Archival Report

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Illness Progression, Recent Stress, and Morphometry of Hippocampal Subfields and Medial Prefrontal Cortex in Major Depression

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ABSTRACT

BACKGROUND: Longitudinal studies of illness progression in patients with major depressive disorder (MDD) indicate that the onset of subsequent depressive episodes becomes increasingly decoupled from external stressors. A possible mechanism underlying this phenomenon is that multiple episodes induce long-lasting neurobiological changes that confer increased risk for recurrence. Prior morphometric studies have frequently reported volumetric reductions in patients with MDD—especially in medial prefrontal cortex (mPFC) and the hippocampus—but few studies have investigated whether these changes are exacerbated by prior episodes.

METHODS: In a sample of 103 medication-free patients with depression and control subjects with no history of depression, structural magnetic resonance imaging was performed to examine relationships between number of prior episodes, current stress, hippocampal subfield volume and cortical thickness. Volumetric analyses of the hippocampus were performed using a recently validated subfield segmentation approach, and cortical thickness estimates were obtained using vertex-based methods. Participants were grouped on the basis of the number of prior depressive episodes and current depressive diagnosis.

RESULTS: Number of prior episodes was associated with both lower reported stress levels and reduced volume in the dentate gyrus. Cortical thinning of the left mPFC was associated with a greater number of prior depressive episodes but not current depressive diagnosis.

CONCLUSIONS: Collectively, these findings are consistent with preclinical models suggesting that the dentate gyrus and mPFC are especially vulnerable to stress exposure and provide evidence for morphometric changes that are consistent with stress-sensitization models of recurrence in MDD.

Keywords: Dentate gyrus, Hippocampus, MAGeT brain, Major depression, mPFC, MRI

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Major depressive disorder (MDD) is a debilitating disease that affects >20 million Americans every year (1), drains billions of dollars from the economy (2), and was recently declared the second leading cause of disability worldwide (3). A substantial portion of these staggering societal costs is attributable to the episodic course of the disorder; individuals with one prior episode have a 60% chance of a recurrence, and the likelihood of an additional episode after three to four episodes is ~90% (4,5). Consequently, understanding the mechanisms that underlie the development of subsequent major depressive episodes (MDEs) is crucial for alleviating the impact of this devastating disorder on public health.

Over the last several decades, accruing evidence suggests that although stressful life events play a central role in triggering the onset of an initial MDE, their role in episode onset progressively diminishes as the number of episodes increases (6,7). In several prospective studies with large samples, individuals who developed a first depressive episode over the study period reported significantly higher levels of chronic stress compared with individuals who experienced recurrent MDEs (8–10). Along similar lines, epidemiologic research has shown that the predictive validity of reported stress levels before MDE onset declines monotonically with each successive episode (9,11–13).

These findings raise the possibility that illness progression in individuals with MDD is linked to specific biological changes that may mediate the interplay between external stressors and recurrence. One candidate mechanism is structural abnormalities within the medial prefrontal cortex (mPFC) and the hippocampus. These regions are known to regulate behavioral and neuroendocrine responses to stress and can be damaged by excessive exposure to stress-induced release of steroidal and inflammatory signaling molecules (11–13). In patients with depression, numerous magnetic resonance imaging (MRI) studies and meta-analyses have found evidence for diminished gray matter volume in aspects of mPFC, including rostral

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and dorsal subdivisions of the anterior cingulate cortex as well as subgenual and subcallosal cortex, and limbic regions such as the hippocampus and amygdala (14–17). Postmortem studies also show evidence for structural alterations in these regions, including decreased cellular density (18–20) and reduced expression of critical proteins involved in neurogenesis and synaptic plasticity (21–23). Further implicating these areas, similar structural differences were reported in a large sample of individuals with no history of depression and a high polygenic risk score for MDD, suggesting that these differences may partly reflect a biological diathesis for MDD (24).

Although such effects are generally present on the aggregate level, it is unclear whether they relate to the mere presence of a depressive state, a biological diathesis, or an accumulative effect of prior depressive episodes. Prior cross-sectional and longitudinal studies have suggested that volumetric changes associated with MDD fluctuate with state (25,26) but also depend on prior number of episodes (21–23,27). The relative contribution of state and depressive history, however, remains unclear, which partly reflects a historical emphasis on group comparisons rather than dimensional approaches (28,29).

