Published in final edited form as:

Neuroscience. 2014 April 25; 266: 1–12. doi:10.1016/j.neuroscience.2014.01.058.

Differential Effects of Acute Stress on Anticipatory and Consummatory Phases of Reward Processing

Poornima Kumar^{a,b,*}, Lisa H. Berghorst^c, Lisa D. Nickerson^{b,d}, Sunny J. Dutra^e, Franziska Goer^a, Douglas Greve^f, and Diego A. Pizzagalli^{a,b,d,*}

^aCenter for Depression, Anxiety and Stress Research, McLean Hospital, Belmont, MA, USA

^bDepartment of Psychiatry, Harvard Medical School, MA, USA

^cDepartment of Psychology, Harvard University, Cambridge, MA, USA

^dMcLean Imaging Center, McLean Hospital, Belmont, MA, USA

^eDepartment of Psychology, Yale University, New Haven, CT, USA

^fDepartment of Radiology, Massachusetts General Hospital, Charlestown, MA, USA

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 reward anticipation consistent with non-human findings. Supporting our hypotheses, significant *Phase* (Anticipation/Consumption) x *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.

© 2014 IBRO. Published by Elsevier Ltd. All rights reserved.

*Corresponding Authors: Drs. Poornima Kumar/Diego A. Pizzagalli, Centre for Depression, Anxiety and Stress Research, McLean Hospital, 115 Mill Street, Belmont, MA USA 02478, Telephone: +1 617-855-4244, pkumar@mclean.harvard.edu/dap@mclean.harvard.edu.

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

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.

Keywords

Stress; Basal ganglia; Reward; Anticipation; Consumption; Monetary Incentive Delay

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 (Gold and Chrousos, 2002; Hammen, 2005; Kendler et al., 1999), 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 (Berridge et al., 2009; Dillon et al., 2008; Knutson et al., 2001; Schott et al., 2008).

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; Berghorst et al., 2013; Bogdan and Pizzagalli, 2006). 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 corticotropin-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 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 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 (Berghorst et al., 2013; Bogdan and Pizzagalli, 2006) 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 fMRI studies have examined stress-induced effects on reward processing (Born et al., 2010; Osseward 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 task, an acute stress manipulation and functional magnetic resonance imaging (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, nucleus accumbens (NAc)), indexing increased “cue-triggered motivation” and consistent with findings in non-human animals exposed to acute mild stressors (Lemos et al., 2012; Cabib and Puglisi-Allegra, 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 (Knuston et al., 2001) and subjective perceived stress (Treadway et al., 2013), we hypothesized that acute stress would decrease mPFC activation during the consummatory phase.

2 EXPERIMENTAL PROCEDURES

2.1 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 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.

2.2 Procedure

Participants underwent a single imaging session during which they performed a monetary incentive delay task (Knuston et al., 2000; described in section 2.3). 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. 1A). The stress manipulation involved negative performance evaluations (described in section 2.4). All reaction times 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.

2.3 Monetary Incentive Delay Task

The monetary incentive delay 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 “0\$” (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 reaction times 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’ reaction times fell outside of the 66th percentile window or with no-incentive trials. The task included 4 runs of 33 trials (~ 9 minutes 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.

2.4 Stress Manipulation

In line with manipulations employed in previous studies (Berghorst et al., 2013; Bogdan & Pizzagalli, 2006), 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 6 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.

2.5 Imaging Data Acquisition

A 1.5-T Symphony/Sonata scanner (Siemens Medical Systems, Iselin, N.J.) was used to acquire the MRI data. High-resolution structural data were acquired using a T1-weighted magnetization-prepared rapid acquisition with gradient echo (MPRAGE) imaging sequence with the following acquisition parameters: repetition time = 2730 ms; echo time = 3.39 ms; field of view = 256 mm; voxel dimensions = $1 \times 1 \times 1.33$ mm; 128 slices). Functional MRI data were acquired using a gradient echo T2*-weighted echoplanar imaging sequence with tilted slice acquisition and z-shimming to recover signal in regions affected by susceptibility artifacts (Deichmann et al., 2003; Dillon et al., 2008) with the following acquisition parameters: repetition time = 2500 ms; echo time = 35 ms; field of view = 200 mm; voxel dimensions = $3.125 \times 3.125 \times 3$ mm; 35 interleaved slices.

