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Striatal hyper-sensitivity during stress in remitted individuals with recurrent depression

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Abstract

Background—Increased sensitivity to stress and dysfunctional reward processing are two primary characteristics of Major Depressive Disorder (MDD) that may persist following remission. Preclinical work has established the pivotal role of the striatum in mediating both stress and reward responses. Human neuroimaging studies have corroborated these preclinical findings and highlighted striatal dysfunction in MDD in response to reward, but have yet to investigate striatal function during stress, in particular in individuals with recurrent depression.

Methods—Thirty three remitted individuals with a history of recurrent MDD (rMDD) and 35 matched healthy controls underwent a validated mild psychological stress task involving viewing of negative stimuli during fMRI. Cortisol and anxiety levels were assessed throughout scanning. Stress-related activation was investigated in three striatal regions: caudate, nucleus accumbens

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(Nacc), and putamen. Psychophysiological interaction (PPI) analyses probed connectivity of those regions with central structures of the neural stress circuitry, the amygdala and hippocampus.

Results—The task increased cortisol and anxiety levels, although to a greater extent in rMDD than healthy controls. In response to the negative stimuli, rMDD individuals, but not controls, also exhibited significantly potentiated caudate, Nacc, and putamen activations, as well as increased caudate-amygdala and caudate-hippocampus connectivity.

Conclusions—Findings highlight striatal hyper-sensitivity in response to a mild psychological stress in rMDD, as manifested by hyper-activation and hyper-connectivity with the amygdala and hippocampus. Striatal hyper-sensitivity during stress might thus constitute a trait mark of depression, providing a potential neural substrate for the interaction between stress and reward dysfunction in MDD.

Keywords

Depression; Stress; Reward; Caudate; fMRI; Psycho-physiological interaction (PPI)

Introduction

Major Depressive Disorder (MDD) is a highly recurrent psychiatric condition, and thus a significant public health problem (1). According to the “kindling/sensitization” theory, depression recurrence may stem from sensitization of the stress response, rendering remitted individuals particularly susceptible to the effects of minor daily stressors (2, 3). Indeed, stress was found to be a robust predictor of depression relapse rates (4). In addition to increased stress susceptibility, remitted individuals continue to exhibit reduced response to positive stimuli, a cardinal symptom of MDD (5, 6). Critically, animal (7–11) and human (12–16) studies provided converging evidence that stress can disrupt behavioral responses to rewards, suggesting that dysfunctional interactions between stress and reward may underlie anhedonia and MDD (17).

Interestingly, extensive preclinical evidence has established the mediating role of the ventral (i.e., nucleus accumbens (Nacc)) and dorsal (i.e., caudate, putamen) striatum in both reward and stress processing (18, 19), raising the possibility that the striatum might be a structure in which stress and reward processing interact. Specifically, electrophysiological studies in non-human primates have shown that striatal (and midbrain) dopamine (DA) signaling track reward-related prediction errors (20–22), while stressors (e.g., foot shock, social defeat) were shown to elicit robust DA release in the rat striatum and medial prefrontal cortex (23–25). Findings from human neuroimaging studies have corroborated the key role of the striatum within the reward circuitry (26, 27), and described abnormal striatal responses that might account for dysregulated reward processing in current (28–34) and remitted (35, 36) MDD. Less attention, however, has been devoted to striatal function in humans *during* acute stress, particularly in individuals with recurrent depressive episodes. The majority of the human neuroimaging stress literature focused on the amygdala and hippocampus as pivotal mediators of the stress response (37, 38) and its regulation (39). Along those lines, current (40–43) and remitted (44–48) MDD exhibited hyper-active amygdala and hippocampus in

response to negative affective stimuli and stress, including in a subgroup of females from the current sample (49).

