Association of disease course and brain structural alterations in major depressive disorder

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Abstract
Introduction: The investigation of disease course-associated brain structural alterations in Major Depressive Disorder (MDD) have resulted in heterogeneous findings, possibly due to low reliability of single clinical variables used for defining disease course. The present study employed a principal component analysis (PCA) on multiple clinical variables to investigate effects of cumulative lifetime illness burden on brain structure in a large and heterogeneous sample of MDD patients.

Methods: Gray matter volumes (GMV) was estimated in n = 681 MDD patients (mean age: 35.87 years; SD = 12.89; 66.6% female) using voxel-based-morphometry. Five clinical variables were included in a PCA to obtain components reflecting disease course to associate resulting components with GMVs.

Results: The PCA yielded two main components: Hospitalization reflected by patients’ frequency and duration of inpatient treatment and Duration of Illness reflected by the frequency and duration of depressive episodes. Hospitalization revealed negative associations with bilateral dorsolateral prefrontal cortex (DLPFC) and left insula volumes. Duration of Illness showed significant negative associations with left hippocampus and right DLPFC volumes. Results in the DLPFC and hippocampus remained significant after additional control for depressive symptom severity, psychopharmacotherapy, psychiatric comorbidities, and remission status.

Conclusion: This study shows that a more severe and chronic lifetime disease course in MDD is associated with reduced volume in brain regions relevant for executive...
INTRODUCTION

Course of disease is probably the most crucial aspect of disease burden in patients suffering from Major Depressive Disorder (MDD). Within 2 years, more than half of patients with MDD experience depressive relapse (Kanai et al., 2003) and the probability of experiencing recurrent depressive episodes rises up to 90% after 3–4 lifetime episodes (Monroe & Harkness, 2011). The interplay of MDD disease course and brain morphologic alterations can enhance our understanding of neuropathological mechanisms of severe or chronic disease trajectories to improve illness prediction and treatment response. In the last decades, effects of MDD disease course on brain morphometry represented by single clinical variables (e.g., number of depressive episodes, age of onset) have reported inconsistent findings. The aim of this study was to incorporate multiple clinical variables of MDD disease course and to link these measures to brain morphometric alterations in a large sample of MDD patients to provide a reliable measure of disease course employable in clinical research and practice.

Underlying neuropathological models of MDD emphasize a critical role of chronic or long lasting stress exposure on brain structure (Belleau et al., 2019). During stress exposure, the adrenal gland releases glucocorticoids which bind to glucocorticoid and mineralocorticoid receptors located in various brain regions (López et al., 1998) resulting in cell loss and cell atrophy, for example in the dorsolateral prefrontal cortex (DLPFC), cingulate cortex or hippocampus (Rajkowska, 2000; Reagan & McEwen, 1997). These stress-related neuroplastic changes have been associated with depression by neuroimaging studies demonstrating gray matter volume (GMV) loss in patients with MDD compared to healthy controls (Belleau et al., 2019; Schmaal et al., 2016, 2017). Measures of illness burden in MDD, commonly reflected by longer and more frequent illness episodes rather than acute depression severity, may result in enhanced stress exposure followed by potential neuronal loss in these brain regions (Sapolsky, 2000; Zaremba et al., 2018b).

Previous research on brain structural correlates of disease course in MDD mainly focused on single clinical variables as indicators for disease severity. Early age of onset (McKinnon et al., 2009; Schmaal et al., 2016, 2017; Takahashi et al., 2010), a higher number of depressive episodes (Bora et al., 2012; McKinnon et al., 2009; Stratmann et al., 2014; Treadway et al., 2015) and cumulative time in depressive episodes (Bora et al., 2012; McKinnon et al., 2009; Stratmann et al., 2014; Treadway et al., 2015) and cognitive functions and emotion regulation in a large sample of patients representing the broad heterogeneity of MDD disease course. These findings were only partly influenced by other clinical characteristics (e.g., remission status, psychopharmacological treatment).

KEYWORDS
disease course, dorsolateral prefrontal cortex, hippocampus, insula, major depressive disorder, structural neuroimaging
The main goal of the current study was to improve the characterization of disease course of MDD by incorporating several clinical measures into comprehensive component scores and to link these components to brain structural alterations in a large sample of MDD patients. We included currently depressed and remitted patients as well as first-episode and recurrent patients to ensure sufficient sample heterogeneity regarding disease course. We expected the following:

(1) To find a similar two-component structure with Hospitalization and Duration of Illness characterizing lifetime disease course by employing a PCA (Lemke et al., 2021; Zaremba et al., 2018b).

