released in response to acute stressors, causes DA
release through co-activation of the receptors CRFR1
and CRFR2, which in turn facilitates “cue-triggered
motivation” (Lemos et al., 2012). However chronic
stress selectively abolishes CRF’s ability to modulate
DA levels, specifically in the nucleus accumbens (NAc),
and it is thought to switch “cue-triggered appetitive
motivation” into “aversive motivation”, which in turn
might reflect the lack of motivation observed to
previously motivated behaviors in Major Depressive
Disorder (MDD).

Consistent with this, MDD individuals have been shown
to exhibit reduced brain activation in striatal regions
during both reward anticipation and consumption.
Furthermore, in healthy volunteers, both acute stress
(Bogdan and Pizzagalli, 2006; Berghorst et al., 2013)
and pharmacological challenges thought to decrease phasic
DA firing (Pizzagalli et al., 2008a) led to a behavioral
profile of blunted reward responsiveness in a probabilistic
reward task that was similar to what observed in MDD
individuals at baseline (i.e., without stress or drug
manipulation) (Pizzagalli et al., 2008b). Collectively,
these findings strongly suggest a potential link between
anhedonia and stress and highlight the importance of
studying the effects of stress on brain activation
associated with reward processing in healthy volunteers,
which might provide valuable insight for MDD research.

Surprisingly, few human functional magnetic
correlation imaging (fMRI) studies have examined
stress-induced effects on reward processing (Born et al.,
2010; Ossewaarde et al., 2011; Porcelli et al., 2012),
with none focusing on the putative differential effects
of stress on brain activation during reward anticipation
and consumption. To fill this gap, we used a monetary
incentive delay (MID) task, an acute stress manipulation
and fMRI to examine the impact of stress on reward
processing in healthy volunteers. We had two primary
hypotheses. First, we hypothesized that stress would
elicit blunted striatal responsiveness during the
consummatory phase, reflecting blunted “liking” and
reminiscent of patterns observed in MDD under no-
stress conditions (Pizzagalli et al., 2009). Second,
during the anticipatory phase, we expected increased
activation under stress in DA-rich striatal regions (e.g.,
caudate, putamen, NAc), indexing increased “cue-
triggered motivation” and consistent with findings in
non-human animals exposed to acute mild stressors
(Cabib and Puglisi-Allegra, 2012; Lemos et al., 2012).

In addition, the amygdala and medial prefrontal cortex
(mPFC) have been critically implicated in stress response
and regulation. As the amygdala has been associated
with both stress (Veer et al., 2011) and approach
behaviors (Mahler and Berridge, 2011), we
hypothesized that acute stress would increase
responses in this region during anticipation. Conversely,
since the mPFC has been preferentially associated with
consumption (Knutson et al., 2001) and subjective
perceived stress (Treadway et al., 2013), we
hypothesized that acute stress would decrease mPFC
activation during the consummatory phase.

EXPERIMENTAL PROCEDURES

Participants
Eighteen healthy volunteers (11 females, mean age:
31.7 ± 12.3 years) were recruited from the community.
All participants provided written informed consent to a
protocol approved by the Committee on the Use of
Human Subjects in Research at the Harvard University
and the Partners Human Research Committee. All
participants were right-handed, and reported no medical
or neurological illnesses, no current or past
psychopathology (as assessed by the Structured
Clinical Interview for the DSM-IV (First et al., 2002)),
and no current or past use of psychotropic medications.

Procedure
Participants underwent a single imaging session during
which they performed a MID task (Knutson et al., 2000;
described in Section “MID task”). There were four
separate runs of the MID task: two runs under no-stress
conditions and two runs under stress conditions in the
following order: (1) No-stress, (2) Stress, (3) Stress, (4)
No-stress. The order of Stress/No-stress conditions was
not randomized (Fig. 1 A). The stress manipulation
involved negative performance evaluations (described in
Section “Stress manipulation”). All reaction times (RTs)
associated with task performance were recorded. In
addition, following each run, and prior to receiving
performance evaluation, participants rated the degree to
which they experienced 12 different emotions (e.g.,
tense, anxious, relaxed, in control) during the prior run
on scales from 1 to 5 (1 = not at all/very slightly,
3 = moderately, 5 = extremely). In addition,
physiological data (skin conductance) were collected
using an MRI-compatible PowerLab 16-SP Data
Acquisition System manufactured by AD Instruments
Inc. Participants were compensated $55 for their time
and earned between $10 and $60 from the task.