To fill this gap in the literature, we evaluated activation and connectivity of striatal regions during stress in healthy and remitted individuals with recurrent depression (rMDD). In the context of the “kindling/sensitization” theory, suggesting that remitted individuals are particularly susceptible to the effects of minor stressors (2, 3), we exposed 32 rMDD and 35 matched healthy controls to a mild psychological stress task during fMRI, while focusing on striatal activation. Furthermore, psycho-physiological interaction (PPI) (50–52) connectivity analyses were implemented to investigate stress-specific changes in striatal connectivity with core stress circuitry regions, such as the amygdala and hippocampus. In light of {1} stress hypersensitivity in rMDD, {2} hyperactivity in amygdala and hippocampus in response to negative stimuli in rMDD (44–49), and {3} preclinical evidence indicating that acute stressors elicit robust DA release in striatum (23–25), which in turn has been linked to increased fMRI responses (53), we hypothesized that, during stress, the rMDD group would exhibit increased striatal activation, as well as increased connectivity with the amygdala and hippocampus.

Methods and Materials

Participants

Participants were offspring of women who took part in the large ($n = 17,741$) Boston and Providence Collaborative Perinatal Project (CPP), also known as the New England Family Study (54). Structured Clinical Interviews (SCID) of a subsample of these offspring identified 205 individuals diagnosed with recurrent episodes of MDD and 706 healthy controls. From this group, 33 individuals diagnosed with recurrent depression in remission (rMDD) were recruited for neuroimaging based on current mood status and MRI eligibility criteria. Remission was defined as not meeting DSM-IV-R criteria for MDD for 30 days prior to scanning. In addition, on the morning of the study visit, participants in the rMDD group completed the 17-item Hamilton Rating Scale for Depression [HAM-D₁₇] (55) to assess depressive symptoms (Table 1). Among the rMDD group, HAM-D₁₇ scores ranged from 0 (reported by $N = 13$ or 39.4%) to 10 (reported by $N = 2$ or 6.1%). Twenty-seven of the 33 rMDD individuals (81.2%) had a HAM-D₁₇ score ≤ 7 , confirming full remission. The mean HAM-D₁₇ score was 4.2 (S.D. = 4.2).

Thirty-five healthy controls matched with respect to sex, ethnicity, handedness, parental socioeconomic status (SES), education, general intelligence, and mean menstrual cycle day for female subjects were also recruited (Table 1). No woman was taking oral contraceptives or hormone replacement therapy or was menopausal. No participants in the control group and 13 members of the rMDD were taking psychotropic medication at the time of the study (Table 1). Comorbid current and/or past Axis I diagnoses are also reported in Table 1. Given that rMDD group was slightly older than control group, participants' age (as well as SES) was added as covariates in all analyses. Participants received payment for their time and provided written informed consent to a protocol approved by the Committee on the Use of Human Subjects in Research at Harvard and Brown University.

Stress task

The task and its ability to evoke mild psychological stress response have been described and validated in multiple studies and populations (49, 56–58). Briefly, 144 International Affective Picture System (IAPS) images were selected and sorted into two sets, one of negative valence/high arousal and the other of neutral valence/low arousal. A set of fixation images was created by applying Fourier transforms on the neutral valence/low arousal images. Each image was presented for five seconds within a 30-second block consisting of six images of unified content (negative/high arousal or neutral/low arousal or fixation). For each content, 12 blocks were presented during scanning in a counterbalanced order, yielding three 6-minute functional scans. To maintain attention to the stimuli, participants were asked to press a button each time the picture changed, regardless of its content.

Stress response assessment

Following the scan, participants rated the negative and neutral images for arousal and valence using self-assessment manikin (SAM) scales (59). Anxiety levels pre- and post-scanning were assessed using the state form of the Spielberger State-Trait Anxiety Inventory (STAI-S) (60). Cortisol stress response was assessed using serial blood samples collected during fMRI. To account for the potential effects of the scanning environment, baseline cortisol level was defined using in-scanner draw, conducted approximately five minutes after the subject was introduced into the magnet (after the first few set-up scans) and just prior to the start of the first stress functional scan (Time 0). Two in-scanner blood samples were drawn, between the second and the third functional scan of the stress paradigm (Time 15 minutes), and at Time 30 minutes post-task presentations (timed for pituitary responses). Two out-of-scanner blood samples were drawn in a quiet room (Times 60 and 90 minutes) to assess steroid hormone responses to stress. Subjects remained inside the bore of the magnet during in-scanner blood draws. See Supplementary Table S2 for further details and a complete list of absolute cortisol values. Given significant variability in baseline (pre-stress) cortisol levels, individuals' cortisol response to stress was calculated as percentage of change from Time 0 (i.e., controlling for baseline level in scanner).