2.6 Behavioral Data Analyses

2.6.1 Skin Conductance Level—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.

2.6.2 Reaction time—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), reaction times 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 2×2 repeated measures ANOVA with *Incentive* (Reward/No-Incentive) $\times$ *Stress* (Stress/No-Stress) as factors was run to assess the effects of stress on incentive type.

2.6.3 Affective ratings—Positive and negative affect were calculated by averaging the scores obtained on 5 positive (in control, alert, energetic, relaxed and happy) and 7 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 2×2 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.

2.7 fMRI Analyses

Functional MRI data were analyzed using FMRIB’s FSL 4.1.5 (Smith et al., 2004; <http://fsl.fmrib.ox.ac.uk/fsl/fslwiki/>). Data pre-processing included: motion correction using MCFLIRT (Jenkinson et al., 2002), slice timing correction, removal of non-brain structures using BET (Smith et al., 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 MNI standard space template was done using 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 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). Regions of interest (ROIs) included the left putamen ($x = -29, y = -13, z = -5$), left nucleus accumbens ($x = -8, y = -11, z = -15$), 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 10mm 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 nucleus accumbens 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 2-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 carryover 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.

3 RESULTS

3.1 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 feedbacks 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).

3.1.1. Skin conductance levels (SCLs)—Unfortunately, due to technical difficulties, hardware malfunction and general recommendation ($2 - 20 \mu S$) (Dawson et al., 2007), peripheral physiological data were unusable for 8 subjects. An exploratory analysis was conducted on the tonic SCL from the remaining 7 participants. Overall, stress showed a trend towards 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).

3.1.2 Affective Ratings—As hypothesized, a significant *Valence* $\times$ *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).

3.1.3 Reaction times (RT)—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 reaction times exceeded three standard deviations from the mean RT.

An *Incentive* (Reward/No-incentive Cue) $\times$ *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 ($p > 0.1$).

3.2 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 ($p < 0.05$ 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 four runs. The gain vs. no-change feedback contrasts revealed activation in the putamen, insula, visual, orbital and inferior frontal cortices (Dillon et al., 2008; Knuston et al., 2001; Pizzagalli et al., 2009; Treadway et al., 2013).

3.2.1 ROI Analyses: Overall Effects – All four runs—Contrary to our hypotheses, no significant *Phase* $\times$ *Stress* interactions were observed between the averaged stress (runs 2 and 3) and no-stress (runs 1 and 4) conditions in the amygdala, caudate, nucleus accumbens and putamen.

3.2.2 ROI Analyses: Effect of Acute Stressor (Run 1 vs. Run 2)

Left Putamen: The *Phase* (Anticipation/Consumption) x *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 ($t(14) = 2.80$, $p = 0.014$), whilst there was no significant difference between these two phases during no-stress.

Left Nucleus Accumbens (NAc): A significant *Phase* x *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 sources of artifact, thus the values for this participant were removed from caudate analyses. A *Phase* x *Stress* x *ROI* ANOVA on the remaining 14 participants revealed a significant 3-way interaction ($F(1,13) = 4.41$, $p = 0.009$). To disentangle the triple interaction, a *Phase* x *Stress* ANOVA was run for individual caudate ROIs. Significant *Phase* x *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, 6D].

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).

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

3.2.3 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 (Run2) when compared with no-stress (Run1) during anticipation. Similarly during consumption, acute stress blunted activity in the occipital, orbitofrontal cortices, caudate, lingual gyrus, amygdala and thalamus (Table 2).

4 DISCUSSION

This study investigated the effects of an acute stress manipulation on anticipatory and consummatory phases of reward processing in healthy volunteers using the monetary incentive delay task. Consistent with prior research, the stress manipulation successfully increased negative and decreased positive affect (Bogdan & Pizzagalli, 2006) but did not modulate MID performance, including reaction time and the amount of reward feedbacks 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) x *Stress* (Stress/No-stress) 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, whilst 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.

