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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

SEE COMMENTARY ON PAGE 210

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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

that you could not cope with all the things that you had to do?'' Participants rated their response to each item using a 0–4 scale where 0 is defined as "never" and 4 is defined as "very often." Total scores for each subject were generated by summing across the total number of items, resulting in a total range of 0–56.

Number of Prior MDEs

During the clinical interview, all MDD subjects reported the number of MDEs they had previously experienced, which ranged from 1–15 prior episodes (including the current episode). Because the distribution of the number of episodes was skewed to the right, the MDD sample was divided into groups of individuals with one episode ($n = 21$), two to four episodes ($n = 12$), and five or more episodes ($n = 21$). This variable was used as a predictor of structural changes across all subjects (including control subjects), and ranged from 0 (healthy control subjects) to 3 (MDD subjects with five or more MDEs). As an alternative approach to normalizing the number of episodes variable, we also used a logarithmic transform; this produced a variable that was highly correlated with the subgroup approach ($r = .98$). However, the grouping approach is preferable because it is less sensitive to variability in retrospective report, which can be subject to bias.

Procedure

All subjects were recruited via advertising within the community. When subjects responded to ads, a trained research assistant administered a telephone screening to assess the presence of general inclusion and exclusion criteria. Subjects deemed eligible were scheduled for an initial clinical assessment session, during which the Structured Clinical Interview for DSM was administered by a certified master's level clinician or psychiatrist and self-report questionnaires were completed. Subjects meeting study inclusion returned for a second session, which included an MRI scan. Structural and functional MRI scans were acquired.

MRI Data Acquisition

Imaging data were acquired using a 1.5-T Symphony/Sonata scanner (Siemens Medical Systems, Iselin, New Jersey). For the purposes of morphometric analysis, a T1-weighted magnetization prepared rapid acquisition gradient-echo image was acquired with the following parameters: repetition time = 2730 msec; echo time = 3.39 msec; field of view = 256 mm; voxel size = 1 × 1 × 1.33; 128 slices.

Hippocampal Subfields and Amygdala Segmentation

Hippocampal and amygdala segmentations of MRI data were performed using the Multiple Automatically Generated Templates for different Brains (MAGeT Brain), a recently published modified multi-atlas algorithm (30,31,37). In more traditional multi-atlas segmentation algorithms, an atlas library is used to obtain several representations of the underlying neuroanatomy of interest. Typically, these libraries contain 20–80 atlases that have been laboriously manually delineated by neuroanatomic experts (38–40). However, these methods are limited by the specific demographics of the atlas library at hand and may be difficult to adapt to new datasets (e.g., using a library of young healthy control subjects to segment a population with a neurodegenerative disorder). These methods are not easily used with atlases that are unique or time-consuming to develop (e.g., atlases derived from reconstructed serial histologic data (41) or high-resolution MRI data) (30). Instead of using multiple input atlases, MAGeT Brain uses the variability inherent in any dataset to limit the number of manually labeled atlases required as input (31,38). The process starts by using five high-resolution atlases of the hippocampus, the hippocampal subfields, and the amygdala as inputs. A subset of the dataset to be segmented is then taken and used as a "template library." For the purpose of the work presented here, 10 control subjects and 11 MDD subjects were used in the template library. Each of the manually labeled atlases was then nonlinearly warped to each subject in the template library, yielding five different possible labels for the different neuroanatomic structures. Each subject to be segmented was then nonlinearly warped to each of the subjects in the template library, and each of the five labels from each subject's template library was warped to fit each subject. This process yielded 105 candidate labels for each subject that were fused using a "majority vote" by taking the most frequently occurring label at every voxel (31). This algorithm has been shown to have limited proportional bias in its estimation of hippocampal volume, and subfield segmentations for MRI data acquired at 3 T were also shown to be accurate.

To this end, five high-resolution atlases of the hippocampus and its subfields were used as input for the automated segmentation (30). The amygdala was manually segmented in the same five high-resolution T1-weighted images following a previously established protocol for manual segmentation of the amygdala (42). All segmentations were checked visually by a trained observer (MTMP) before analysis, based on 15 representative slices encompassing the individual segmentations (Figure 1). After strict quality control, 99 subjects remained for hippocampal subfield analysis. For purposes of methodologic comparison, the relationships between hippocampal volume estimates produced by MAGeT as well as those generated through standard FreeSurfer subcortical volume segmentation (see later) are reported.