MID task
The MID task (Fig. 1B) was designed to elicit brain
responses during reward anticipation and consumption
(Knutson et al., 2000). At the onset of each trial,
participants were presented with a visual cue (1.5 s)
indicating a reinforcer associated with performance
(“+$” (reward) or “-$” (no-incentive)). After a variable
inter-stimulus interval (3, 4.5, or 6 s), participants saw a visual target (a red square, 0.2 s) that signaled they should press a button as quickly as possible. After response execution and a variable delay (2.8, 4.3 or 5.8 s), visual outcome (1.5 s) based on trial type (gain/no-change on reward trials and no-change on no-incentive trials) was provided and a variable intertrial interval ensued (3, 4.5, or 6 s). Participants were instructed that the speed with which they pressed the button after the presentation of the target determined the probability of success. Monetary gain was associated with successful performance in reward trials, and occurred if RTs were within the 66th percentile of those obtained in the previous run (for run 1, a practice run was used for these calculations). Gains for successful reward trials were between $0.95 and $1.15 (mean: $1.05). The magnitudes of the gains were pseudo-randomly varied around the mean magnitude, and no information about overall performance (i.e., total earnings) was provided during the run to avoid online monitoring. There was no gain associated with reward trials in which participants’ RTs fell outside of the 66th percentile window or with no-incentive trials. The task included four runs of 33 trials (~9 min each), with 22 reward and 11 no-incentive trials pseudo-randomized in each run. Subjects completed a brief practice run immediately before the first run. The practice run was identical to the design described above except that no feedback was displayed.

Stress manipulation

In line with manipulations employed in previous studies (Bogdan and Pizzagalli, 2006; Berghorst et al., 2013), the stressor involved a social-evaluative component (negative feedback about task performance) and partial uncontrollability. Participants received negative feedback about their performance during runs 1 and 2 (i.e., prior to the two stress runs 2 and 3, respectively), whereas they received positive feedback about their performance during practice and run 3 (i.e., prior to the two no-stress runs 1 and 4, respectively). During the stress runs, they were told that they were performing worse than prior participants and that, as a result, there was a chance they could receive sudden $5 penalty deductions if they continued to perform poorly. During the no-stress runs, there was no threat of penalties. Prior to runs 1 and 4, participants were told that their performance was above average and that there was no risk of penalties during this run.

To sustain the stress manipulation, a multicolored bar was visible at the bottom of the screen throughout the task. During the stress runs, the bar contained three different colored zones: red (“$5 Penalty”), yellow (“neutral”), and green (“Penalty Not Possible”). A vertical pointer within the bar indicated the likelihood of receiving the $5 penalty. The location of the pointer was actually unrelated to task performance and changed every six trials in line with a fixed pattern to ensure that all participants received the same number of penalties. In an effort to maintain the stress manipulation, the pointer moved close to the red “$5 penalty” zone throughout the stress runs, with penalties occurring twice during run 2 and once during run 3. When the pointer moved into the “$5 penalty zone”, a $5 loss immediately incurred, and a red-colored screen border flashed to indicate a “$5 penalty”. During the no-stress runs, the multicolored bar was shades of yellow, green, and blue (“safe”), and participants were informed that they could disregard the bar for those runs.

Imaging data acquisition

A 1.5-T Symphony/Sonata scanner (Siemens Medical Systems, Iselin, NJ, USA) was used to acquire the MRI
To assess the effects of stress on skin conductance, measures were averaged for the no-stress (runs 1 and 4) and stress runs (runs 2 and 3) separately, and analyzed using a paired t-test.

**Behavioral data analyses**

**Skin conductance level (SCL).** To assess the effects of stress on skin conductance, measures were averaged for the no-stress (runs 1 and 4) and stress runs (runs 2 and 3) separately, and analyzed using a paired t-test.