fMRI data analysis

See Supplementary Text for MRI data acquisition parameters. fMRI data were preprocessed using Statistical Parametric Mapping (SPM8) and included realignment and geometric unwarping of EPI images using magnetic fieldmaps, correction for head motion, nonlinear volume-based spatial normalization [Montreal Neurological Institute (MNI) template], and spatial smoothing with a Gaussian filter [6 mm (FWHM)]. Additional software (<http://web.mit.edu/swg/software.htm>) was used to identify and exclude outliers in the global mean image time series (threshold: 3.5 standard deviations (SD) from the mean) and movement (threshold: 0.7mm; measured as scan-to-scan movement, separately for translation and rotation) parameters.

Hemodynamic responses were modeled using a gamma function and convolved with onset times of negative, neutral and fixation blocks to form the general linear model (GLM) at the single subject level. Outlier time points as well as the six rigid-body movement parameters were included in the GLM as covariates of no interest. In order to test *a priori* hypotheses

targeting striatal activations during stress, we conducted region of interest (ROI) analyses in which activations (beta weights) were extracted from anatomical masks of the caudate, Nacc and putamen for each participant separately for negative and neutral conditions relative to baseline. Anatomical masks for those ROIs were defined using a manually segmented MNI-152 brain and implemented as overlays on the SPM8 canonical brain (Figure 2A). For each participant and ROI, activations from the left and right mask were entered into a mixed ANOVA with *Group* (Controls vs. rMDD) and *Gender* (Male vs. Female) as between-subject factors, *Side* (Left vs. Right) and *Condition* (Negative vs. Neutral) as repeated measures, and with or without *Age* and *SES* as covariates.

Given the lack of laterality effects on activations in any ROI, the left and right masks of each ROI were merged to create a single bilateral mask, from which timecourses were extracted for PPI analyses. For each participant, subject-level GLMs were constructed as described above, with the addition of the bilateral seed timecourse as a regressor and two additional PPI regressors (the interaction of the seed timecourse with the regressors for negative and neutral condition). These interaction regressors are orthogonal to the task and seed regressors, and thus describe the contribution of the interaction above and beyond the main effects of the task and seed timecourse. In addition, the orthogonality of the task and PPI regressors ensures that seed ROI activation and PPI connectivity are independent (52).

Striatal connectivity was measured at the single subject level by estimating the difference between the interaction of the seed timecourse with the regressor for negative vs. neutral pictures (each relative to baseline), and this was done separately for each ROI. Single subject activation maps were then entered into second-level random effects analysis to probe group differences in striatal connectivity during negative vs. neutral condition. Given extensive prior evidence for hyper-active amygdala and hippocampus in response to negative stimuli and stress in rMDD (44–49), striatal connectivity was investigated by applying small volume correction (SVC) on anatomical masks of the amygdala and hippocampus. False positives were controlled using family-wise error (*FWE*) correction. Average connectivity (beta weights of PPI regressors) in amygdala and hippocampal clusters that survived *FWE* correction was extracted and entered into a mixed ANOVA with *Group* (Controls vs. rMDD) and *Gender* (Male vs. Female) as between-subject factors, *Condition* (Negative vs. Neutral) as the repeated measure, and with or without *Age* and *SES* as covariates. Finally, exploratory whole brain analyses probed group differences in activation and connectivity outside *a priori* ROIs, with *Age* and *SES* as covariates, and at $p < 0.005$ uncorrected in more than 10 contiguous voxels.

Results

Stress response assessment

The ANOVA on subjective ratings of neutral and negative stimuli revealed the expected main effect of *Condition* on arousal ($F_{1,63} = 300.42$, $p < 0.001$) and valence ($F_{1,63} = 185.46$, $p < 0.001$) scales, with no *Group* by *Condition* interaction (arousal, $p = 0.242$; valence, $p = 0.579$). The ANOVA of pre- and post-scan anxiety (STAI-S) revealed a significant main effect of *Time* ($F_{1,57} = 8.11$, $p = 0.006$), and *Group* ($F_{1,57} = 9.23$, $p = 0.004$), but no *Group* by *Time* interaction ($p = 0.92$). These results indicate that participants across groups rated

the negative stimuli as more arousing and more negative compared to the neutral stimuli, and experienced increased anxiety post-task, yet rMDD exhibited overall significantly higher anxiety than controls (Figure 1A–C).