Group-Level Analysis of Hippocampal Subfield and Amygdalar Volumes

For the remaining 99 subjects, extracted estimates of hippocampal volume for each subfield were analyzed using linear mixed-effect models with hemisphere as the repeated variable and age, sex, and total intracranial volume included as additional covariates. All linear mixed-effects model analyses were performed using IBM SPSS Statistics for Windows, Version 21 (IBM Corp, Armonk, New York).

VBCT

The VBCT was estimated using FreeSurfer with a processing stream that has previously been described in detail (43). Briefly, the T1-weighted image was preprocessed and segmented to separate cortical gray matter from white matter and subcortical structures. The white-gray boundary was tessellated to form a triangular mesh defining the cortical surface.

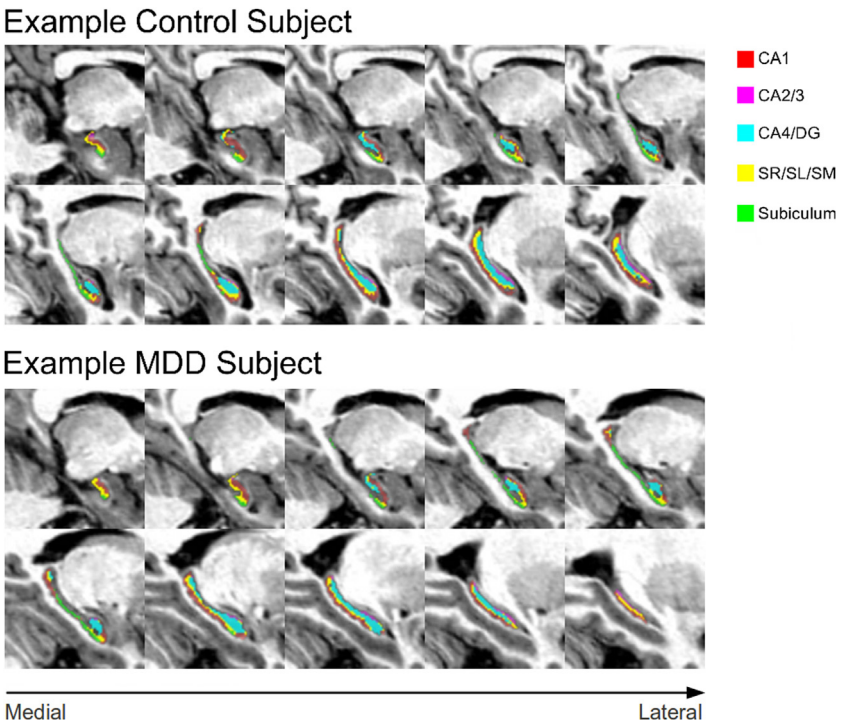

Figure 1. Examples of representative hippocampal subfield segmentations for MDD and control subjects. CA, cornu ammonis; DG, dentate gyrus; MDD, major depressive disorder; SL, stratum lacunosum; SM, stratum moleculare; SR, stratum radiatum.

This mesh was deformed following intensity gradients for optimal location of the white-gray and gray-pial surfaces, and cortical thickness was defined as the shortest distance between the two surfaces at each vertex (44). Additionally, the local curvature of the gray-white surface was calculated and used to drive a nonlinear registration to a common template, which aligned the VBCT maps across subjects for the group analysis (45). The outputs of this automated workflow were visually inspected, and any defects were manually corrected. Consistent with other cortical thickness studies in psychiatric populations (40,41), the VBCT maps were smoothed along the cortical surface with an approximate 15-mm full-width at half maximum Gaussian kernel to account for anatomic variability and to improve the normality of error distributions. A mass-univariate random-effects multiple regression was performed on the resulting maps with an additive model that included number of episodes as a regressor of interest while controlling for age and sex. All 103 subjects were included. Clusters were formed with an uncorrected height threshold of $p < .05$, and correction for multiple comparisons was achieved by using a Monte Carlo simulation of the cluster size distribution under the null hypothesis to threshold the resulting clusters at $p_{corrected} < .05$ (46).