**RT.** After removal of outliers (defined as values less than 150 ms or greater than 1000 ms and as responses exceeding three standard deviations from the mean for each individual participant). RTs from no-stress (runs 1 and 4) and stress (runs 2 and 3) runs were averaged separately for each trial type (Reward and No-incentive). A $2 \times 2$ repeated measures analysis of variance (ANOVA) with Incentive (Reward/No-incentive) × Stress (Stress/No-stress) as factors was run to assess the effects of stress on incentive type.

**Affective ratings.** Positive and negative affect were calculated by averaging the scores obtained on five positive (in control, alert, energetic, relaxed and happy) and seven negative (tense, anxious, powerless, defeated, challenged, stressed and out of control) emotions, respectively, after every run. These ratings were then averaged for the no-stress (runs 1 and 4) and stress runs (runs 2 and 3) separately, and analyzed using a $2 \times 2$ repeated measures ANOVA with Valence (Positive/Negative) × Stress (Stress/No-stress) as factors. The relevant subscale ratings such as “in control”, “stressed”, “anxious”, “happy”, were also explored individually to further investigate the effect of stress manipulation.

**fMRI analyses**

fMRI data were analyzed using FSL 4.1.5 (Smith et al., 2004; http://fsl.fmrib.ox.ac.uk/fsl/fslwiki/). Data pre-processing included: motion correction using Motion Correction using FSL’ Linear Image Registration Tool (MCFLIRT; Jenkinson et al., 2002), slice timing correction, removal of non-brain structures using Brain Extraction Tool (BET; Smith, 2002), spatial smoothing (Gaussian kernel with 6 mm full width at half maximum), grand mean intensity normalization of the entire 4D dataset by a single multiplicative factor, and highpass temporal filtering (Gaussian-weighted least squares straight line fitting with $\sigma = 60$ s). Registration of functional data to the high-resolution structural images was done using FLIRT and registration of structural images to 2 mm Montreal Neurological Institute (MNI) standard space template was done using FSL’s Non-linear Image Registration Tool (FNIRT; Jenkinson et al., 2002).

Statistical analyses of single-subject fMRI data were implemented using a general linear model (GLM) with regressors corresponding to reward cue, no-incentive cue, successful reward feedback, unsuccessful reward feedback, no-change feedback (corresponding to no-incentive) trials. Each event was constructed as a hemodynamic response function (modeled using a gamma function) convolved with onset times of the events. The six rigid-body motion time courses from the motion correction and target, errors (i.e., trials in which the button was pressed before the target presentation) and penalties (only during stress runs, when $\$ 5 penalty was randomly presented) trials were included as covariates of no interest with a total of 14 regressors in each single-subject design matrix. Contrast maps were constructed for reward anticipation (reward vs. no-incentive cue) and consumption (gain vs. no-change feedback). Note that because of the double subtraction these maps reflect Incentive (Reward/No-incentive) × Stress (Stress/No-stress) interactions. These contrast maps were utilized for both region of interest (ROI)-based statistical analyses testing our primary hypotheses as well as for a whole-brain main effects analysis evaluating brain regions affected by the task.

To test *a priori* hypotheses that stress would be associated with dissociable effects on anticipation and consumption and, in particular, would elicit blunted striatal responsiveness during the consummatory phase reminiscent of patterns observed in MDD (Pizzagalli et al., 2009), six 10-mm spherical ROIs were created around MNI coordinates from regions that showed blunted activation in MDD patients during the anticipatory or consummatory phase of the MID task in a prior study (Pizzagalli et al., 2009). ROIs included the left putamen ($x = -29$, $y = -13$, $z = -5$), left NAc ($x = -8$, $y = -11$, $z = -15$), left caudate ($x = -20$, $y = -25$, $z = 20$ and $x = -12$, $y = -1$, $z = 19$) and right caudate ($x = 16$, $y = 19$, $z = 6$ and $x = 19$, $y = 3$, $z = 16$). These spherical ROIs were multiplied with the anatomical MNI ROIs constructed from the Harvard-Oxford Subcortical Atlas, to ensure that they fell within the anatomical boundaries of each structure. In addition, anatomical ROIs of the right and left amygdala were constructed from the Harvard-Oxford Subcortical Atlas. The mPFC ROI was created by drawing a 10-mm sphere around the peak voxel ($x = 0$, $y = 50$, $z = 4$) extracted from Treadway et al. (2013), as this region was reported to be modulated by the subjective perceived stress.