The ANOVA of cortisol response across the five time points revealed a main effect of *Time* ($F_{3,168} = 2.72, p = 0.047$), due to an overall increase in cortisol levels 60 minutes following the onset of the stress task compared to baseline ($p = 0.012$). Critically, a significant *Group* by *Time* interaction emerged ($F_{3,168} = 3.63, p = 0.014$), due to higher cortisol response in rMDD compared to controls both 60 ($p = 0.006$) and 90 ($p < 0.001$) minutes following stress onset (Figure 1D). Similarly, classifying participants according to whether they demonstrated an increase (responders) or decrease (non-responders) in cortisol levels from baseline to the expected peak response time (60 minutes post-stress onset) resulted in 69% (22 out of 32 with full data) rMDD individuals being classified as responders compared to 27% (8 out of 29 with full data) control individuals classified as responders. This classification was significantly different between groups ($\chi^2 = 10.3; p = 0.001$), indicating greater cortisol responsivity to stress in rMDD compared to controls. Thus, cortisol data confirmed that the task elicited a stress response across participants, and that rMDD individuals experienced a more marked response to this mild stressor.

Striatal activation during stress

ANOVAs comparing group activations for negative and neutral conditions separately for each striatal ROI yielded no main effect of *Group* or *Gender*. In the caudate and putamen there was a significant main effect of *Condition* attributed to overall increased striatal response to negative compared to neutral stimuli (Caudate, $F_{1,60} = 10.63, p = 0.002$; Putamen, $F_{1,60} = 21.19, p < 0.001$). Relevant to the study hypotheses, a significant *Group* by *Condition* interaction emerged for all three ROIs (Caudate, $F_{1,60} = 9.84, p = 0.003$; Nacc, $F_{1,60} = 4.51, p = 0.038$; Putamen, $F_{1,60} = 7.58, p = 0.008$), due to the fact that the increase in striatal response to negative compared to neutral stimuli was present in the rMDD, but not control, group (Caudate, $P < 0.001$; Nacc, $p = 0.013$; Putamen, $p < 0.001$; Figure 2B–D). For the caudate, there was also a significant group difference such that rMDD exhibited increased caudate activation compared to controls in response to negative but not neutral stimuli ($p = 0.03$). Analogous analyses accounting for *Age* and *SES* as covariates confirmed the significant *Group* by *Condition* interactions (Caudate: $p = 0.006$; Nacc: $p = 0.042$; Putamen: $p = 0.019$).

Finally, regression analyses highlighted a significant positive correlation between caudate activation in response to negative stimuli and peak cortisol release (60 minutes post-stress onset relative to in-scanner baseline) in the rMDD ($r = 0.412, p = 0.036$), but not control ($r = -0.058, p = 0.765$) group (Figure 3), and these independent correlations were significantly different ($Z = 1.952, p = 0.05$). Thus, in parallel with their elevated behavioral and hormonal responses to the mild stress challenge, rMDD individuals, but not controls, exhibited significantly increased activations in all three striatal regions in response to the negative stimuli, and in the caudate such increased activation correlated with stress-induced cortisol release.