(2) Based on former literature that the hippocampus, insula and DLPFC are specifically related to disease progression in cross-sectional and longitudinal studies (Frodl et al., 2008; Schmaal et al., 2017; Zaremba et al., 2018a, 2018b), we expected negative associations between component scores and GMV reductions in these three brain areas employing a regions of interest (ROI) approach.

2 | METHODS AND MATERIALS

2.1 | Participants

N = 681 patients were included from the Marburg-Münster-Affective-Cohort-Study (MACS) study which was conducted at two different sites in Germany, Münster and Marburg (for details see Kircher et al., 2019, Supporting Information S1). Patients were recruited in psychiatric hospitals or through newspaper advertisements. Inclusion criterion was either a current or lifetime diagnosis of MDD. Exclusion criteria are provided in Supporting Information S2.

All patients underwent the Structured Clinical Interview (SCID-I) to assess clinical diagnoses according to DSM-IV-TR criteria (Wittchen et al., 1997). During the SCID-I, trained personnel obtained patients disease course including the five variables: number of lifetime psychiatric hospitalizations, cumulative lifetime duration of psychiatric hospitalizations, time since the first psychiatric symptoms, number of lifetime depressive episodes and cumulative lifetime duration of depressive symptoms.

The current level of depressive symptoms was acquired with the 21-item Hamilton Depression Rating Scale (HDRS, (Hamilton, 1960)). To evaluate the possible impact of current psychopharmacological treatment, a medication load index was calculated (Hassel et al., 2008; Redlich et al., 2015). Each medication was coded as absent = 0, low/average dose = 1 or high dose = 2 according to the average daily dose range recommended by the Physician’s-Desk-Reference and summed up in a composite score. Demographic and clinical characteristics can be found in Table 1 and Supporting Information S3.

The study was performed in accordance with the ethical guidelines and regulations and was approved by the ethics committees of the Medical Faculties of the University of Münster and

| TABLE 1 | Sociodemographic and clinical characteristics of the sample (n = 681) |
|----------|---------------------------------------------------------------|
|          | Mean | SD  | Range    |
| Sociodemographic and depressive characteristics |      |      |          |
| Sex (female/male) | 454/227 |      |          |
| Age                           | 35.87 | 12.89 | 18–65   |
| Years of education             | 13.30 | 2.63  | 8–18    |
| Scanner settings (MR-BCpre/MR-BCpost/MS) | 196/53/432 |      |          |
| HDRS scores                     | 9.49  | 7.27  | 0–32    |
| Remission status (acute/remitted) | 288/393 |      |          |
| First/Recurrent MDD (first/recurrent) | 259/422 |      |          |
| Medical characteristics*   |      |      |          |
| Medication load index             | 1.31  | 1.49  | 0–10    |
| None                               | 274   | -     | -       |
| SNRI                               | 100   | -     | -       |
| SSRI                               | 101   | -     | -       |
| NaSSA                              | 40    | -     | -       |
| NDRI/NaRI                           | 9     | -     | -       |
| Antipsychotics                      | 68    | -     | -       |
| Tricyclic antidepressants            | 21    | -     | -       |
| Mood stabilizers                    | 10    | -     | -       |
| Others                              | 28    | -     | -       |
| Disease course variables           |      |      |          |
| Number of lifetime hospitalizations | 1.40  | 1.74  | 0–17    |
| Lifetime duration of hospitalization (weeks) | 11.31 | 17.55 | 0–187   |
| Number of lifetime depressive episodes | 3.47  | 5.74  | 1–90    |
| Lifetime duration of depressive episodes (months) | 41.31 | 58.3  | 1–432   |
| Time since first psychiatric symptoms (months) | 120.72 | 113.86 | 0–600   |
| Lifetime comorbidities*            |      |      |          |
| None                               | 394   | -     | -       |
| Social anxiety disorder             | 73    | -     | -       |
| Panic disorder with agoraphobia     | 24    | -     | -       |
| Panic disorder without agoraphobia  | 23    | -     | -       |
| Agoraphobia without history of panic disorder | 5     | -     | -       |
| Specific phobia                    | 49    | -     | -       |
| Generalized anxiety disorder        | 22    | -     | -       |
| Obsessive-compulsive disorder       | 20    | -     | -       |
| Eating disorder                     | 62    | -     | -       |

(Continues)
Marburg. All participants gave written informed consent and received financial compensation for their participation.

