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Reduced thalamic volumes in major depressive disorder

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Abstract

Altered function in the limbic-cortical-striatal-pallidal-thalamic (LCSPT) circuit has been implicated in the pathophysiology of major depressive disorder (MDD). This study evaluated volumetric differences in subcortical volumes between depressed subjects with MDD (N=142), subjects with MDD in remission (N=72), and healthy controls (N=169). Participants underwent magnetic resonance imaging (MRI) scanning, and subcortical volumes were extracted using FIRST (FMRIB's Integrated Registration and Segmentation Tool, University of Oxford, UK). The depressed MDD subjects exhibited significantly smaller volumes in the bilateral thalamus and hippocampus compared to control subjects, and the differences in the bilateral thalamus remained significant after controlling for total intracranial volume. In a smaller subset of healthy controls and depressed MDD subjects matched to the remitted MDD subjects, significant differences in volume were observed across groups in the bilateral thalamus, as well as the right lateralized caudate, hippocampus, and pallidum; these were primarily accounted for by differences between the depressed MDD subjects versus both the remitted and healthy subjects, though none of these changes remained significant after controlling for total intracranial volume (TIV). Volumetric reductions in the thalamus and hippocampus may contribute to dysfunction within subcortical-cortical networks, consistent with previous evidence of metabolic and hemodynamic abnormalities in these regions in MDD.

Keywords

Depression; Magnetic Resonance Imaging; Morphometry

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1. Introduction

Major depressive disorder (MDD) is a potentially debilitating psychiatric disorder characterized by feelings of guilt, anhedonia, and sadness, and may involve dysfunction in cognition, sleep, appetite, and energy. Abnormalities in multiple brain regions have been implicated in the disorder, many of which are part of the limbic-cortical-striatal-pallidal-thalamic (LCSPT) network (Drevets et al., 2008; Sheline, 2000). The importance of this network in the development of depression has been established in subjects suffering from post-stroke depression or depression associated with degenerative diseases of the basal ganglia, which are associated with neuropathological changes within the structures of the network (Beblo et al., 1999; Levada and Slivko, 2006). The results of in vivo neuroimaging and post-mortem histopathological studies involving subjects with primary mood disorders have also implicated the LCSPT network in the pathophysiology of depression.

Of the subcortical structures, the hippocampus has been particularly well studied in depression. Although the literature is far from unanimous, most reviews (for example, (Lorenzetti et al., 2009)) and meta-analyses (Koolschijn et al., 2009) conclude that hippocampal volumes are smaller in individuals with MDD compared to healthy control samples. Furthermore, hippocampal volume has been found to be inversely correlated with total time spent depressed (Sheline et al., 1999). Despite the strong associations between dysfunction in the basal ganglia and thalamus in MDD, relatively few studies have assessed the volumes of these structures.

We are aware of only one magnetic resonance imaging (MRI) study explicitly examining thalamic volumes using manual segmentation (Caetano et al., 2001); no significant difference was observed between MDD and control subjects. The paucity of volumetric imaging studies assessing the thalamus may be attributable to the low tissue contrast resolution between the thalamus and adjacent white matter in neuromorphological MRI scans. In contrast, voxel-based morphometry studies that do not rely on hand segmentation have generally found smaller thalamic volumes in MDD (Kim et al., 2008; Soriano-Mas et al., 2011; Vasic et al., 2008). Furthermore, one post-mortem study found significantly increased neuron numbers in the anteroventral/anteromedial and mediodorsal nuclei of the thalamus, and a trend towards increased total thalamic volume compared to a non-psychiatric control group (Young et al., 2004). Another post-mortem study also found increased thalamic volume associated with MDD and suicidality, and smaller thalamic volumes associated with antidepressant use (Young et al., 2008).

The corpus striatum, which comprises the caudate and putamen, has been more extensively studied with MRI, at least partly due to the clarity of its boundaries on standard T₁ scans. A recent meta-analysis (Koolschijn et al., 2009) concluded that striatal volume was smaller in MDD, primarily accounted for by smaller volume of the putamen specifically. Individual studies, however, present more equivocal results. In the caudate, MRI-based, manual segmentation studies have shown reductions (Krishnan et al., 1992; Matsuo et al., 2008; Parashos et al., 1998) or no changes (Lacerda et al., 2003; Lenze and Sheline, 1999; Pillay et al., 1998) in individuals with MDD compared to healthy subjects. One study showing no change in caudate volume did show that female subjects who responded to treatment had larger caudate volumes than females who did not respond, and depression scores correlated negatively with left caudate volume (Pillay et al., 1998). In the putamen, MRI segmentation studies have found reductions (Husain et al., 1991; Parashos et al., 1998), or no change (Lacerda et al., 2003; Lenze and Sheline, 1999; Matsuo et al., 2008; Pillay et al., 1998). MRI-based voxel-based morphometry (VBM) studies also have shown reductions in the caudate (Amico et al., 2011; Kim et al., 2008; Wagner et al., 2011) in depressed subjects, and have associated this reduction with suicidality (Wagner et al., 2011). Reductions in the