Averaged contrasts of parameter estimates within each ROI were extracted from reward vs. no-incentive cue (hereby referred to as “Anticipation”) and gain vs. no-change feedback (hereby referred to as...
“Consumption”) contrast maps output from the subject-level GLMs. Next, parameter estimates from stress runs (2 and 3) and no-stress runs (1 and 4) were averaged separately for each ROI and entered into SPSS (version 20). A 2 × 2 repeated measures ANOVA with Phase (Anticipation/Consumption) × Stress (Stress/No-stress) as factors were run for the left putamen and NAc ROIs. Since there were four caudate ROIs, ROI was entered as an additional factor to help control the family-wise error. If a significant Phase × Stress × ROI interaction emerged, follow-up Phase × Stress ANOVAs were run for each caudate ROI. Across the analyses, significant two-way interactions were followed by post hoc t-tests.

Finally, for the amygdala, parameter estimates from the left and right amygdala during anticipation were averaged and a paired t-test between stress and no-stress runs was run. Similarly, a paired t-test between stress and no-stress runs during consumption was run for the mPFC ROI.

While positive feedback was given after run 3 to mitigate potential carry-over effects of the stress manipulation, in addition to analyses of all four runs, we also conducted analyses that focused on the first two runs, as putative differences between these two runs may more strongly reflect the effects of “acute” stress and would eliminate possible carry-over effects of stress.

Throughout the analyses, data were inspected for the presence of outliers. Values that exceeded three times the inter-quartile range (the difference between the third and first quartile) of mean parameter estimates were deemed to be outliers and were further investigated to identify if these were due to motion, registration error, or other sources of artifacts. If no problems could be identified and corrected, outlier data points were removed from the analyses.

RESULTS

Behavioral results

On average, across all participants and runs, approximately 65% of reward trials (~14 trials) were successful (i.e., participants were faster than the set threshold of 66%), and 35% (~8 trials) were not successful (i.e., participants were slower than the 66% threshold). There was no difference in the number of reward feedback delivered during the stress and no-stress runs (13.74 ± 0.93 vs. 15.12 ± 1.07; t(14) = 1.43, p > 0.3). Similarly, no behavioral differences were observed between only runs 1 and 2 (see Table 1).

SCLs. Unfortunately, due to technical difficulties, hardware malfunction and general recommendation (2–20 μS) (Dawson et al., 2007), peripheral physiological data were unusable for eight subjects. An exploratory analysis was conducted on the tonic SCL from the remaining seven participants. Overall, stress showed a trend toward an increase in SCL values in these participants (Fig. 2A, t(6) = 2.3, p = 0.06) when compared with no-stress runs. Further analyses revealed that SCL during run 2 was significantly higher than run 1 (t(6) = 2.9, p = 0.03), whereas runs 2 and 3 did not differ (Fig. 3).

Affective ratings. As hypothesized, a significant Valence × Stress interaction emerged (F(1, 14) = 47.72, p < 0.001), with post hoc t-tests revealing that the stress manipulation significantly increased negative and decreased positive affect (ps < 0.001; Fig. 2B). Similarly, subscale ratings of “stressed” (p < 0.05), “anxious” (p < 0.05), were greater during stress and subscale ratings of “happy” (p < 0.05) and “in control” (p = 0.06) were reduced during stress when compared with no-stress conditions (Fig. 4).

RTs. A total of 0.07% of reward trials were removed as outliers as the RT were less than 150 ms or greater than 1000 ms. An additional 0.7% of reward trials were removed as their RTs exceeded three standard deviations from the mean RT.