### 2.2 Image acquisition

T1-weighted high-resolution anatomical data were collected at 3T magnetic resonance imaging (MRI) scanners at both sites. Detailed descriptions of MRI sequence parameters are provided in Supporting Information S4. During data acquisition, the body-coil in Marburg was exchanged resulting in three different scanner settings for all analyses (Marburg body-coil pre, Marburg body-coil post and Münster) (Vogelbacher et al., 2018).

### 2.3 Voxel-based morphometry (VBM)

T1-weighted images were pre-processed using a default processing pipeline implemented in the VBM8-toolbox (http://dbm.neuro.uni-jena.de/vbm, Version r445) including bias-correction, normalization to MNI-space using linear and nonlinear transformation (including high-dimensional DARTEL-normalization) and tissue classification. As the nonlinear modulations directly allows the correction for different head sizes, total intracranial volume is not needed as covariate in second level statistical models. Quality checks were performed following the quality assurance protocol by the MACS-study (Vogelbacher et al., 2018). Modulated gray matter segments were smoothed with an 8 mm full width half maximum Gaussian kernel.

### 2.4 Statistical analyses

First, we performed a PCA including the five clinical variables of disease course using IBM SPSS Statistics 28 (SPSS Inc.). An oblique promax rotation was applied to increase interpretability of the components as the clinical variables showed significant intercorrelations (range $r=.158-.828$). Eligibility of the data to perform a PCA were assured by adducing the Kaiser-Meyer-Olkin criterion and Bartlett’s test. The number of components to be extracted was determined using the Kaiser-Guttman criterion of an eigenvalue >1 and by conducting a parallel analysis (Horn, 1965). For each patient, a regression score for resulting components was extracted.

GMV analyses were performed using Statistical Parametric Mapping (SPM12, Wellcome Department of Cognitive Neurology, London, UK, v7771). For the hippocampus, insula and DLPFC separate bilateral ROIs were created according to the AAL-atlas definitions (Tzourio-Mazoyer et al., 2002) integrated in the WFU-pickatlas (Maldjian et al., 2003). The ROI of the DLPFC was constructed using the bilateral middle frontal gyrus (dilated by 2 mm) as suggested in previous studies (Coelho et al., 2012; Liu et al., 2016). Allocation of effects in the insula (anterior or posterior) were more closely examined using the neuromorphometrics atlas (Neuromorphometrics, Inc., Somerville, MA, USA). We applied threshold-free cluster enhancement (TFCE) implemented in the TFCE-toolbox (http://dbm.neuro.uni-jena.de/tfce, v222) with significance threshold using a family-wise-error (FWE) correction of $p<.05$ and 5000 permutations per test.

In a second step, to investigate the relationships between the obtained component scores and GMV of the ROIs, we conducted regression analyses for each component separately. Age, sex and scanner settings (Münster, Marburg body-coil pre/post) were included as control variables.

Third, to further elucidate whether the association of component scores with GMV remained significant when taking into account other disease characteristics, the regression analyses were repeated in SPM with HDRS scores, Medication Load Index, remission status (acute vs. remitted) and comorbidities (yes vs. no) as additional control variables.

Fourth, sensitivity analyses with the five single clinical variables were performed to evaluate the benefits of performing a PCA, controlling for age, sex and scanner settings.

Fifth, to explore whether the significant associations between disease components and GMVs of the three ROIs (from step two) might interact with other sample or disease characteristics, we performed additional interaction analyses in SPM. Patients were subgrouped according to sex, age, remission status, first or recurrent episodes, medication load index and HDRS scores (details on subgroups in Supporting Information S5), respectively. Based on these subgroups, we performed interaction analyses between disease components and each characteristic using $F$-tests including scanner settings, age and sex (if not used to group patients for the analysis) as control variables.