RESULTS

Relationships Between Reported Current Stress and Number of Depressive Episodes

Data from the PSS were unavailable for one control subject and two MDD subjects. The MDD subjects reported significantly higher PSS scores (mean = 34.2, SD = 7.2) compared with controls (mean = 15.6, SD = 6.0) [$t_{98} = -14.10$, $p < .001$]. As would be predicted by the stress-sensitization model, as the number of depressive episodes increased, PSS scores began to decline, creating an inverted U–shaped curve across the entire sample. When comparing linear versus quadratic fits across the sample, the R^2 of the model including a quadratic term ($R^2 = .68$, $p < .001$) was stronger than that of the linear model ($R^2 = .41$, $p < .001$) (Figure 2A). When assessing the MDD group alone, the number of episodes regressor showed a significant inverse relationship to perceived stress ($b = -.24$, $p < .05$ [one-tailed]), indicating that increasing number of prior depressive episodes was associated with decreased PSS scores (Figure 2B). The number of episodes was not associated with differences in average Beck Depression Inventory (BDI) scores [$F_{2,48} = 1.57$, $p = .22$].

Relationships Between Hippocampal Subfield Volume and Number of Depressive Episodes

Full results of hippocampal volume in relationship to number of episodes across all subjects (including control subjects) as well as within the MDD group alone are reported in Table 2. Whole hippocampus volume showed general agreement across the subfield segmentation and standard FreeSurfer segmentation for both hemispheres (left, $r = .857$, $p < .001$; right, $r = .860$, $p < .001$). Across all participants, only the dentate gyrus was associated with a significant reduction in volume as the number of episodes increased ($b = -8.13$, $p = .011$), although cornu ammonis (CA) area CA2/3 exhibited trend-level significance ($b = -2.65$, $p = .054$) (Figure 3). However, within the MDD group alone, all five subregions showed significant declines in volume as a function of multiple episodes, with the strongest effects in the dentate gyrus and stratum (both $p < .0005$). The significance of these within-group