4.1 Stress and reward regions

Consistent with our results, animal and human studies have shown that acute stressors increase motivation and approach behaviors (Cabib & Puglisi-Allegra, 1996; Lupien et al., 2007) but blunt 'liking' towards positive stimuli (Anisman & Matheson, 2005; Berghorst et al., 2013; Bogdan & Pizzagalli, 2006). 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 (Jackson et al., 2006; Zorawski et al., 2005), especially for emotionally arousing stimuli (Roosendaal et al., 2009). This might be due to increased attention and memory towards positive stimuli (Lupien et al., 2009). On a neural level, anticipation and cue-triggered wanting have been linked to striatal function (Berridge et al., 2009; Schott et al., 2008). Accordingly, the current findings of stress-induced striatal activation (specifically in the caudate) may reflect increased attention/motivation towards 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 & 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 & 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 & Matheson, 2005; Berghorst et al., 2013; Bogdan & Pizzagalli, 2006, Bogdan et al., 2011). 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.

4.2 Stress and Limbic regions

The amygdala has been strongly associated with both stress and approach behaviors, and plays an important 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 et al., 2006). Specifically, the amygdala has been shown to have a role in translating Pavlovian associations into appetitive and aversive motivation (Knapska et al., 2006). In particular, the central amygdala is crucial for reward-related DA release, specifically in the nucleus accumbens, which is important for the generation of 'approach' behaviors (Mahler & 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 (Baumann & Turpin, 2010; Morgan & LeDoux, 1999; Phelps et al., 2004). 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.

4.3 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 (Chrapusta et al., 2002; Serrano et al., 1989) 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 & Puglisi-Allegra, 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 & Frankenhaeuser, 1989), 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 (Hajnal et al., 2004; Liu & Weiss, 2003). 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 (Berridge, 2012; Leyton et al., 2002). 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 & 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 (Berghorst et al., 2013; Bogdan and Pizzagalli, 2006; Pani et al., 2000).

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.

4.4 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 7 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 & Pizzagalli, 2006). A final limitation is that the sample size was small, hence results need to be considered with caution and replications are warranted.

5. 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 (Berenbaum & Connelly, 1993; Berghorst et al., 2013; Bogdan & Pizzagalli, 2006). 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 towards a better understanding of the etiology of this prevalent and debilitating disorder.

Acknowledgments

This work was supported by NIMH R01 grant to DAP (R01 MH068376). PK was supported by The John and Charlene Madison Cassidy Fellowship in Translational Neuroscience through McLean Hospital. LB was supported in part by the Sackler Fellowship in Psychobiology and an NRSA Predoctoral Training Grant in Advanced Multimodal Neuroimaging. Over the past three years, Dr. Pizzagalli has received honoraria/consulting fees from Advanced Neurotechnology North America, AstraZeneca, Ono Pharma USA, Pfizer, Servier, and Shire for studies unrelated to this project. In addition, authors would like to thank Dr. Daniel G. Dillon for his invaluable comments on this manuscript.

References

- Abercrombie ED, Keefe KA, DiFrischia DS, Zigmond MJ. Differential effect of stress on in vivo dopamine release in striatum, nucleus accumbens, and medial frontal cortex. *J Neurochem.* 1989; 52:1655–1658. [PubMed: 2709017]
- Adler CM, Elman I, Weisenfeld N, Kestler L, Pickar D, Breier A. Effects of acute metabolic stress on striatal dopamine release in healthy volunteers. *Neuropsychopharmacology.* 2000; 22:545–550. [PubMed: 10731630]
- Anisman H, Matheson K. Stress, depression, and anhedonia: Caveats concerning animal models. *Neurosci Biobehav Rev.* 2005; 29:525–546. [PubMed: 15925696]
- Baumann N, Turpin JC. Neurochemistry of stress. An overview. *Neurochem Res.* 2010; 35:1875–1879. [PubMed: 20978849]
- Berenbaum H, Connelly J. The effect of stress on hedonic capacity. *J Abnorm Psychol.* 1993; 102:474–481. [PubMed: 8408960]