putamen have been found in healthy subjects with a family history of affective disorder compared to controls not considered to be at risk for depression (Amico et al., 2011). Post-mortem studies have shown smaller putamen volumes (Baumann et al., 1999) in depression, but we are not aware of any studies examining the post-mortem caudate in depression.

The globus pallidus also has been investigated in connection with MDD. One manual segmentation study found no volumetric difference in the pallidum, but a decreased hemispherical asymmetry in MDD subjects compared to healthy controls; in addition, left globus pallidus volume was larger in subjects with more depressive episodes (Lacerda et al., 2003). Two post-mortem studies found smaller pallidum volume in MDD (Baumann et al., 1999; Biellau et al., 2005).

On balance, these studies would seem to indicate probable reductions in hippocampus and putamen in subjects with MDD. Additional evidence suggests that pallidum, caudate, and thalamus volumes are also smaller, although the available data do not support a firm conclusion.

Most previous volumetric studies relied heavily on manual segmentation or post-mortem dissection rather than automated processing. However, post-mortem studies are limited by sample size and often include only geriatric patients; such individuals may be suffering from late-onset depression, a condition thought to have a distinct etiology from early-onset MDD. Manual segmentations may be limited by sample size, due to the tedious nature of the measurement process, as well as by inter-rater reliability concerns; their generalizability is also limited by the landmarks chosen for each study. While VBM is not hampered by sample size, constraints, or rater skill, VBM results are highly dependent upon the selection of spatial normalization technique. Furthermore, most of these studies are potentially confounded by heterogeneity of patient characteristics and medication status.

The current study investigated subcortical volumetric differences between healthy controls (HC) and subjects with MDD scanned in either the depressed or the remitted phases, using an automated segmentation routine. Although segmentation of the entire LCSPT network would be informative, the method we chose in this investigation—the FSL subcortical segmentation tool FIRST—allowed unbiased and reliable investigation of caudate, putamen, thalamus, pallidum, and hippocampus volume (while other subcortical volumes are provided by this tool, not all were found reliable on similar data (Nugent et al., 2012)). This study differs from previous ones in that it examines all of these regions in an unprecedented number of subjects. Consistent with the literature, we expected to see smaller volumes in depressed subjects than healthy controls.

2. Materials and Methods

2.1. Subjects

All participants were recruited by the Mood and Anxiety Disorders Program at the National Institute of Mental Health. Participants were drawn from multiple imaging studies carried out over a nine-year period. Participants were medically healthy as established by screening blood tests, ECG, urinalysis, medical history, and physical examination.

All depressed subjects met Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition-Text Revision (DSM-IV-TR; (APA, 2000) criteria for MDD. Diagnosis was established using the Structured Clinical Interview for DSM-IV-TR (First et al., 2002) administered by clinicians previously assessed for reliability, as well as an unstructured interview with a psychiatrist. Currently depressed subjects also met criteria for a major depressive episode without psychotic features (MDD-D), and had not received psychotropic

medications for at least two weeks (four weeks for fluoxetine). Some studies from which the present analysis drew data allowed for discontinuation of current medications, but only when both the subject and physician deemed the response to those medications inadequate.

Subjects classified as having MDD in remission (MDD-R) had Hamilton Depression Rating Scale (HDRS) (17-item) scores in the non-depressed range (<7), met DSM-IV-TR criteria for MDD in full remission, and had not been treated with a psychotropic drug within three months of scanning. Current psychotropic medication use was an exclusion criterion, and maintenance medications were not discontinued for the purpose of the studies from which these data were drawn.

Healthy volunteers with a first degree relative with a major psychiatric disorder were excluded. Subjects with a history of substance or alcohol abuse or dependence in the last 90 days were also excluded. All participants provided written informed consent as approved by the combined neurosciences NIH Institutional Review Board.