Striatal connectivity during stress

PPI analyses were focused on group differences in striatal connectivity with the amygdala and hippocampus in response to negative versus neutral stimuli. These analyses revealed two clusters, one in left amygdala and one in left hippocampus that showed greater functional connectivity with the caudate in rMDD compared to controls ($p < 0.05$, *FWE-corrected*; Figure 4A and Table 2). To further investigate these results, connectivity values for each *Condition* (Negative vs. Neutral) were entered into an ANOVA with *Group* (Controls vs. rMDD) and *Gender* (Male vs. Female) as between-subject factors. Main effects of *Condition*, *Group*, and *Gender* were not significant; however, a significant *Group* by *Condition* interaction emerged for both caudate-amygdala and caudate-hippocampus connectivity ($F_{1,63} = 10.92$, $p = 0.002$; $F_{1,63} = 9.18$, $p = 0.004$, respectively; or $p = 0.003$ and $p = 0.023$, respectively, when controlling for *Age* and *SES*). Mirroring the activation results, these interactions stemmed from the fact that rMDD individuals, but not controls, exhibited increased caudate-amygdala and caudate-hippocampus connectivity in response to the negative vs. neutral stimuli ($p = 0.013$; $p = 0.009$, respectively) (Figure 4B & C). In addition, for caudate-amygdala connectivity, there was a significant group difference such that rMDD exhibited increased connectivity compared to controls in response to the negative but not neutral stimuli ($p = 0.033$). Similar analyses conducted with respect to Nacc and putamen connectivity also revealed greater functional connectivity with clusters in left amygdala and left hippocampus in rMDD compared to controls during stress, yet none survived *FWE* correction (Table 2). Finally, even at a liberal threshold of $P < 0.05$ uncorrected, no clusters in the amygdala or hippocampus showed stronger striatal connectivity in controls compared to rMDD.

Exploratory whole-brain analyses

In addition to the striatum, bilateral hippocampus activation was also increased in rMDD relative to controls in response to negative stimuli. No brain regions were more active in controls than rMDD in response to negative stimuli. Whole brain analyses examining caudate connectivity in response to negative stimuli in rMDD relative to controls revealed, as expected, a large cluster encompassing the left amygdala and hippocampus, as well as a cluster in the left fusiform gyrus (see Supplementary text, Supplementary Figure S1A & B, and Supplementary Table S1). No regions were more connected to the caudate in controls than rMDD in response to negative stimuli.

Control analyses—Correlational analyses revealed no associations between HAM-D₁₇ scores among the rMDD group and striatal activation or connectivity magnitudes (all $p > .22$), indicating that the current findings were not modulated by residual depressive symptoms.

Discussion

The goal of the current study was to probe striatal activation and connectivity during mild stress in healthy and remitted individuals with recurrent depression (rMDD). Affective and endocrinological findings confirmed a mild psychological stress response, as intended, in both the healthy and remitted group; rMDD individuals, however, exhibited a stronger stress

response than controls. fMRI results indicated that heightened stress responsivity in rMDD was accompanied by increased activation to negative stimuli in three key striatal regions: the caudate, Nacc, and putamen – a pattern that was not found in controls. PPI analyses further revealed increased caudate connectivity with both the amygdala and hippocampus in response to the negative stimuli in rMDD but not controls. Collectively, findings suggest that rMDD is characterized by striatal hyper-sensitivity during a mild stressor.

Group differences in cortisol response between rMDD and healthy controls fit with previous reports that HPA-axis dysregulation persists following remission from depression. Interestingly, while basal cortisol response seems to be consistently increased following remission from depression (61), stress reactivity studies commonly report reduced cortisol responses in rMDD relative to controls, potentially as a result of adaptation to previous stress exposure (62–64), although inconsistencies abound (65)). Notably, those studies implemented a relatively potent stressor (e.g., the Trier Social Stress Test (TSST) (66)), known to elicit robust increases in cortisol levels in healthy humans, which are considered adaptive (67, 68). The demonstrated increase in cortisol release in response to mild stress in rMDD relative to controls may therefore suggest that remitted individuals are particularly susceptible to the effects of minor stressors; such “hyper-sensitive” physiological response even to a mild stress challenge is consistent with the kindling/sensitization theory of depression (2, 3). Indeed, enhanced cortisol reactivity in rMDD in response to a minor laboratory stressor, but not to a more potent stressor, was found to predict depression relapse in a recent longitudinal study (69).