Last, exploratory whole-brain analyses were performed for the statistical tests of step two (regression analyses with both component scores) and step five (interaction analyses) controlling for age, sex and scanner settings at $p<.001$, uncorrected, and a cluster threshold of $k=50$ voxels.

| TABLE 1 (Continued) |
|----------------------|
| Mean | SD  | Range |
|-------|-----|-------|
| Posttraumatic stress disorder | 55  | -    | -    |
| Somatoform disorder   | 23  | -    | -    |

Abbreviations: HDRS, Hamilton Depression Rating Scale; MDD, major depressive disorder; MR-BCpost, Marburg site, past body-coil change; MR-BCpre, Marburg site prior body-coil change; MS, Münster; NaSSA, noradrenergic and specific serotonergic antidepressant; NDRI/NaRI, norepinephrine-dopamine reuptake inhibitor/noradrenaline reuptake inhibitor; SNRI, serotonin-norepinephrine reuptake inhibitors; SSRI, selective serotonin reuptake inhibitor.

*Multiple entries per patient possible.
3 | RESULTS

3.1 | Principal component analysis

Based on the eigenvalues >1 and the parallel analysis (Horn, 1965), two components were extracted explaining 74.62% of the total variance ($EV_{Component1} = 2.35$; $EV_{Component2} = 1.28$). Detailed results of the PCA are displayed in Supporting Information S6. The first component explained 47.09% of the variance and included the number and cumulative duration of lifetime psychiatric hospitalizations. The second component accounted for 25.59% of the variance and was associated with time since first psychiatric symptoms, and number and duration of lifetime depressive episodes. Relating to both previous studies, the first component was termed Hospitalization and the second component Duration of Illness (Lemke et al., 2021; Zaremba et al., 2018b).

3.2 | Regression analyses of Duration of Illness and GMV

Duration of Illness showed a significant negative association with left hippocampal GMV ($x = -30$, $y = -30$, $z = -12$, $t(675) = 2.97$, $k = 354$, $p_{FWE} < 0.05$).

FIGURE 1  Negative association of Duration of Illness component scores and left hippocampal GMV in patients depicted at $x = -30$, $y = -30$ and $z = -12$ at statistical significance of $p_{FWE} < 0.05$. (a) Sagittal view. The color bar depicts T-values. (b) Scatterplot depicting mean cluster values of the left hippocampus. Continuous line represents regression slope. GMV, gray matter volumes.
$p_{FWE} = .027, r = -.237, \beta = -.121,$ Figure 1) and right DLPFC GMV ($x = 44, y = 36, z = 22, t(675) = 3.33, k = 63, p_{FWE} = .039, r = -.127, \beta = -.126,$ Supporting Information S7). No associations between Duration of Illness and GMV of the right hippocampus, left DLPFC, or bilateral insula were found (all $p > .090$). Regression analysis with Duration of Illness additionally controlling for HDRS scores, Medication Load Index, lifetime comorbidities and remission status remained significant in the left hippocampus GMV ($x = -28, y = -24, z = -17, t(671) = 3.32, k = 158, p_{FWE} = .027, r = -.124, \beta = -.133$). Exploratory whole brain analyses showed an association between Duration of Illness with reduced GMV in the left parahippocampal and fusiform gyrus and right cerebellum (Supporting Information S8).

3.3 | Regression analyses of Hospitalization and GMV

The ROI analyses with Hospitalization revealed significantly decreased GMV in association with higher Hospitalization scores in the bilateral DLPFC (right: $x = 46, y = 34, z = 22, t(675) = 4.44, k = 998, p_{FWE} < .001, r = -.238, \beta = -.137$; left: $x = -50, y = 22, z = 26, t(675) = 3.48, k = 616, p_{FWE} = .011, r = -.234, \beta = -.111$, Figure 2) and left insula ($x = -34, y = 16, z = 2, t(675) = 3.25, k = 377, p_{FWE} = .028, r = -.226, \beta = -.105$, Supporting Information S7). According to the neuromorphometric atlas, the insula effect was located in the anterior subdivision (45.7%) and the frontal operculum (30.8%). No significant associations with bilateral hippocampal and right insula GMVs were found (all $p > .057$). The regression analysis under the additional control of HDRS scores, Medication Load Index, lifetime comorbidities and remission status showed a significant negative association between Hospitalization and GMVs of the right DLPFC ($x = 45, y = 34, z = 21, t(671) = 3.55, k = 499, p_{FWE} = .013, r = -.236, \beta = -.131$). Exploratory whole brain analyses with Hospitalization revealed GMV reductions in the bilateral inferior frontal gyrus, right middle frontal gyrus, right rolandic operculum, superior temporal, supramarginal and post-central gyrus, left middle temporal gyrus and left insula (Supporting Information S8).