2.2. Image Acquisition

Images were acquired on one of three 3T GE scanning platforms. Scanner A was a short bore scanner with an 8-channel coil, running a fast spoiled gradient recalled echo sequence (fSPGR: TE=2.6, TR=5.9, voxel size= $0.9 \times 0.9 \times 1.2$ mm). Scanner B was a long bore scanner with an 8-channel coil, running a magnetization prepared gradient recalled echo sequence (MP-RAGE: TE = 2.7 ms, TR = 7.3 ms, voxel size = $0.9 \times 0.9 \times 1.2$ mm). Scanner C was one of two long bore scanners (one the same as scanner B) maintained to be identical and previously treated as interchangeable (Nugent et al., 2006) with a single channel coil, running an MP-RAGE sequence (TE=2.7, TR=7.3, voxel size = $0.9 \times 0.9 \times 1.2$ mm). Note that for all scans, the TR and TE were both set as the minimum allowable for a full echo. Thus, the figures given are approximate and changes in the operating system of the scanners may have resulted in small changes in these parameters that would not be expected to alter results. Inter- and intra-scanner reliability was previously established on these scanners (Nugent et al., 2012), and reliability measures appear in Supplementary Table 1. Nonetheless, in order to compensate for potential systematic differences between samples, groups were carefully matched by proportion of images acquired on each scanning platform.

2.3. Imaging Processing

Following acquisition, images were corrected for intensity non-uniformity using the N3 algorithm (McConnell Brain Imaging Centre, Montreal Neurological Institute). Images were automatically edited to remove non-brain material using the AFNI tool 3dSkullStrip (Analysis of Functional Neuroimages, NIMH, NIH, Bethesda, MD) and then linearly registered to the 512 MNI whole brain template (McConnell Brain Imaging Centre, Montreal Neurological Institute) using the FSL tool FLIRT (FMRIB, University of Oxford, Oxford, UK) (Jenkinson et al., 2002). A secondary registration was performed to optimize registration of the sub-cortical structures by using a sub-cortical mask. FIRST version 1.2 (FSL toolbox, FMRIB, Oxford, UK) was used to automatically segment the following sub-cortical regions: bilateral thalamus, caudate, putamen, hippocampus, and pallidum. A previous study describing the analysis of image data from the same scanners found amygdala and accumbens measurements to be unreliable; therefore, these structures were not included as regions of interest in the current study (Nugent et al., 2012).

FIRST employs an iterative procedure to derive a surface mesh segmentation of structures derived from a set of 317 basis functions (Patenaude et al., 2011). FIRST then performs a boundary correction to remove extraneous voxels on the surface of the mesh segmentation. All segmentations were visually inspected to ensure that there were no gross failures of the

registration or segmentation algorithm. Total intracranial volume (TIV) was calculated by removing non-brain material using AFNI's 3dSkullStrip, and then co-registering each image to the stripped MNI template using the FSL tool FLIRT. The determinant of the Jacobian of the transformation matrix was used to express the TIV as a proportion of the template volume.

2.4. Statistical Analysis

All statistical analyses were carried out in IBM SPSS. Volumetric differences between groups were assessed using MANCOVA. Diagnosis, gender, and scanner were included as factors, and age was used as a covariate. Results for individual regions were corrected for multiple comparisons over the 10 regions of interest using Bonferroni correction. For the analyses comparing three groups (MDD-D, MDD-R, and HC), post-hoc *t*-tests were performed to determine significant differences between groups, and the results were considered significant if $p < 0.0167$ (0.05/three pair-wise tests). Differences in TIV also were assessed with ANCOVA. Where groups significantly differed in TIV, regions found to be significantly different between groups were re-examined with TIV as an additional covariate, and *p*-values were corrected for the number of regions tested. While it is true that TIV could be regarded as a confound, it is also true that alterations in TIV between diagnostic groups may have been partially driven by disease-related processes in specific brain areas, potentially including those examined here.

3. Results

The demographic characteristics of subjects are shown in Table 1. These data are reported for the entire group of HC subjects (N=169), as well as for the subsets of this HC group that were matched to the MDD-D (N=141) and MDD-R (N=71) groups. Groups did not differ with regard to age, proportion of each gender, and proportion scanned on each of the three scanners ($p > 0.05$). Three subjects were scanned in both the depressed phase and the remitted phase. These subjects are included as MDD-D in the HC vs. MDD-D analysis, but are included only as MDD-R in the analysis comparing all three groups.