Importantly, animal work has shown that stress-induced corticosteroid release can modulate DA striatal signaling (70–72). Similarly, human PET studies revealed a positive association between cortisol increase and DA release in the ventral striatum and putamen (73, 74). Although fMRI cannot be used to infer DA signaling, pharmacological and metabolic evidence suggest that fMRI BOLD signal from the striatum is indicative of striatal DA release (53, 75–77). Our results thus may be regarded as supportive of a potential relation between cortisol and striatal function by showing that elevated cortisol release in the rMDD group was accompanied by increased striatal activations and connectivity during stress, and furthermore, that caudate reactivity and stress-induced cortisol release were positively correlated among the rMDD sample. Along similar lines, PET studies found stress-induced striatal DA release in individuals with low parental care (73) or at risk for affective (78, 79) or mood disorders (80), but not in healthy controls (81, 82), again consistent with our results. Notably, findings from animal work suggest that stress-induced striatal DA release may amplify the incentive salience of stimuli (19). In humans such enhanced saliency may translate to increased attention or emotional engagement during presentation of negative cues; processes which were shown to involve the striatum, as well as the amygdala, and hippocampus. Over time, striatal hyper-sensitivity in rMDD, through its association with chronic exposure to high glucocorticoid levels, may sensitize the mesolimbic DA system (76), resulting in increased susceptibility to mild stressors.

Striatal hyper-sensitivity during stress may be particularly detrimental for the encoding of subsequent rewards, given shared reliance of stress and reward responses on striatal DA signaling (18, 19). In support of this, reductions in hedonic behavior following various

forms of stress have been reported in the animal (7–11) and human (12–16) literature. Moreover, individuals with heightened cortisol response to stress were found to be specifically vulnerable to the disruptive effect of an acute stressor on reward sensitivity (83). Finally, recent fMRI studies demonstrated reduced reward-related striatal activation in healthy individuals after acute laboratory stress (84, 85) and after prolonged combat stress (86), with the latter also linking reward-related striatal bunting with greater severity of depressive symptomatology (86). Altogether, when seen in the context of emerging evidence, the current findings suggest that striatal hyper-sensitivity during stress may play a crucial role in the interaction between increased sensitivity to mild stressors and dysfunctional reward processing, two primary characteristics of MDD that persist following remission.

Additional studies will need to validate this novel idea and address limitations of the present work. First, throughout the paper, we refer to the striatum in general due to the fact that all three striatal regions (caudate, Nacc, and putamen) exhibited similar activation patterns. Increased connectivity with the amygdala and hippocampus was also consistent across striatal nuclei, although group differences were significant only for the caudate. Nevertheless, animal and human work has clearly demonstrated that the function and connections of different striatal nuclei and their sub-components vary greatly and include many signaling pathways (87, 88). Future studies should delineate the specific involvement of each striatal nuclei in response to stress in both healthy control and rMDD samples. Second, some of the rMDD participants were taking psychotropic medication and presented current and/or past comorbidities. Importantly however, with the exception of Nacc activation, all group differences in activation and connectivity during stress remained significant when analyses were repeated solely with rMDD individuals who were not taking psychotropic medication (n=20) or without comorbid diagnoses (n=15), suggesting that medication and comorbidities did not affect our main findings (for more detail, see Supplementary Text and Supplementary Figures S2 & S3). Nevertheless, Nacc results should be regarded with caution given the insignificant group differences in Nacc activation in these sub-samples, and the observation that group differences in Nacc activation at the whole sample level may have been partially driven by reduced activation in response to the neutral condition in rMDD. Finally, our study did not include a stress-free control group or a measure of reward sensitivity, and thus we cannot test the specificity of our findings or the effects of stress on reward function. By combining stress and reward manipulations in a single design as well as a stress-free control group, future studies could test whether rMDD individuals require a lower stressor in order to observe perturbation in reward processing. It would also be of great interest to directly compare reward function and/or stress sensitivity among remitted and current MDD. For example, a recent study found that both currently depressed adolescent daughters of mothers with a history of MDD and never-depressed daughters of mothers with a history of MDD exhibit reduced striatal response to reward compared to control daughters with no maternal history of psychopathology (89), strengthening the claim that reward dysfunction represents a promising endophenotype of depression. Future studies directly comparing current and remitted MDD will be needed to evaluate whether similar patterns are evident in adult cohorts.