![FIGURE 2](image_url) Negative association of Hospitalization component scores and bilateral DLPFC GMV in patients depicted at $x = 46, y = 34$ and $z = 19$ at statistical significance of $p_{FWE} < .05$. (a) Left = axial view, right = sagittal view. The colour bar depicts t-values. (b) Scatterplot depicting mean cluster values of right (grey) and left (black) DLPFC. Continuous lines represent regression slopes. GMV, gray matter volumes
3.4 Additional analyses

In the regression analyses with the five single variables (Supporting Information S9), number (left: \( p_{\text{FWE}} = .013 \)) and duration (right: \( p_{\text{FWE}} = .016 \); left: \( p_{\text{FWE}} = .037 \)) of depressive episodes were negatively associated with hippocampal GMVs. Duration of psychiatric hospitalization (right: \( p_{\text{FWE}} = .016 \); left: \( p_{\text{FWE}} = .025 \)) and time since first psychiatric symptoms (right: \( p_{\text{FWE}} = .007 \)) were associated with reduced GMVs of the DLPFC. Number of psychiatric hospitalization was associated with reduced GMVs of the DLPFC (right: \( p_{\text{FWE}} = .001 \); left: \( p_{\text{FWE}} = .004 \)) and insula (right: \( p_{\text{FWE}} = .034 \); left: \( p_{\text{FWE}} = .045 \)).

The interaction analyses showed no significant interactions between disease components and any sample or disease characteristic on GMVs of the three ROIs (all \( p_{\text{FWE}} > .074 \)). The exploratory whole-brain interaction analyses revealed interactions between the disease components on GMVs for age (supplementary motor area frontal gyrus, precuneus), sex (frontal gyrus and fusiform gyrus) remission status (occipital and frontal gyrus and anterior and middle cingulate), HDRS scores (caudate nucleus), Medication Load Index (middle cingulate cortex and temporal gyrus), first versus recurrent depression (middle frontal, occipital and temporal gyrus) and psychiatric comorbidity (posterior cingulate cortex and hippocampus) (Supporting Information S10).

4 DISCUSSION

The present study investigated associations of lifetime disease course and brain structural alterations in a large and heterogeneous sample of MDD patients. Employing data reduction on several clinical variables, we show that previous lifetime disease course was related to lower GMV in the bilateral DLPFC, left hippocampus and left insula. Furthermore, interaction analyses revealed that these negative associations did not interact with other sample or disease characteristics such as age, sex, acute symptom severity, remission status and psychiatric comorbidity.

Employing a PCA approach to characterize disease course, our study confirmed a two-component structure with Duration of Illness and Hospitalization as previously described in two studies (Lemke et al., 2021; Zaremba et al., 2018b). The component Duration of Illness showed a negative correlation with left hippocampus and right DLPFC GMVs. The negative association in the hippocampus remained significant when taking into account other disease characteristics such as current symptomatology and medication. This finding is in line with previous studies reporting negative associations between smaller hippocampal volumes and single clinical variables (MacQueen et al., 2003; McKinnon et al., 2009; Schmaal et al., 2014). Reduced hippocampal GMV in MDD has been suggested to either represent a risk factor for the development of MDD or constitute a marker for a more severe disease course (Redlich et al., 2018; Schmaal et al., 2016).

The component Hospitalization revealed negative associations with GMV of the DLPFC and insula. Structural and functional neuroimaging data suggest a pivotal role of the DLPFC and insula in the pathophysiology of MDD, namely deficits in cognitive and executive functions as well as emotion regulation (Mayberg, 2003; Nagai et al., 2007). Evidence for a detrimental effect of course of disease on GMV comes from longitudinal imaging studies, for example relapse (Zaremba et al., 2018a) and chronic disease course (Frodl et al., 2008), resulting in GMV loss in the DLPFC, insula and hippocampus. Our effect in the insula was mainly located in the anterior subdivision. This part is reciprocally connected to the DLPFC and has been implicated in cognitive processes such as salience detection and attention (Menon & Uddin, 2010) but also awareness of subjective feelings (Craig, 2009). Thus, our results may provide evidence that particularly the anterior insula could be sensitive to illness severity, although the effect did not remain significant after controlling for medication, remission status and psychiatric comorbidities. Further, our whole brain results point towards negative associations between the component Hospitalization and frontal and temporal brain regions as well as negative associations between Duration of Illness and parahippocampal and fusiform gyrus. However, the exploratory, uncorrected results need to be interpreted with caution.