An Incentive (Reward/No-incentive Cue) × Stress (Stress/No-stress) ANOVA on the RTs revealed a main effect of Incentive (F(1, 14) = 16.41, p < 0.001), with participants responding faster during reward than no-incentive trials (Fig. 2C). No other effects emerged, suggesting that the stress manipulation did not influence RT (p > 0.1).

fMRI results

Three participants had to be excluded due to excessive movement (>3 mm), leaving 15 participants (10 females) for further analyses. Fig. 5 depicts regions with significant main effects of the task (averaged across stress and no-stress runs). Specifically, Fig. 5A shows regions with significant results for the reward vs. no-incentive cue contrast (p < 0.05 Family Wise Error (FWE) cluster-corrected) in red overlaid onto the 2-mm MNI standard brain. Fig. 5B shows regions with significant results for the gain vs. no-change feedback contrast (p < 0.05 FWE cluster-corrected) in yellow overlaid onto the 2-mm MNI standard brain. Consistent with prior fMRI studies using the MID task, brain regions such as the basal ganglia (caudate, putamen, NAc, pallidum), frontal pole and cerebellum were significantly activated during reward vs. no-incentive cue across all

Table 1. Behavioral performance across all four runs

<table>
<thead>
<tr>
<th>Variables</th>
<th>Run 1 (no-stress)</th>
<th>Run 2 (stress)</th>
<th>Run 3 (stress)</th>
<th>Run 4 (no-stress)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reaction times (ms)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Reward</td>
<td>304.03 (8.19)</td>
<td>296.79 (9.18)</td>
<td>295.38 (9.33)</td>
<td>294.59 (9.35)</td>
</tr>
<tr>
<td>Neutral</td>
<td>329.28 (9.69)</td>
<td>314.48 (10.9)</td>
<td>325.99 (14.41)</td>
<td>315.88 (10.44)</td>
</tr>
<tr>
<td>Rewards received</td>
<td>15.5 (1.21)</td>
<td>14.6 (0.8)</td>
<td>12.87 (1.07)</td>
<td>14.07 (0.84)</td>
</tr>
</tbody>
</table>
four runs. The gain vs. no-change feedback contrasts revealed activation in the putamen, insula, visual, orbital and inferior frontal cortices (Knutson et al., 2001; Dillon et al., 2008; Pizzagalli et al., 2009; Treadway et al., 2013).

ROI analyses: Overall effects – All four runs. Contrary to our hypotheses, no significant Phase × Stress interactions were observed between the averaged stress (runs 2 and 3) and no-stress (runs 1 and 4) conditions in the amygdala, caudate, NAc and putamen.

ROI analyses: Effect of acute stressor (run 1 vs. run 2). Left putamen: The Phase (Anticipation/Consumption) × Stress (Stress/No-stress) ANOVA revealed a significant interaction (F(1,14) = 4.71, p = 0.048) in the left putamen. Contrary to our prior study in MDD (Pizzagalli et al., 2009), post hoc t-tests revealed that this interaction was driven mainly by consumption (No-stress > Stress, t(14) = 2.05, p = 0.06), although the test showed only a trend (Fig. 6A). Moreover, during stress, putamen activation was greater during anticipation than consumption (t(14) = 2.80, p = 0.014), while there was no significant difference between these two phases during no-stress.

Left NAc: A significant Phase × Stress interaction (F(1,14) = 5.13, p = 0.040) emerged (Fig. 6B), but follow-up post hoc t-tests were not significant (Anticipation: p > 0.30, Consumption: p > 0.17).

Caudate: An extreme outlier as listed by SPSS was identified in the right caudate (X = 16, Y = 19, Z = 6). Careful inspection of the data revealed that this outlier was not due to motion, registration error, or other

Fig. 2. Skin conductance levels (A), affective ratings (B) and reaction times (C) across stress (averaged runs 2 and 3) and no-stress (averaged runs 1 and 4) runs. Means and SE are shown. * indicate p < 0.05.