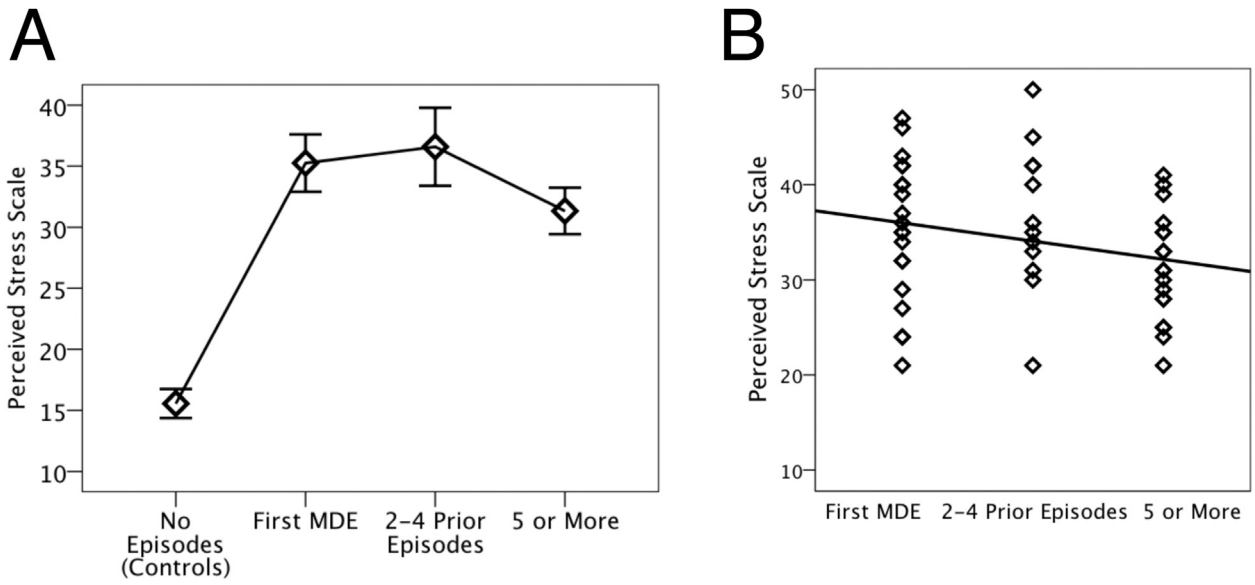

Figure 2. Linear and quadratic relationship between recent stress levels and number of prior episodes. **(A)** Across all subjects, a quadratic model had a significantly better fit (R^2 = .68, p < .001) than the linear model (R^2 = .41, p < .001). Error bars represent ± 95% confidence interval. **(B)** In patients with current depression, the Perceived Stress Scale showed a significant inverse relationship to with number of episodes (b = −.24, p < .05 [one-tailed]). MDE, major depressive episode.

effects was unchanged when BDI or PSS scores were controlled for, and there were no subfields that showed a significant interaction between BDI scores and number of episodes (all p > .28). Finally, we also tested for interactions with gender and number of episodes, but no evidence of a significant interaction was found for any subfield (all p > .20).

On further examination of the data, we observed a general pattern across subfield volume such that MDD subjects with a first MDE typically exhibited slightly enlarged hippocampal volumes compared with control subjects. This pattern was present across all regions. To test whether this pattern represented a significant increase in volume, we repeated the above-mentioned analyses while restricting our sample to healthy control subjects and MDD subjects with a first MDE. No subfields showed a significant difference (all p > .41).

Amygdala Volume Analysis

Similar to the hippocampus, volumetric changes in the amygdala have also been implicated in depression (32), making the amygdala a useful control region for examination of the specificity of the association between repeated episodes and hippocampal subfield volume. For both groups, amygdala and hippocampal volumes were highly correlated (controls subjects, r = .80, p < .001; MDD subjects, r = .72, p < .001). However, across all subjects, we did not observe any association with number of episodes and amygdala volume (b = −1.09, p = .86), and we did not observe any association within the MDD group alone (b = −20.09, p = .14). This finding was unchanged when BDI and PSS scores were controlled for. Additionally, we observed no significant difference between control subjects and MDD subjects with a first MDE (b = 10.80, p = .49).

Whole-Brain VBCT Analysis

For cortical thickness, the number of prior episodes was associated with significant decreases in left mPFC, including aspects of Brodmann areas 24 and 25, bilateral parahippocampal gyrus, and bilateral portions of motor and premotor cortex (Figure 4A and Table 2). No other regions showed a significant negative association with prior depressive episodes, and there were no regions characterized by increased cortical thickness as a function of number of MDEs. These results were unchanged when controlling for both depression symptom severity as assessed by the BDI and perceived stress as measured by the PSS. Neither the BDI nor the PSS showed any significant association with cortical thickness. Additionally, no region showed a significant interaction between gender and number of episodes (Table 3).

DISCUSSION

The overarching goal of the present study was to evaluate changes in gray matter morphometry as a function of illness progression in patients with MDD. Our findings are broadly consonant with sensitization models of recurrence. As expected, reported perceived stress levels were lower in individuals with multiple episodes compared with patients with a first episode, although still higher than control subjects with no history of depression. We also observed that the number of prior MDEs was a strong predictor of structural changes in two key brain areas associated with both depression and stress: the hippocampus and mPFC.

The identification of both hippocampal and mPFC regions as showing a relationship to number of episodes is consistent with both theoretical models and preclinical evidence relating stress with structural microdamage in these areas. Both

Table 2. Results from Linear Mixed Models Analysis of Effects of Number of Episodes on Hippocampal Subfield Volume

Model Tested	β (Unstandardized)	SE	*p* Value
Number of Episodes (All Subjects)			
CA1	−6.31	4.56	.167
CA2-3	−2.65	1.36	.054
CA4/dentate gyrus[a]	−8.13	3.15	.011
Stratum	−5.25	3.74	.162
Subiculum	.38	2.71	.887
Whole hippocampus	−22.36	13.09	.089
Number of Episodes (MDD Only)			
CA1[b]	−27.81	8.07	.00086
CA2-3[a]	−6.11	2.59	.02028
CA4/dentate gyrus[c]	−23.19	5.74	.00011
Stratum[c]	−25.64	6.67	.00023
Subiculum[a]	−12.69	5.14	.01534
Whole hippocampus[c]	−95.72	22.61	.00006

All models include, sex, age, and total brain volume as covariates. Model results are shown for each subfield as examined across all subjects and within MDD subjects.