In summary, compared to healthy controls, remitted individuals with a history of recurrent depression exhibited potentiated cortisol responses as well as striatal hyper-sensitivity in response to a mild psychological stress, as manifested by hyper-activation and hyper-connectivity with the amygdala and hippocampus. Striatal hyper-sensitivity during stress might thus constitute a trait mark of MDD, providing a potential neural substrate for the interaction between stress and reward dysfunction in depression.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1. Stress response assessment

Both groups rated the negative stimuli as (A) more arousing and (B) more negative compared to the neutral stimuli, as well as experienced an increase in (C) anxiety and (D) cortisol levels (60 minutes post-stress onset relative to baseline) following the mild stress paradigm. Notably, relative to healthy controls, rMDD individuals exhibited overall significantly higher anxiety and cortisol response (60 and 90 minutes post-stress onset relative to baseline). Bars $\pm$ 1 S.E.M. * $p < 0.05$, ** $p < 0.001$. rMDD – Remitted individuals with a history of recurrent MDD. HC – Healthy controls.

Figure 2. Striatal activation during stress

(A) Location of anatomically defined masks for the Caudate (blue), Nacc (yellow), and Putamen (turquoise). Mask volumes were 169 and 195 voxels for the left and right caudate, respectively; 25 and 34 voxels for the left and right Nacc, respectively; 226 and 239 voxels for the left and right putamen, respectively. rMDD individuals, but not controls, exhibited significantly increased activation in all three striatal regions, the (B) Caudate, (C) Nacc, and (D) Putamen, in response to the negative stimuli compared to the neutral stimuli. Bars $\pm$ 1 S.E.M. * $p < 0.05$, ** $p < 0.001$. rMDD – Remitted individuals with a history of recurrent MDD. HC – Healthy controls.

Figure 3. Caudate activation during stress and cortisol release

For the rMDD ($r = 0.412$, $p = 0.036$), but not control ($r = -0.058$, $p = 0.77$) group, caudate activation in response to the negative stimuli was positively associated with peak cortisol release (60 minutes post-stress onset relative to baseline). Cortisol level at 90 minutes post-stress onset relative to baseline, as well as area under the curve (AUC) of cortisol release were not correlated with caudate activation in rMDD ($r = -0.13$, $p = 0.54$; $r = 0.05$, $p = 0.79$, respectively) or control ($r = 0.21$, $p = 0.38$; $r = -0.12$, $p = 0.60$, respectively) groups. rMDD – Remitted individuals with a history of recurrent MDD. HC – Healthy controls.

Figure 4. Striatal connectivity during stress

(A) PPI analyses revealed one cluster in the left amygdala (red) and one in the left hippocampus (green) that were more functionally connected to the caudate (blue) in rMDD compared to healthy controls during stress ($P < 0.05$, FWE-corrected). Specifically, rMDD individuals, but not controls, exhibited increased (B) caudate-amygdala and (C) caudate-hippocampus connectivity in response to the negative stimuli compared to the neutral stimuli. Bars ± 1 S.E.M. * $p < 0.05$. rMDD – Remitted individuals with a history of recurrent MDD. HC – Healthy controls.

Table 1

Demographic and clinical characteristics of remitted individuals with a history of recurrent MDD (rMDD) and healthy controls.

Characteristic	Healthy Controls (<i>N</i> =35)		rMDD Group (<i>N</i> =33)	
	Mean	SD	Mean	SD
Age (years) [*]	45.7	2.7	47.4	1.8
Parental SES ^a	6.2	1.8	5.7	1.9
Education (years)	14.5	2.4	13.5	2.0
Estimated Full Scale IQ ^{bc}	110.7	13.5	107.6	12.5
Age at onset of major depression (years)	—	—	24.5	8.8
Duration of illness (years)	—	—	21.6	9.3
Number of prior major depressive episodes	—	—	5.0	2.3
Duration of remission (years)	—	—	7.3	6.3
Hamilton Depression Rating Scale (17-item)	—	—	4.2	4.2
	N	%	N	%
Female	16	45.7	17	51.5
Caucasian	35	100	33	100
Handedness (right) ^c	34	97.1	32	96.9
Current psychotropic medication ^d	—	—	13	39.4
Comorbid diagnosis				
Current ^e	—	—	18	54.6
Past ^f	11	30.6	24	72.7

* Significant difference between groups ($p < 0.05$)

^a Parental socioeconomic status (SES) was a composite index of family income, education, and occupation and ranged from 0.0 (low) to 9.5 (high).