Fig. 3. Skin conductance levels across all four runs. Means and SE are shown. * indicate p < 0.05.
sources of artifact, thus the values for this participant were removed from caudate analyses. A Phase × Stress × ROI ANOVA on the remaining 14 participants revealed a significant three-way interaction ($F(1,13) = 4.41, p = 0.009$). To disentangle the triple interaction, a Phase × Stress ANOVA was run for individual caudate ROIs. Significant Phase × Stress interactions were observed for one right ($X = 16, Y = 19, Z = 6; F(1,13) = 7.62, p = 0.016$) and one left ($X = -20, Y = -25, Z = 20; F(1,13) = 10.26, p = 0.007$) caudate ROIs. For the right caudate, post hoc tests revealed that the interaction was driven by a significant difference during anticipation (No-stress < Stress, $t(13) = -2.46, p = 0.028$; Fig. 6C). On
the other hand, for the left caudate, post hoc tests revealed that the interaction was driven by consumption (No-stress > Stress, $t(13) = 3.77$, $p = 0.002$; Fig. 6D). In addition, the differential effect of stress on phases of reward processing was further evident by a significant increase in BOLD response under stress in both of the caudate ROIs during anticipation when compared with consumption [right caudate: $t(13) = 2.45$, $p = 0.029$; left caudate: $t(13) = 2.49$, $p = 0.027$, Fig. 6C, D].

Amygdala: A paired t-test on mean left and right amygdala parameter estimates during anticipation revealed a significant effect of stress (No-stress < Stress, $p = 0.011$; Fig. 6E).

mPFC: A paired t-test of parameter estimates during consumption revealed no effect of stress in this region ($p > 0.5$).

Whole-brain analyses. An exploratory whole-brain analysis of runs 1 and 2 was also performed to investigate other potential brain regions that were affected by acute stress during anticipation and consumption. No significant effects emerged from this analysis. However, at an uncorrected $p < 0.01$ level, the rostral ACC, inferior gyrus, putamen and superior frontal gyrus had increase activation during stress (run 2) when compared with no-stress (run 1) during anticipation. Similarly during consumption, acute stress blunted activity in the occipital, orbitofrontal cortices, caudate, lingual gyrus, amygdala and thalamus (Table 2).

DISCUSSION

This study investigated the effects of an acute stress manipulation on anticipatory and consummatory phases of reward processing in healthy volunteers using the MID task. Consistent with prior research, the stress manipulation successfully increased negative and decreased positive affect (Bogdan and Pizzagalli, 2006) but did not modulate MID performance, including RT and the amount of reward feedback received. Overall, when considering the entire dataset, stress did not have an effect on brain activation in a priori defined ROIs. However, when comparing the acute effect of stress (runs 1 vs. 2), differential effects emerged in striatal regions and the amygdala depending on the phase of reward processing. Importantly, significant Phase (Anticipation/Consumption) $\times$ Stress (Stress/No-stress) interactions were observed in these regions.
interaction emerged in these regions, with stress increasing activation in the amygdala and right caudate during anticipation, while decreasing responsiveness in the left caudate and putamen (trend) during consumption. Further supporting this differential effect of stress, BOLD responses in the putamen and bilateral caudate during stress was significantly higher during anticipation than consumption, while there was no difference under the no-stress condition.

Critically, between-run feedback was purported to reflect performance and thus participants under stress were likely motivated to improve performance, which might explain the increased striatal (caudate) activation during anticipation. However, just mere seconds later, participants showed decreased striatal responsiveness to monetary gains. These findings indicate that stress might potentiate incentive motivation (‘wanting’) in situations in which participants perceive control (a possible correlate of active coping behavior) but blunt hedonic capacity (‘liking’). A unique feature of the current results is that dissociable phases of reward processing were affected by the same acute stressor in opposite ways.

### Stress and reward regions

Consistent with our results, animal and human studies have shown that acute stressors increase motivation and approach behaviors (Cabib and Puglisi-Allegra, 1996; Lupien et al., 2007) but blunt ‘liking’ toward positive stimuli (Anisman and Matheson, 2005; Bogdan and Pizzagalli, 2006; Berghorst et al., 2013). Specifically, human studies have described stress-induced increases in performance in eye blink conditioning and visual spatial navigation (Duncko et al., 2007) and other associative learning paradigms (Zorawski et al., 2005; Jackson et al., 2006), especially for emotionally arousing stimuli (Roizzendaal et al., 2009). This might be due to increased attention and memory toward positive stimuli (Lupien et al., 2009). On a neural level, anticipation and cue-triggered wanting have been linked to striatal function (Schott et al., 2008; Berridge et al., 2009). Accordingly, the current findings of stress-induced striatal activation (specifically in the caudate) may reflect increased attention/motivation toward rewarding stimuli due to the goal of improving performance (obtain more rewards and avoid penalties).