Relating to the limbic-cortical dysregulation model of MDD (Mayberg, 2003) and the critical role of stress-related effects (Belleau et al., 2019), more severe disease course might be associated with enhanced stress exposure in MDD. Repetitious stress which can be defined as recurrence or frequency of depressive episodes results in cell loss in several brain regions including the DLPFC and hippocampus (Rajkowska, 2000; Reagan & McEwen, 1997; Sapolsky, 2000). Our findings of reduced hippocampal, DLPFC and insula GMVs are in line with these neural mechanisms of stress. As our study was cross-sectional in nature, reduced GMV could be a result from more frequent and longer depressive episodes and inpatient treatment or represent a vulnerability factor for more unfavorable courses of disease. This highlights the importance to further elucidate longitudinal effects of disease course on brain structure to understand causal relationships.

These findings remained partly significant after taking into account current remission status, current symptom severity, psycho-pharmacological intake and presence of lifetime comorbidities. In addition, we neither found any significant interactions with these illness characteristics nor with age and sex in the three ROIs. This allows the conclusion that the relationship between lifetime disease course and reduced GMVs of the hippocampus and DLPFC might not interact with other disease characteristics. Nonetheless, our exploratory whole-brain interaction analyses suggest that there may be associations between disease course and GMVs (e.g., in the cingulate cortex, temporal/frontal regions) that could be moderated by other sample or illness characteristics (Supporting Information S10). As effects of current disease status (Arnone et al., 2013) and neuroprotective effects of psychopharmacotherapy (Liu et al., 2017) have been found, these clinical information should, however, be considered in future studies to further evaluate their potential influence. Interestingly, acutely depressed patients showed higher...
scores on disease course variables compared to remitted patients. This could indicate a general higher frequency and severity of MDD in this subgroup, but also another factor which we did not consider might underlie this disparity.

The present study holds several strengths. First, the successful implementation of a data driven PCA to combine multiple clinical variables into superordinate component scores in a large and heterogeneous sample of MDD patients. The additional analyses of the single clinical variables showed that the underlying variables result in comparable effects reported for the PCA components. Thus, the combination of multiple variables requires less multiple testing and is more robust to extreme values of patients self-reports on single clinical variables and therefore may provide a more reliable measure of MDD disease course in research and clinical practice. Another strength of our study is that we examined interaction with additional sample or illness characteristics (age, sex, remission status, etc.) which could have potential influence on the association between disease course and impaired brain structure.

Some methodological aspects of this study need to be addressed. The heterogeneity of our study sample was on one side a main goal, but on the other side a challenging aspect when investigating generalized effects of disease course on brain structure. Former studies mainly used specific subgroups of patients (e.g., remitted vs. acutely depressed) with comparably small sample sizes. Large and heterogeneous samples are necessary to investigate psychopathological mechanisms of MDD that are valid across the heterogeneous entity of patients. Second, the component Duration of Illness was based on self-reported clinical variables which can be affected by memory bias or due to difficulties retrieving the preceding course of illness (Patten et al., 2012; Williams et al., 2007). Methodological improvements deploying assessments of episode patterns (Post et al., 1988) could enhance precision of characterization of disease course. Third, inpatient treatment is indicated for moderate/severe episodes or presence of suicidal ideation/behavior. This raises the question whether our Hospitalization component may reflect general symptom severity or specific symptomatology related to suicidality.

In conclusion, our study confirmed the implementation of a data driven technique to incorporate different clinical variables into component scores reflecting disease course in a heterogeneous sample of MDD patients. Our findings show that a more severe and chronic lifetime disease course is associated with lower GMVs in the hippocampus, DLPFC and insula. In this context, stress-driven technique to incorporate different clinical variables into component scores reflecting disease course in a heterogeneous sample of MDD patients. Our findings show that a more severe and chronic lifetime disease course is associated with lower GMVs in the hippocampus, DLPFC and insula. In this context, stress-driven technique to incorporate different clinical variables into component scores reflecting disease course in a heterogeneous sample of MDD patients. Our findings show that a more severe and chronic lifetime disease course is associated with lower GMVs in the hippocampus, DLPFC and insula. In this context, stress-driven technique to incorporate different clinical variables into

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DATA AVAILABILITY STATEMENT
All PIs take responsibility for the integrity of the respective study data and their components. All authors and coauthors had full access to all study data. The data that support the findings of this study are available from the corresponding author upon reasonable request.

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SUPPORTING INFORMATION  
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