- Berghorst LH, Bogdan R, Frank MJ, Pizzagalli DA. Acute stress selectively reduces reward sensitivity. *Front Hum Neurosci.* 2013; 7 (133):1–12. [PubMed: 23355817]
- Berridge KC, Robinson TE. What is the role of dopamine in reward: hedonic impact, reward learning, or incentive salience? *Brain Res Rev.* 1998; 28:309–369. [PubMed: 9858756]
- Berridge KC, Robinson TE, Aldridge JW. Dissecting components of reward: ‘liking’, ‘wanting’, and learning. *Curr Opin Pharmacol.* 2009; 9:65–73. [PubMed: 19162544]
- Berridge KC. From prediction error to incentive salience: mesolimbic computation of reward motivation. *Eur J Neurosci.* 2012; 35:1124–1143. [PubMed: 22487042]
- Bogdan R, Pizzagalli DA. Acute stress reduces reward responsiveness: Implications for Depression. *Biol Psychiatry.* 2006; 60:1147–1154. [PubMed: 16806107]
- Bogdan R, Santesso DL, Fagerness J, Perlis RH, Pizzagalli DA. Corticotropin-releasing hormone receptor type 1 (CRHR1) genetic variation and stress interact to influence reward learning. *J Neurosci.* 2011; 31:13246–13254. [PubMed: 21917807]
- Born JM, Lemmens SGT, Rutters F, Nieuwenhuizen AG, Formisano E, Goebel R, Westerterp-Plantenga MS. Acute stress and food-related reward activation in the brain during food choice during eating in the absence of hunger. *Int J Obes (Lond).* 2010; 34:172–181. [PubMed: 19844211]
- Cabib S, Puglisi-Allegra S. Stress, depression and the mesolimbic dopamine system. *Psychopharmacology.* 1996; 128:331–342. [PubMed: 8986003]
- Cabib S, Puglisi-Allegra S. The mesoaccumbens dopamine in coping with stress. *Neurosci Biobehav Rev.* 2012; 36 (1):79–89. [PubMed: 21565217]
- Chrapusta SJ, Wyatt RJ, Masserano JM. Effects of single and repeated footshock on dopamine release and metabolism in the brains of Fischer rats. *J Neurochem.* 2002; 68:2024–2031. [PubMed: 9109528]
- Dawson, ME.; Schell, AM.; Filion, DL. The Electrodermal System. In: Cacioppo, J.; Tassinary, LG.; Berntson, GG., editors. *Handbook of Psychophysiology.* 3. Cambridge: Cambridge University Press; 2007. p. 159-181.
- Deichmann R, Gottfried JA, Hutton C, Turner R. Optimized EPI for fMRI studies of the orbitofrontal cortex. *NeuroImage.* 2003; 19:430–441. [PubMed: 12814592]
- Dillon DG, Holmes AJ, Jahn AL, Bogdan R, Wald LL, Pizzagalli DA. Dissociation of neural regions associated with anticipatory versus consummatory phases of incentive processing. *Psychophysiology.* 2008; 45:36–49. [PubMed: 17850241]
- Duncko R, Cornwell B, Cui L, Merikangas KR, Grillon C. Acute exposure to stress improves performance in trace eyeblink conditioning and spatial learning tasks in healthy men. *Learn Mem.* 2007; 14:329–335. [PubMed: 17522023]
- Dunlop BW, Nemeroff CB. The role of dopamine in the pathophysiology of depression. *Arch Gen Psychiatry.* 2007; 64:327–337. [PubMed: 17339521]
- First, MB.; Spitzer, RL.; Gibbon, M.; Williams, JBW. *Structured Clinical Interview for DSM-IV-TR Axis I Disorders, Research Version, Patient Edition (SCID-I/P).* New York: New York State Psychiatric Institute, Biometrics Research; 2002.
- Frank MJ, O'Reilly RC. A mechanistic account of striatal dopamine function in human cognition: psychopharmacological studies with cabergoline and haloperidol. *Behav Neurosci.* 2006; 120:497–517. [PubMed: 16768602]
- Gradin VB, Kumar P, Waiter G, Ahearn T, Stickle C, Milders M, Reid I, Hall J, Steele JD. Expected value and prediction error abnormalities in depression and schizophrenia. *Brain.* 2011; 134 (Pt 6): 1751–1764. [PubMed: 21482548]
- Gold PW, Chrousos GP. Organization of the stress system and its dysregulation in melancholic and atypical depression: high vs low CRH/NE states. *Mol Psychiatry.* 2002; 7:254–275. [PubMed: 11920153]
- Gottfried JA, O'Doherty J, Dolan RJ. Encoding predictive reward value in human amygdala and orbitofrontal cortex. *Science.* 2003; 301:1104–1107. [PubMed: 12934011]
- Grace AA. Phasic versus tonic dopamine release and the modulation of dopamine system responsivity: a hypothesis for the etiology of schizophrenia. *Neuroscience.* 1991; 41:1–24. [PubMed: 1676137]