^b Full Scale IQ estimated using the sum of age-scaled scores from the WAIS-R Vocabulary and Block Design subtests, and the conversion table C-37 from Sattler, 1992 (p. 851). [Sattler J (1992): Assessment of Children. 3 ed. San Diego].

^c Data missing for 1 rMDD and 1 HC subject.

^d 13 rMDD (6 men) were currently taking the following medications: fluoxetine (n=3); citalopram (n=2); citalopram+alprazolam (n=1); duloxetine+trazadone (n=1); fluoxetine+clonazepam (n=1); clozapine (n=1); quetiapine (n=1); sertraline+methylphenidate+clomipramine+gabapentin (n=1); sertraline+bupropion (n=1); venlafaxine+bupropion (n=1).

^e Current comorbid Axis 1 diagnoses in the rMDD group included: 2 subjects with Dysthymic Disorder; 2 subjects with Obsessive-Compulsive Disorder (OCD); 3 subjects with Anxiety Disorder, not otherwise specified (NOS); 1 subject with Post-Traumatic Stress Disorder (PTSD); 5 subjects with Panic Disorder, without Agoraphobia; 2 subjects with Attention Deficit Hyperactivity Disorder (ADHD), NOS; 1 subject with Alcohol Dependence; 2 subjects with Social Phobia.

^f Past comorbid Axis 1 diagnoses in the rMDD group included: 2 subjects with Panic Disorder, with Agoraphobia; 3 subjects with Alcohol Dependence; 9 subjects with Alcohol Abuse; 2 subjects with Cocaine Dependence; 1 subject with Cannabis Dependence; 3 subjects with Cannabis Abuse; 2 subjects with Opioid Dependence; 1 subject with Sedative Dependence; 1 subject with Anxiety Disorder, NOS. In the HC group, past Axis 1 diagnoses included: 1 subject with Dysthymic Disorder; 2 subjects with Alcohol Dependence; 1 subject with Uncomplicated Alcohol Withdrawal; 2 subjects with Cannabis Abuse; 1 subject with Hallucinogen Abuse; 3 subjects with Alcohol Abuse; 1 subject with Caffeine-Induced Anxiety Disorder.

Table 2

Striatal connectivity abnormalities during stress in rMDD.

Contrast	Region	# of voxels	X ^a	Y ^a	Z ^a	Z score	T value	Un-corrected P value ^b	FWE-corrected P value ^c
<i>Caudate Connectivity</i>									
Negative vs. Neutral stimuli (<i>rMDD > HC</i>)	L. Amygdala	60	-15	-7	-20	3.24	3.39	0.001	0.022
	L. Hippocampus	22	-33	-19	-14	3.34	3.51	0.000	0.038
<i>Nacc Connectivity</i>									
Negative vs. Neutral stimuli (<i>rMDD > HC</i>)	L. Amygdala	18	-27	-13	-14	2.43	2.49	0.008	0.162
	L. Hippocampus	20	-30	-16	-14	2.59	2.67	0.005	0.263
<i>Putamen Connectivity</i>									
Negative vs. Neutral stimuli (<i>rMDD > HC</i>)	L. Amygdala	9	-24	-7	-26	2.69	2.77	0.004	0.098
	L. Hippocampus	33	-24	-28	-11	3.01	3.13	0.001	0.108

^aCoordinates are presented in MNI space.^bWithin an anatomic ROI, results identified using small volume correction (SVC) with voxel-wise peak-level height threshold: $p < 0.05$, uncorrected for multiple comparisons.^cFalse positives controlled using family-wise error (FWE) correction. Results are reported (in bold) as significant only if they met the peak-level threshold of $p < 0.05$, FWE-corrected. Notably, even at a liberal threshold of $P < 0.05$ uncorrected, no clusters in the amygdala or hippocampus showed stronger striatal connectivity in healthy controls (HC) compared to rMDD during stress. L – Left. rMDD – Remitted individuals with a history of recurrent MDD. HC – Healthy controls.