Of the 141 MDD-D subjects, at least 83 presented with clinically significant symptoms of anxiety, although this is likely an underestimate given that this information was not systematically collected. One hundred and fourteen subjects endorsed having a first degree relative with a mood disorder; information was not available for four subjects. Subjects had previously been exposed to antidepressants (N=94), benzodiazepines (N=20), mood stabilizers (N=12), antipsychotics (N=17), stimulants (N=17), and other pharmacologic agents (N=17). A detailed medication history was not available for two subjects, and 35 subjects were treatment-naïve. Average Montgomery Asberg Depression Rating Scale (MADRS) score for those with ratings available was 26.5 (N=99). Average age of onset was 19 for those reporting an estimated age (N=129), and average duration of illness (age – age of onset) was 16.6 (N=129). Average IQ was 115 (N=86). Six subjects were left-handed, one was ambidextrous, and handedness was unknown for five subjects. Six subjects were Asian or Pacific Islander, 41 were African American, 14 were Hispanic, one was Middle Eastern, and the remainder was Caucasian.

Of the 71 MDD-R subjects, at least 17 reported a history of clinically significant anxiety, although again this is an underestimate given that this information was not routinely collected for this patient group. Sixty-eight subjects endorsed having a first-degree relative with a mood disorder, with information available from all subjects. Subjects reported previous exposure to antidepressants (N=49), benzodiazepines (N=4), mood stabilizers (N=3), antipsychotics (N=2), stimulants (N=2), and other pharmacologic agents (N=6). Treatment history was unavailable for one subject, and 14 subjects reported no prior use of

psychotropic medications. Average age of onset was 21.4 (N=69), average IQ was 123 (N=30). Average MADRS score was 2.5 (N=43). Two subjects were left-handed, and handedness was unknown for one subject. Eight subjects were African American, four subjects were Hispanic, and race/ethnicity was unknown for one subject; all other subjects were Caucasian.

A subset of the HC sample was matched for mean age, percent female, and percent acquired on each scanner to the MDD-D group. Demographics of the samples for the comparison of the MDD-D subjects versus the matched HC subset (N=159) appear in Table 2 and Figure 1. Main effects of gender ($F_{10,285}=16.08$, $p<0.001$), age ($F_{10,285}=5.403$, $p<0.001$), scanner ($F_{20,570}=4.149$, $p<0.001$), and diagnosis ($F_{10,285}=2.209$, $p=0.017$) were significant. The mean volume was significantly smaller in the MDD-D subjects as compared to the HC following Bonferroni correction for multiple comparisons in the bilateral thalamus and bilateral hippocampus. A univariate general linear model showed that TIV showed a significant main effect of group ($F_{1,294}=9.003$, $p=0.003$). Univariate results for regions showing significant reductions in the depressed group in the original analysis were repeated using TIV as a covariate. The group differences in the left and right thalamus ($F_{1,293}=6.82$, $p=0.009$ and $F=6.90$, $p=0.009$, respectively) remained significant after Bonferroni correction (over four regions tested). There was a trend ($F_{1,293}=5.84$, $p=0.016$) towards a significant reduction in right hippocampal volume.

Because the MDD-R group was the smallest, subsets of the MDD-D and HC groups were matched to this group on mean age, percent female, and percent acquired on each scanner. Two healthy subjects had scans acquired on two separate scanners; in both cases one scan was used for the MDD-D versus HC analysis, and the other was used in the three-group comparison to achieve the best matching of groups on proportion acquired on each scanner. Again, volumes were previously validated for reliability across scanners (Nugent et al., 2012). Results for the MDD-R subjects relative to subgroups of the HC and MDD-D subjects matched for age, gender, and scanner appear in Table 3. Volumes significantly differed between groups following Bonferroni correction for multiple comparisons in the bilateral thalamus, right caudate, right hippocampus, and right pallidum. Post-hoc tests in the significant regions revealed that the MDD-D subjects exhibited smaller volumes than the MDD-R group in all regions; MDD-D subjects exhibited smaller volumes than the HC subjects in all regions excepting the right putamen. The HC and MDD-R groups did not differ from each other in any region. Again, the TIV significantly differed between groups ($F_{2,286}=8.59$, $p<0.001$). In post-hoc *t*-tests, the TIV was lower in MDD-D subjects compared to both HC ($p=0.008$) and MDD-R ($p=0.009$) subjects. The TIV of the MDD-R subjects was increased compared to the HC subjects ($p=0.009$). When the ANCOVA analyses between the MDD-R group and the matched HC and MDD-D subgroups were repeated using TIV as an additional covariate, no significant regional differences emerged.