CA, cornu ammonis; MDD, major depressive disorder.

[a] $p < .05$.

[b] $p < .005$.

[c] $p < .0005$.

regions express high numbers of glucocorticoid receptors, which are believed to play a critical role in mediating negative-feedback regulation of glucocorticoid release during stress (47,48). In animal models, chronic stress exposure and local corticosteroid injections produce structural alterations in these regions, including dearborization and loss of dendritic spines (49–52). This stress-induced microdamage has been linked to behavioral changes that mimic aspects of a depressive state, including impaired working memory, decision making, and goal-directed behavior (53–55). In humans, similar relationships have been observed among stress, cortisol, glutamate pathways, and gray-matter volume in these regions in both samples with depression and samples without depression (56–60).

Prior studies have indicated that hippocampal volume is sensitive to course of illness in MDD, with initial reports suggesting that volumetric deficits in the hippocampus were inversely related to both number of episodes (22) and duration of untreated illness (21). Further research confirmed the sensitivity of this structure to clinical course, with evidence that reduced hippocampal volumes were partially remediated by antidepressant treatment (23,25,61) as well as a remitted state obtained without treatment (25). However, these past studies did not examine the relationship between number of prior episodes and subfields within the hippocampus. Although our analysis of hippocampal subfields suggested that number of prior episodes was broadly associated with reduced volumes among patients with current depression, the strongest effects for both within-group and between-group analyses were found in the dentate gyrus. This region is believed to be the primary site of newly developing cells (62), which may render it especially vulnerable to the noxious effects of glucocorticoids and inflammation (13,63). Damage to this region may underlie well-documented impairments in memory functioning in patients with MDD (26,64,65), which also have been strongly linked to number of prior episodes (66). A more recent study found that hippocampal subfield volume—especially in the dentate gyrus—was correlated with memory performance in healthy older adults (67).

Whole-brain VBCT analysis revealed an association with the number of episodes and decreased cortical thickness in the left mPFC, including aspects of rostral and subgenual anterior cingulate as well as reductions in bilateral parahippocampal gyrus and surrounding temporal cortex. The mPFC is of particular interest given its key role in mediating adaptive versus "learned helplessness" responses to stress (68). In particular, deactivation of mPFC projections to key midbrain monoaminergic nuclei can result in learned helplessness behavior after stress exposure in rodents (69,70). Similarly in humans, function and structure of this region has

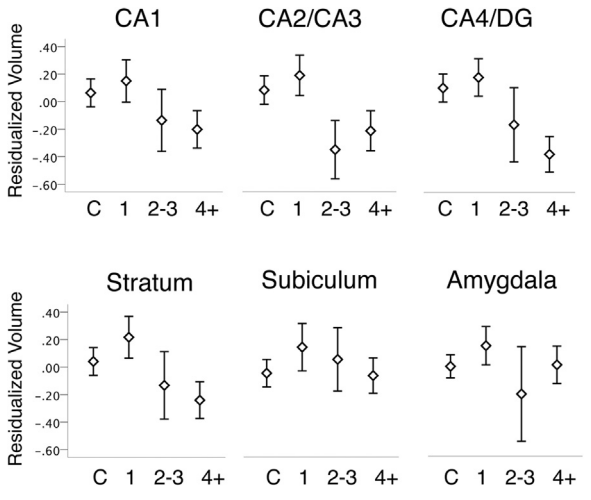

Figure 3. Effects of number of episodes on volume of hippocampal subfields and amygdala (averaged across hemisphere). The x axis shows number of prior depressive episodes with "C" denoting never-depressed control subjects. The y axis shows residualized volume after controlling for sex, age, and total brain volume. Error bars represent ± SEM. CA, cornu ammonis; DG, dentate gyrus.