Similarly, prior studies have shown that both acute and chronic stress can reduce reward responsiveness. One of the earliest human studies on this topic found that real-life acute stressors, including military training and final examinations, reduced self-reported pleasure and positive affect in two separate samples (Berenbaum and Connelly, 1993). We and others have extended these findings to laboratory settings, in which acute stress was found to blunt reward responsiveness, specifically the ability to modulate behavior as a function of rewards (Bogdan and Pizzagalli, 2006; see Bogdan et al., 2011 and Liu et al., 2011, for independent replications). In recent fMRI studies, acute stress reduced putamen and caudate activation to both primary (Born et al., 2010) and monetary (Porcelli et al., 2012) rewards. Decreased sensitivity to rewards may have important implications, particularly in light of data suggesting that an increase in life stress and decrease in striatal activation to rewards predicted low levels of positive affect on a depression scale (Nikolova et al., 2012). In this context, it is interesting to note that in our healthy volunteers, only the stress-induced reduction in striatal reactivity to rewards mirrored the neural profile of MDD patients tested with the MID at baseline (no-stress) condition (Pizzagalli et al., 2009). When interpreted in the context of prior findings, the current findings are consistent with the assumption that stress-induced anhedonic behavior might explain the robust link between depression and stress (Anisman and Matheson, 2005; Bogdan and Pizzagalli, 2006; Bogdan et al., 2011; Berghorst et al., 2013). In sum, our results of increased ‘wanting’ (caudate) but reduced ‘liking’ (putamen and caudate) as shown by increased and decreased striatal activation to acute stress, respectively, are consistent with yet critically extend the existing literature.

### Stress and limbic regions

The amygdala has been strongly associated with both stress and approach behaviors, and plays an important role in response to threat. Specifically, the amygdala has been linked to the stress response and has been shown to be activated in response to emotional stimuli, particularly in the context of threat or danger. This activation in the amygdala is thought to be important for the processing of fear and other negative emotions, as well as for the integration of these emotions with other brain regions involved in cognitive and motor functions. The amygdala is also involved in the regulation of autonomic responses, such as heart rate and blood pressure, which are often increased in response to stress. Overall, the amygdala plays a critical role in the stress response and is thought to be a key component of the brain's stress systems.
role in relaying emotional salience information to the rest of the brain to prepare for action (LeDoux, 2000; Phillips et al., 2003; Veer et al., 2011). Consistent with our hypothesis, we observed that the stressor had an effect on the anticipatory phase of reward processing. This fits the evidence that has implicated the amygdala in appetitively motivated learning (Gottfried et al., 2003; Knapska, 2006). Specifically, the amygdala has been shown to have a role in translating Pavlovian associations into appetitive and aversive motivation (Knapska, 2006). In particular, the central amygdala is crucial for reward-related DA release, specifically in the NAc, which is important for the generation of ‘approach’ behaviors (Mahler and Berridge, 2011). When seen in the context of extant literature, the current evidence of increased amygdala activation during reward anticipation might thus reflect increased appetitive motivation to undertake an action to cope with the stressor, acquire rewards and avoid penalties.

Lesion studies suggest that the mPFC has an inhibitory effect on the amygdala (Morgan and LeDoux, 1999; Phelps et al., 2004; Baumann and Turpin, 2010). Recently, Veer and colleagues reported that the resting state functional connectivity between the amygdala and mPFC increased during the recovery stage after an acute stress manipulation, consistent with the notion that this circuitry might be important for protecting the individual from developing stress-related disorders (Veer et al., 2011). Unlike prior preclinical (McEwen, 2007) and human (Ossewaarde et al., 2011; Porcelli et al., 2012; Treadway et al., 2013) studies highlighting that mPFC activation is modulated by stress, no modulation was observed in the current study, possibly due to the small sample size.

**Candidate neurobiological underpinnings of the dissociable effects of stress on reward processing**

The DA system has long been associated with stress. Animal studies indicate that stress modulates mesolimbic DA transmission in the striatum (Serrano et al., 1989; Chrupusta et al., 2002) and prefrontal cortex (Adler et al., 2000), but its effects depend on the characteristics of the stressor (Suridjan et al., 2012). More specifically, while acute and controllable/escapable stress triggers enhanced DA in the striatum, chronic and uncontrollable/inescapable exposure to the same stress reduces DA release (Abercrombie et al., 1989; Cabib and Puglisi-Allegre, 1996; Lucas et al., 2007).