- Hajnal A, Smith GP, Norgren R. Oral sucrose stimulation increases accumbens dopamine in the rat. *Am J Physiol Regul Integr Comp Physiol*. 2004; 286:R31–7. [PubMed: 12933362]
- Hammen C. Stress and depression. *Annu Rev Clin Psychol*. 2005; 1:293–319. [PubMed: 17716090]
- Horvitz JC. Dopamine gating of glutamatergic sensorimotor and incentive motivational input signals to the striatum. *Behav Brain Res*. 2002; 137:65–74. [PubMed: 12445716]
- Jackson ED, Payne JD, Nadel L, Jacobs WJ. Stress differentially modulates fear conditioning in healthy men and women. *Biol Psychiatry*. 2006; 59:516–522. [PubMed: 16213468]
- Jenkinson J, Bannister P, Brady M, Smith S. Improved optimisation for the robust and accurate linear registration and motion correction of brain images. *NeuroImage*. 2002; 17(2):825–841. [PubMed: 12377157]
- Keedwell PA, Andrew C, Williams SCR, Brammer MJ, Phillips ML. The neural correlates of anhedonia in major depressive disorder. *Biol Psychiatry*. 2005; 58:843–853. [PubMed: 16043128]
- Kendler KS, Mohs RC, Davis KL. The effects of diet and physical activity on plasma homovanillic acid in normal human subjects. *Psychiatry Res*. 1983; 8:215–223. [PubMed: 6574541]
- Kendler KS, Karkowski LM, Prescott CA. Causal relationship between stressful life events and the onset of major depression. *Am J Psychiatry*. 1999; 156:837–841. [PubMed: 10360120]
- Knapaska E. Differential involvement of the central amygdala in appetitive versus aversive learning. *Learn Mem*. 2006; 13:192–200. [PubMed: 16547163]
- Knutson B, Westdorp A, Kaiser E, Hommer D. fMRI visualization of brain activity during a monetary incentive delay task. *NeuroImage*. 2000; 12:20–27. [PubMed: 10875899]
- Knutson B, Adams CM, Fong GW, Hommer D. Anticipation of increasing monetary reward selectively recruits nucleus accumbens. *J Neurosci*. 2001; 21:RC159. [PubMed: 11459880]
- Knutson B, Bhanji JP, Cooney RE, Atlas LY, Gotlib IH. Neural responses to monetary incentives in major depression. *Biol Psychiatry*. 2008; 63:686–692. [PubMed: 17916330]
- Kumar P, Waiter G, Ahearn T, Milders M, Reid I, Steele JD. Abnormal temporal difference reward-learning signals in major depression. *Brain*. 2008; 131:2084–2093. [PubMed: 18579575]
- LeDoux JE. Emotion circuits in the brain. *Annu Rev Neurosci*. 2000; 23:155–184. [PubMed: 10845062]
- Lemos JC, Wanat MJ, Smith JS, Reyes BAS, Hollon NG, Van Bockstaele EJ, Chavkin C, Phillips PEM. Sever stress switches CRF action in the nucleus accumbens from appetitive to aversive. *Nature*. 2012; 490:402–407. [PubMed: 22992525]
- Leyton M, Boileau I, Benkelfat C, Diksic M, Baker G, Dagher A. Amphetamine-induced increases in extracellular dopamine, drug wanting, and novelty seeking: a PET/[11C] raclopride study in healthy men. *Neuropsychopharmacology*. 2002; 27:1027–1035. [PubMed: 12464459]
- Lighthall NR, Gorlick MA, Schoeke A, Frank MJ, Mather M. Stress modulates reinforcement learning in younger and older adults. *Psychol Aging*. 2013; 28:35–46. [PubMed: 22946523]
- Liu WH, Chan RC, Wang LZ, Huang J, Cheung EFC, Gong QY, Gollan JK. Deficits in sustaining reward responses in subsyndromal and syndromal major depression. *Prog Neuropsychopharmacol Biol Psychiatry*. 2011; 35:1045–1052. [PubMed: 21371518]
- Liu X, Weiss F. Stimulus conditioned to foot-shock stress reinstates alcohol-seeking behavior in an animal model of relapse. *Psychopharmacology*. 2003; 168:184–191. [PubMed: 12447607]
- Lucas LR, Wang CJ, McCall TJ, McEwen BS. Effects of immobilization stress on neurochemical markers in the motivational system of the male rat. *Brain Res*. 2007; 1155:108–115. [PubMed: 17511973]
- Lupien SJ, Maheu F, Tu M, Fiocco A, Schramek TE. The effects of stress and stress hormones on human cognition: Implications for the field of brain and cognition. *Brain Cogn*. 2007; 65:209–237. [PubMed: 17466428]
- Lupien SJ, McEwen BS, Gunnar MR, Heim C. Effects of stress throughout the lifespan on the brain, behaviour and cognition. *Nat Rev Neurosci*. 2009; 10:434–445. [PubMed: 19401723]
- Mahler SV, Berridge KC. What and when to “want?” Amygdala-based focusing of incentive salience upon sugar and sex. *Psychopharmacology*. 2011; 221:407–426. [PubMed: 22167254]
- McCabe SB, Gotlib IH. Selective attention and clinical depression: performance on a deployment-of-attention task. *J Abnorm Psychology*. 1995; 104:241–245.