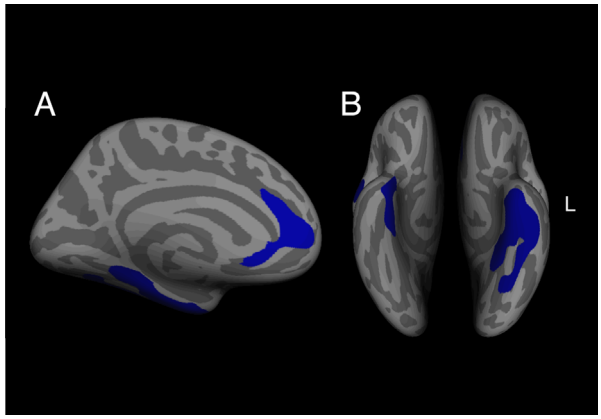

Figure 4. Areas showing an association between cortical thickness and number of depressive episodes across all subjects, cluster-corrected. Regions shown include the left medial prefrontal cortex **(A)** and bilateral parahippocampal gyrus and medial temporal cortex **(B)**. L, left.

Table 3. Results from Whole-Brain Analysis of Effects of Number of Episodes on Cortical Thickness

Region	Talairach Coordinates x	y	z	*z* Score	*p* Value (Cluster)
Effects of Prior MDEs (Including Controls)					
Right precentral gyrus	56	1	33	−3.75	.0001
Left middle frontal gyrus	−31	6	49	−3.58	.0024
Left parahippocampal gyrus	−29	−41	−5	−3.31	.0001
Right parahippocampal gyrus	34	−14	−26	−3.30	.038
Left anterior cingulate	−2	22	3.1	−2.87	.026

Sex and age are included as covariates.
MDE, major depressive episode.

consistently been related to regulation of negative affect (71–74). The laterality of this effect is also notable, given long-standing evidence for prefrontal hemispheric differences in MDD, including a meta-analysis showing asymmetry in the magnitude of volumetric reductions in left versus right prefrontal cortex (15), reduced white matter integrity in left prefrontal cortex associated with duration of illness (75), and hyporecruitment of left prefrontal electroencephalogram activity (76–78).

Taken together, these results highlight structural damage to mPFC as being a critical factor in risk for recurrence. Such damage may occur as a consequence of prior MDEs, consistent with stress-sensitization models. Alternatively, naturally occurring variation in cortical thickness of mPFC may reflect a biological diathesis that confers risk for multiple depressive episodes. Consistent with this latter interpretation, similar patterns of cortical thinning in mPFC have been observed in individuals with no history of depression with elevated polygenic risk for MDD (24). Given the cross-sectional nature of our study, we are unable to speculate on the direction of causality. However, in either case, these findings isolate the structural integrity of the mPFC as a potential bulwark against MDE relapse because individuals with reduced thickness in this region reported more prior episodes despite lower levels of recent stress.

The present study has some limitations. First, our subjects were scanned on a 1.5-T scanner, which has reduced sensitivity compared with images acquired at higher field strengths. Second, sample sizes within the number of episodes categories were modest, with one cell with 12 participants, although the concern of low power is tempered by focus on linear trend analysis across all categories. Second, the cross-sectional nature of the study limits our ability to characterize fully the fluctuations in structure that may occur as individuals move in and out of depressive episodes. Finally, we relied on retrospective report regarding the number of episodes. Although this metric has been used in prior studies, retrospective reports can be subject to biases. We attempted to limit such biases by grouping the number of episodes into several categories so as to minimize the effect of inaccurate recall; this approach also helped to normalize the distribution of scores.

In conclusion, this study provides important evidence for stress-sensitization models of illness progression in MDD and points to pathophysiologic correlates of the apparent decoupling between external stressors and subsequent episodes. These results suggest that stress-linked microdamage in mPFC may be a critical mechanism in this process, although the role of premorbid structural abnormalities cannot be ruled out. More generally, by providing a critical link between MDE history and animal models of structural degeneration, these findings help further our understanding of the pathophysiology of MDD. Finally, these results also have potential implications for treatment. In particular, they contribute to the growing literature suggesting that hippocampal volume may be a potential biomarker for depression (26). In addition, these results highlight the dentate gyrus as a potential treatment target for novel compounds or cognitive retraining protocols that may help remediate volumetric reductions (67).

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