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Striatal Hypersensitivity 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 after 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: A validated mild psychological stress task involving viewing of negative stimuli during functional magnetic resonance imaging was conducted in 33 remitted individuals with a history of recurrent major depressive disorder (rMDD) and 35 matched healthy control subjects. Cortisol and anxiety levels were assessed throughout scanning. Stress-related activation was investigated in three striatal regions: caudate, nucleus accumbens, and putamen. Psychophysiologic interaction analyses probed connectivity of regions with central structures of the neural stress circuitry, such as the amygdala and hippocampus.

RESULTS: The task increased cortisol and anxiety levels, although to a greater extent in rMDD individuals than healthy control subjects. In response to the negative stimuli, rMDD individuals, but not controls, also exhibited significantly potentiated caudate, nucleus accumbens, and putamen activations and increased caudate-amygdala and caudate-hippocampus connectivity.

CONCLUSIONS: The findings highlight striatal hypersensitivity in response to a mild psychological stress in rMDD, as manifested by hyperactivation and hyperconnectivity with the amygdala and hippocampus. Striatal hypersensitivity 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: Caudate, Depression, fMRI, Psychophysiologic Interaction (PPI), Reward, Stress

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Major depressive disorder (MDD) is a highly recurrent psychiatric condition and thus a significant public health problem (1). According to the "kindling/sensitization" theory, recurrence of depression 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).

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, electrophysiologic studies in nonhuman primates showed that striatal (and midbrain) dopamine (DA) signaling track reward-related prediction errors (20–22), whereas 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 abnormal striatal responses have been described that might account for dysregulated reward processing in current (28–34) and remitted (35,36) MDD. However, less attention has been devoted to striatal function in humans during acute stress, particularly in individuals with recurrent depressive episodes. Most of the human neuroimaging stress literature focuses on the amygdala and hippocampus as pivotal mediators of the stress response (37,38) and its regulation (39). Along those lines, individuals with current MDD (40–43) and remitted individuals (44–48) exhibited hyperactive amygdala and hippocampus in response to negative affective stimuli and stress, including in a subgroup of female subjects from the present sample (49).

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To fill this gap in the literature, we evaluated activation and connectivity of striatal regions during stress in healthy and remitted individuals with recurrent major depressive disorder (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 remitted individuals with a history of rMDD and 35 matched healthy control subjects to a mild psychological stress task during functional magnetic resonance imaging (fMRI), focusing on striatal activation. Furthermore, psychophysiologic interaction (PPI) (50–52) connectivity analyses were performed 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 has been linked to increased fMRI responses (53), we hypothesized that during stress the rMDD group would exhibit increased striatal activation and 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, also known as the New England Family Study (54). Structured Clinical Interview for DSM performed in a subsample of these offspring identified 205 individuals with a diagnosis of recurrent episodes of MDD and 706 healthy control individuals. From this group, 33 individuals with a diagnosis of rMDD were recruited for neuroimaging based on current mood status and magnetic resonance imaging eligibility criteria. Remission was defined as not meeting DSM-IV-R criteria for MDD for 30 days before scanning. In addition, on the morning of the study visit, participants in the rMDD group completed the 17-item Hamilton Depression Rating Scale (HAM-D_{17}) (55) to assess depressive symptoms (Table 1). Among the rMDD group, HAM-D_{17} scores ranged from 0 (reported by n = 13 [39.4%]) to 10 (reported by n = 2 [6.1%]). Full remission was confirmed in 27 of the 33 rMDD individuals (81.2%) who had a HAM-D_{17} score ≤7. The mean HAM-D_{17} score was 4.2 (SD = 4.2).

We also recruited 35 healthy control subjects matched with regard to sex, ethnicity, handedness, parental socioeconomic status (SES), education, general intelligence, and mean menstrual cycle day for female subjects (Table 1). No woman was taking oral contraceptives or hormone replacement therapy or was menopausal. At the time of the study, 13 participants of the rMDD group were taking psychotropic medication, and no participants in the control group were taking psychotropic medication (Table 1). Comorbid current or past Axis I diagnoses are also reported in Table 1. Given that the rMDD group was slightly older than the control group, participants' age and SES were 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

Table 1. Demographic and Clinical Characteristics of Remitted Individuals with a History of rMDD and Healthy Control Subjects

	Healthy Control Group (n = 35)		rMDD Group (n = 33)	
Characteristic	Mean	SD	Mean	SD
Age (Years)[a]	45.7	2.7	47.4	1.8
Parental SES[b]	6.2	1.8	5.7	1.9
Education (Years)	14.5	2.4	13.5	2.0
Estimated Full Scale IQ[c,d]	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
	No.	%	No.	%
Female	16	45.7	17	51.5
Caucasian	35	100	33	100
Handedness (Right)[d]	34	97.1	32	96.9
Current Psychotropic Medication[e]	—	—	13	39.4
Comorbid Diagnosis				
Current[f]	—	—	18	54.6
Past[g]	11	30.6	24	72.7

rMDD, recurrent major depressive disorder; SES, socioeconomic status.

[a]Significant difference between groups ($p < .05$).

[b]Parental SES was a composite index of family income, education, and occupation and ranged from .0 (low) to 9.5 (high).

[c]Full Scale IQ estimated using the sum of age-scaled scores from the Wechsler Adult Intelligence Scale–Revised Vocabulary and Block Design subtests and the conversion table C-37 from Sattler JM (1992): Assessment of Children, 3rd ed. San Diego: Jerome M. Sattler, 851.

[d]Data missing for one subject from the rMDD group and one subject from the HC group.

[e]In the rMDD group, 13 subjects (6 men) were currently taking the following medications: fluoxetine (n = 3); citalopram (n = 2); citalopram + alprazolam (n = 1); duloxetine + trazodone (n = 1); fluoxetine + clonazepam (n = 1); clozapine (n = 1); quetiapine (n = 1); sertraline + methylphenidate + clomipramine + gabapentin (n = 1); sertraline + buproprion (n = 1); venlafaxine + bupropion (n = 1).

[f]Current comorbid Axis I diagnoses in the rMDD group included two subjects with dysthymic disorder; two subjects with obsessive-compulsive disorder; three subjects with anxiety disorder, not otherwise specified; one subject with posttraumatic stress disorder; five subjects with panic disorder, without agoraphobia; two subjects with attention-deficit/hyperactivity disorder, not otherwise specified; one subject with alcohol dependence; and two subjects with social phobia.

[g]Past comorbid Axis I diagnoses in the rMDD group included two subjects with panic disorder, with agoraphobia; three subjects with alcohol dependence; nine subjects with alcohol abuse; two subjects with cocaine dependence; one subject with cannabis dependence; three subjects with cannabis abuse; two subjects with opioid dependence; one subject with sedative dependence; and one subject with anxiety disorder, not otherwise specified. In the healthy control group, past Axis I diagnoses included one subject with dysthymic disorder, two subjects with alcohol dependence, one subject with uncomplicated alcohol withdrawal, two subjects with cannabis abuse, one subject with hallucinogen abuse, three subjects with alcohol abuse, and one subject with caffeine-induced anxiety disorder.