- McEwen BS. Physiology and neurobiology of stress and adaptation: Central role of the brain. *Physiol Rev.* 2007; 87:873–904. [PubMed: 17615391]
- Morgan MA, LeDoux JE. Contribution of ventrolateral prefrontal cortex to the acquisition and extinction of conditioned fear in rats. *Neurobiol Learn Mem.* 1999; 72:244–251. [PubMed: 10536101]
- Nikolova YS, Bogdan R, Brigidi BD, Hariri AR. Ventral striatum reactivity to reward and recent life stress interact to predict positive affect. *Biol Psychiatry.* 2012; 72 (2):157– 63. [PubMed: 22534456]
- Ossewaarde L, Qin S, Van Marle HJF, van Wingen GA, Fernández G, Hermans EJ. Stress-induced reduction in reward-related prefrontal cortex function. *NeuroImage.* 2011; 55:345–352. [PubMed: 21126593]
- Pani L, Porcella A, Gessa GL. The role of stress in the pathophysiology of the dopaminergic system. *Mol Psychiatry.* 2000; 5:14–21. [PubMed: 10673764]
- Phelps EA, Delgado MR, Nearing KI, LeDoux JE. Extinction learning in humans: role of the amygdala and vmPFC. *Neuron.* 2004; 43:897–905. [PubMed: 15363399]
- Phillips ML, Drevets WC, Rauch SL, Lane R. Neurobiology of emotion perception I: The neural basis of normal emotion perception. *Biol Psychiatry.* 2003; 54:504–514. [PubMed: 12946879]
- Pizzagalli DA, Evins AE, Schetter EC, Frank MJ, Pajtas PE, Santesso DL, Culhane M. Single dose of a dopamine agonist impairs reinforcement learning in humans: Behavioral evidence from a laboratory-based measure of reward responsiveness. *Psychopharmacology.* 2008a; 196:221–232. [PubMed: 17909750]
- Pizzagalli DA, Iosifescu DV, Hallett LA, Ratner KG, Fava M. Reduced hedonic capacity in major depressive disorder: Evidence from a probabilistic reward task. *J Psychiatry Res.* 2008b; 43 (1): 76–87.
- Pizzagalli DA, Holmes AJ, Dillon DG, Goetz EL, Birk JL, Bogdan R, Dougherty DD, Iosifescu DV, Rauch SL, Fava M. Reduced caudate and nucleus accumbens response to rewards in unmedicated individuals with major depressive disorder. *Am J Psychiatry.* 2009; 166:702–710. [PubMed: 19411368]
- Porcelli AJ, Lewis AH, Delgado MR. Acute stress influences neural circuits of reward processing. *Front Neurosci.* 2012; 6:157. [PubMed: 23125822]
- Pruessner JC, Dedovic K, Khalili-Mahani N, Engert V, Pruessner M, Buss C, Renwick R, Dagher A, Meaney MJ, Lupien S. Deactivation of the limbic system during acute psychosocial stress: Evidence from positron emission tomography and functional magnetic resonance imaging studies. *Biol Psychiatry.* 2008; 63:234–240. [PubMed: 17686466]
- Rauste-von Wright M, Frankenhaeuser M. Females' emotionality as reflected in the excretion of the dopamine metabolite HVA during mental stress. *Psychol Rep.* 1989; 64:856–858. [PubMed: 2748779]
- Robinson OJ, Overstreet C, Charney DR, Vytal K, Grillon C. Stress increases aversive prediction error signal in the ventral striatum. *PNAS.* 2013; 110:4129–4133. [PubMed: 23401511]
- Roozendaal B, McEwen BS, Chattarji S. Stress, memory and the amygdala. *Nat Rev Neurosci.* 2009; 10:423–433. [PubMed: 19469026]
- Saal D, Dong Y, Bonci A, Malenka RC. Drugs of abuse and stress trigger a common synaptic adaptation in dopamine neurons. *Neuron.* 2003; 37:577–582. [PubMed: 12597856]
- Santesso DL, Dillon DG, Birk JL, Holmes AJ, Goetz E, Bogdan R, Pizzagalli DA. Individual differences in reinforcement learning: Behavioral, electrophysiological, and neuroimaging correlates. *NeuroImage.* 2008; 42:807–816. [PubMed: 18595740]
- Schott BH, Minuzzi L, Krebs RM, Elmenhorst D, Lang M, Winz OH, Seidenbecher CI, Coenen HH, Heinze HJ, Zilles K, Duzel E, Bauer A. Mesolimbic functional magnetic resonance imaging activations during reward anticipation correlate with reward-related ventral striatal dopamine release. *J Neurosci.* 2008; 28:14311–14319. [PubMed: 19109512]
- Schultz W. The reward signal of midbrain dopamine neurons. *Physiology.* 1999; 14:249–255.
- Schultz W. Getting formal with dopamine and reward. *Neuron.* 2002; 36:241–263. [PubMed: 12383780]