The goal of the present study was to evaluate differences in brain morphology and current stress levels across individuals with no history of depression and individuals with current depression with varying numbers of prior MDEs. This approach is particularly relevant for understanding the biological mechanisms underlying the relationship between stress and recurrence; in particular, if stress-induced abnormalities in specific brain regions mediate the increased risk for subsequent depressive episodes, individuals with more past depressive episodes should exhibit greater structural deficits as well as diminished levels of perceived stress.

To address these questions, we analyzed structural MRI images of 103 individuals with depression and individuals with no history of depression using whole-brain vertex-based cortical thickness (VBCT) and a recently developed methodology for high-quality segmentation of hippocampal subfields (30,31). To test for the specificity of associations with hippocampal subfields, we also examined amygdala volume, which has been implicated in MDD (32) and is generally correlated with hippocampal volume (24,33). Our primary hypotheses were that 1) current stress levels would be greatest in individuals reporting few depressive episodes relative to controls and individuals with a high number of episodes and 2) the number of episodes would be associated with progressive reductions of cortical and limbic areas known to be vulnerable to stress (i.e., mPFC and hippocampus).

METHODS AND MATERIALS

Participants

Sample characteristics are described in Table 1. This study included 103 participants, including 51 healthy control subjects (49% female) and 52 unmedicated subjects with a current diagnosis of MDD (54% female). There were no differences between the MDD subjects with current depression and control subjects with no depression in terms of age [$t_{101} = -1.55$, $p = .13$], sex [$\chi^2(1, n = 103) = .24$, $p = .62$], percent Caucasian [$\chi^2(1, n = 103) = .027$, $p = .87$], years of education [$t_{100} = .62$, $p = .54$], employment status [$\chi^2(1, n = 103) = 5.5$, $p = .14$], or marital status [$\chi^2(1, n = 103) = 5.5$, $p = .14$]. The MDD subjects were recruited through a combination of ongoing treatment studies and community outreach. Healthy control subjects were recruited from the community. For all subjects, exclusion criteria included any history of bipolar disorder, attention-deficit/hyperactivity disorder, psychosis, or substance dependence. Subjects were also excluded if they had any evidence of substance abuse within the last year. Additionally, subjects were excluded if they had any condition that would interfere with an MRI scan (e.g., claustrophobia, cochlear implant, cardiac pacemaker). Control subjects were additionally required to be free of any current or past history of Axis I disorders. Subjects with depression were required to meet full criteria for current MDD as assessed by a Structured Clinical Interview for DSM (34) as well as have a score of ≥16 on the 21-item Hamilton Depression Rating Scale (35) at the time of initial intake. Additionally, MDD subjects were required to be free of any use of psychotropic medications for at least 2 weeks (6 weeks for fluoxetine; 6 months for dopaminergic drugs or neuroleptics) before the MRI scan. All procedures were reviewed and approved by the Committee on the Use of Human Subjects at Harvard University and the Partners Human Research Committee institutional review board, and all participants provided written informed consent.

Table 1. Sample Demographics

	Healthy Control Subjects ($n = 51$)		MDD Subjects ($n = 52$)[a]		
	Mean	SD	Mean	SD	p Value
% Female	49%	—	54%	—	.62
Age (Years)	36.8	14.1	40.9	12.8	.13
% Caucasian	74%	—	73%	—	.87
Years of Education	15.6	2.1	15.3	2.2	.54
% Unemployed	26%	—	45%	—	.14
BDI-II	2.5	3.2	25.0	10.5	<.0001
HDRS (17-item)	—	—	18.0	4.0	—
Number of Episodes	—	—	3.6	3.3	—

BDI-II, Beck Depression Inventory Second Edition; HDRS, Hamilton Depression Rating Scale; MDD, major depressive disorder.

[a]Comorbid conditions: panic disorder ($n = 1$), generalized anxiety ($n = 1$), social phobia ($n = 1$), specific phobia ($n = 2$), obsessive-compulsive disorder ($n = 1$), body dysmorphic disorder ($n = 1$).

Measure of Recent Stress

To assess recent levels of stress, all subjects were administered the Perceived Stress Scale (PSS). The PSS is a brief self-report measure that has been well validated as a measure of the perceived intensity and tolerability of daily-life stressors over the previous month (36). The PSS includes items that ask subjects to rate the perceived predictability and controllability of these stressors as well as how overwhelmed they felt. Examples items include: “In the last month, how often have you felt that you were unable to control the important things in your life?’’ or ‘‘In the last month, how often have you found