Our findings support this dual role of DA, often labeled as the drive-reward paradox (Wise, 2013). It is possible that the pattern we observed in the current study may be due to the fact that stress has a differential effect on the activity states of DA neurons. Stress-induced DA release has been observed in humans in response to various stressors, including painful stimuli (Scott et al., 2006), metabolic stress (Adler et al., 2000), examination stress (Rauste-von Wright and Frankenhaeuser, 1989), psychosocial stress (Pruessner et al., 2008; Saal et al., 2003) and physical activity (Kendler et al., 1983). This stress-induced extracellular DA release is potentially due to the slow changes in the tonic firing of DA neurons, which might in turn subserve changes in motivational state. For example, animals that have undergone extinction training can be provoked to renew food or drug seeking by a mild foot shock stress that elevates extracellular DA levels (Liu and Weiss, 2003; Hajnal et al., 2004). Similarly, PET and dopaminergic manipulation studies have reported that enhanced DA transmission in the mesolimbic system promotes motivated behavior (‘wanting’) and responding to obtain rewards (Leyton et al., 2002; Berridge, 2012). This DA release is thought to be modulated by the CRF receptors, a neuropeptide released in response to acute stress. However, chronic stress abolishes the ability of the CRF to modulate DA levels, which might be a possible contributor to the development of depression. In contrast to these findings, stress-induced increases in tonic DA might blunt reward responsiveness through reduction of phasic DA firing via autoreceptor activation (Grace, 1991). In this context, it is important to consider that DA neurons fire phasically when unexpected rewards or reward predictors are detected (Schultz, 1999) and that single low doses of DA agonists – hypothesized to reduce phasic DA firing through autoreceptor activation – were found to reduce reward responsiveness and learning in healthy volunteers (Frank and O’Reilly, 2006; Pizzagalli et al., 2008a). Therefore, reduced brain activation to reward outcomes observed in this study may be due to stress-induced increases in tonic DA levels inhibiting the phasic firing of DA (Pani et al., 2000; Bogdan and Pizzagalli, 2006; Berghorst et al., 2013).

While this is one possible explanation, it is possible that stress modulates the DA system via different receptors (D1 and D2) that are associated with direct and indirect striatal pathways or that the same DA neurons subserve different states by using different neuronal signaling patterns (Wise, 2013). Critically, as our study did not include any DA pharmacological manipulation, conclusive statements cannot be made regarding the putative neurotransmitter systems involved. Future studies utilizing pharmacological manipulations will help us understand these differential effects of stress.

**Limitations**

Three main study limitations deserve mention. First, although the affective responses to the stress manipulation were in line with our hypothesis, loss of physiological data for more than 50% of the participants limited our ability to confirm the effect of the stress manipulation. However, data from the remaining seven participants showed patterns confirming the effectiveness of the stress manipulation. Second, although findings were consistent with a priori hypotheses on effects of acute stressor, no findings emerged considering all four runs, possibly due to habituation effects, limited statistical power, and/or the use of a mildly aversive stress manipulation. With respect to the latter point, monetary penalties as the ones employed in the current study might not be
particularly aversive, and more potent manipulations (i.e., threat-of-shock) would have triggered more reliable stress responses (Bogdan and Pizzagalli, 2006). A final limitation is that the sample size was small, hence results need to be considered with caution and replications are warranted.

CONCLUSIONS

In spite of these limitations, the current study shows that acute stress has differential effects on striatal regions depending on the phase of reward processing, and replicate prior findings that stress induces anhedonic behavior (Berendam and Connelly, 1993; Bogdan and Pizzagalli, 2006; Berghorst et al., 2013). Of note, the pattern of stress-induced hedonic deficits was similar to the profile we have observed in MDD individuals tested under baseline (no-stress) condition (Pizzagalli et al., 2009). Given that stress is a key vulnerability factor for depression, these results provide important insights toward a better understanding of the etiology of this prevalent and debilitating disorder.

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