- Scott DJ, Heitzeg MM, Koeppe RA, Stohler CS, Zubieta JK. Variations in the human pain stress experience mediated by ventral and dorsal basal ganglia dopamine activity. *J Neurosci*. 2006; 26:10789–10795. [PubMed: 17050717]
- Serrano A, D'Angio M, Scatton B. NMDA antagonists block restraint-induced increase in extracellular DOPAC in rat nucleus accumbens. *Eur J Pharmacol*. 1989; 162:157–166. [PubMed: 2566493]
- Smith SM. Fast Robust Automated Brain Extraction. *Hum Brain Mapp*. 2002; 17(3):143–155. [PubMed: 12391568]
- Smith SM, Jenkinson M, Woolrich MW, Beckmann CF, Behrens TEJ, Johansen-Berg H, Bannister PR, De Luca M, Drobnjak I, Flitney DE, Niazy R, Saunders J, Vickers J, Zhang Y, De Stefano N, Brady JM, Matthews PM. Advances in functional and structural MR image analysis and implementation as FSL. *NeuroImage*. 2004; 23(S1):208–19.
- Suridjan I, Boileau I, Bagby M, Rusjan PM, Wilson AA, Houle S, Mizrahi R. *J Psychiatry Res*. 2012; 46:890–897.
- Tennant C. Life events, stress and depression: a review of recent findings. *Aust N Z J Psychiatry*. 2002; 36:173–182. [PubMed: 11982537]
- Treadway MT, Buckholz JW, Zald DH. Perceived stress predicts altered reward and loss feedback processing in medial prefrontal cortex. *Front Hum Neurosci*. 2013; 7:180. [PubMed: 23730277]
- Tremblay LK, Naranjo CA, Cardenas L, Herrmann N, Busto UE. Probing brain reward system function in major depressive disorder: altered response to dextroamphetamine. *Arch Gen Psychiatry*. 2002; 59:409–416. [PubMed: 11982444]
- Tye KM, Mirzabekov JJ, Warden MR, Ferenczi EA, Tsai HC, Finkelstein J, Kim SY, Adhikari A, Thompson KR, Andalman AS, Gunaydin LA, Witten IB, Deisseroth K. Dopamine neurons modulate neural encoding and expression of depression-related behaviour. *Nature*. 2013; 493(7433):537–41. [PubMed: 23235822]
- Veer IM, Oei NYL, Spinhoven P, van Buchem MA, Elzinga BM, Rombouts SARB. Beyond acute social stress: increased functional connectivity between amygdala and cortical midline structures. *NeuroImage*. 2011; 57:1534–1541. [PubMed: 21664280]
- Wiborg O. Chronic mild stress for modeling anhedonia. *Cell Tissue Res*. 2013; 1007/s00441-013-1664-0
- Wise RA. Dopamine, learning and motivation. *Nat Rev Neurosci*. 2004; 5:483–494. [PubMed: 15152198]
- Wise RA. Dual roles of dopamine in food and drug seeking: The drive-reward paradox. *Biol Psychiatry*. 2013; 73:819–826. [PubMed: 23044182]
- Zacharko RM, Bowers WJ, Kokkinidis L, Anisman H. Region-specific reductions of intracranial self-stimulation after uncontrollable stress: possible effects on reward processes. *Behav Brain Res*. 1983; 9:129–141. [PubMed: 6603854]
- Zorawski M, Cook CA, Kuhn CM, LaBar KS. Sex, stress, and fear: individual differences in conditioned learning. *Cogn Affect Behav Neurosci*. 2005; 5:191–201. [PubMed: 16180625]

Highlights

- Reward processing can be parsed into anticipatory and consummatory phases
- Stress differentially affected striatal activation during distinct reward phases
- Stress-induced striatal blunting to rewards mirrored patterns seen in depression

Fig. 1.
Study procedure (A) and Monetary Incentive Delay task design (B)

Fig. 2. Skin conductance levels (A), Affective ratings (B) and reaction times (C) across stress (averaged runs 2 & 3) and no-stress (averaged runs 1 & 4) runs. Means and SE are shown.

Fig. 3.
Skin Conductance Levels across all four runs. Means and SE are shown.

Fig. 4. Subscale ratings across all four runs. Mean ratings for *Stressed* (A), *Anxious* (B), *Happy* (C), and *In Control* (D) are shown. Mean and SE are shown.

Fig. 5. Main effect of task during anticipation (A) and consumption (B). Fig. 5A shows regions with significant results for the reward vs. no-incentive cue contrast ($p < 0.05$ 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.

Fig. 6. Parameter estimates extracted from functional ROIs during anticipation and consumption in the putamen (A), nucleus accumbens (B), right caudate (C), left caudate (D) and amygdala (E) during stress (Run 1) and no-stress (Run 2) conditions. Means and SE are shown.

Table 1

Behavioral performance across all four runs

Variables	Run 1 (No Stress)	Run 2 (Stress)	Run 3 (Stress)	Run 4 (No Stress)
<i>Reaction Times (msec)</i>				
Reward	304.03 (8.19)	296.79 (9.18)	295.38 (9.33)	294.59 (9.35)
Neutral	329.28 (9.69)	314.48 (10.9)	325.99 (14.41)	315.88 (10.44)
<i>Rewards received</i>	15.5 (1.21)	14.6 (0.8)	12.87 (1.07)	14.07 (0.84)

Table 2

MNI peak coordinates of brain regions involved during anticipation, Reward vs No-incentive cue (Panel A) and Consumption, Gain vs No-change feedback (Panel B) between No-Stress (Run1) and Stress (Run2). $p < 0.01$ uncorrected

A. Stress (Run2) > NoStress (Run1) - Anticipation (Reward vs. No-incentive Cue)			
Brain Region	Cluster size	MNI (x, y, z)	Z score
Rostral ACC	143	10, 48, 8	3.48
Inferior Gyrus	54	-52, 24, 22	3.04
Left Putamen	42	-24, 6, 6	3.27
Right Putamen	29	20, 6, -4	2.84
Superior Frontal Gyrus	39	-22, 24, 36	2.65

B. Stress (Run2) < NoStress (Run1) - Feedback (Reward vs. No-incentive Cue)			
Brain Region	Cluster size	MNI (x, y, z)	Z score
Occipital Cortex	247	40, -54, -24	3.66
Orbitofrontal Cortex	108	32, 34, -2	3.09
Caudate	79	-20, -22, 24	3.1
Lingual Gyrus	68	18, -54, 2	3.04
Amygdala	30	28, 0, -12	3.13
Thalamus	34	14, -26, 0	2.91