4. Discussion

The most robust finding of this study was a significant difference in the volume of the bilateral thalamus between HC and MDD-D subjects after controlling for TIV. In addition, before controlling for TIV these subjects also differed on bilateral hippocampal volume; after controlling for TIV there was a trend towards significantly smaller right hippocampal volumes. When the HC and MDD-D groups were matched to a sample of MDD-R subjects, we found significant group differences in the volumes of the bilateral thalamus, and right lateralized caudate, hippocampus, and pallidum; these differences were accounted for by reductions in the currently depressed group compared to both the remitted and healthy subjects. In contrast, the MDD-R and HC samples did not differ significantly in any region.

Moreover, the volumetric differences observed between the three groups did not remain significant after co-varying for TIV.

As discussed earlier, few studies have examined thalamic volumes in MDD, and those that do exist are contradictory. The present study is the largest to date to examine thalamic volumes in MDD using any technique, and the only one using an unbiased automated method. There is evidence in the literature, however, for thalamic dysfunction in MDD, although given the complex structure of the thalamus—which includes many individual nuclei that appear distinct with respect to function and anatomical connectivity—our finding of smaller volume in the entire thalamus is difficult to interpret more specifically. At rest, the medial thalamus shows abnormally increased cerebral blood flow and glucose metabolism (Drevets et al., 1992) and greater functional connectivity in depressed subjects compared to healthy controls (Greicius et al., 2007). Patients with MDD viewing negative stimuli manifest increased thalamic activity compared to healthy controls (Anand et al., 2005). These data appear consistent with the results of a study of remitted subjects with MDD imaged under acute tryptophan depletion (which often causes transient depressive relapse) that found that remitted MDD subjects showed a greater response in the thalamus to emotional words than healthy controls (Roiser et al., 2009). Furthermore, in a study of depressed MDD subjects imaged as they attempted to attenuate their emotional response to negative stimuli through reappraisal, the resulting autonomic arousal correlated positively with hemodynamic activity in the thalamus (Johnstone et al., 2007). Finally, another study showed that patients with MDD are more likely to experience self-relatedness to negative emotional stimuli, and that this tendency is associated with lower BOLD signal in the dorsomedial thalamus relative to controls, to a degree correlated with negative self concept (Grimm et al., 2009).

In the present study, we only observed significant differences in hippocampal volume when TIV was not corrected for; however, we did observe a trend towards a significant reduction in the right hippocampus after correcting for TIV. It is conceivable that differences in TIV were in part driven by reductions in specific brain areas, potentially including the hippocampus. Abnormalities in the function of the hippocampus in MDD are well established. Numerous functional magnetic resonance imaging (fMRI) and positron emission tomography (PET) studies have demonstrated increased hippocampal activity in depressed individuals (e.g., Drevets et al., 1992; Mayberg, 2003). For example, a recent fMRI study showed abnormalities in the relationship between hippocampal activation and successful encoding of facial identities in MDD (Fairhall et al., 2010). A meta-analysis also found that antidepressant drug treatment decreases hippocampal activity in a variety of functional MRI paradigms involving emotional processing tasks, particularly those assessing response to affectively negative stimuli (Delaveau et al., 2011).

Evidence also exists that thalamic and hippocampal abnormalities may be related, because these structures share extensive anatomical connections; indeed, an “extended hippocampal system” has been postulated, containing the hippocampus and the anterior thalamic nuclei (Aggleton and Brown, 1999). Notably, stimulating electrodes placed in the major anatomical projections from the hippocampus to thalamus alters the synaptic plasticity in the anterior thalamic nucleus (Tsanov et al., 2011).

The etiology of volumetric deficits in the LCSPT tract remains unclear, although several mechanisms have been suggested. The mediodorsal and paraventricular nuclei of the thalamus receive excitatory projections from medial prefrontal cortical regions that appear pathologically increased in their activity during depression, raising the possibility that sustained exposure to reverberatory, excitatory transmission may result in neurotoxicity (reviewed in (Price and Drevets, 2010)). Repeated exposure to elevated glucocorticoid

hormone levels have been shown to reduce axonal length and synapse number in the hippocampus in laboratory animals (Sheline, 2000; Tata and Anderson, 2010), and hypothalamic-pituitary-adrenal (HPA) axis dysregulation and hypercortisolemia are established findings in some patients with MDD (Murphy, 1991). While conventional antidepressant drug treatment and symptom remission appear to arrest further gray matter decrements in the hippocampus (Sheline et al., 2003), the effects of treatment on thalamic volume have not been reported.

Several limitations of our study design merit comment. While automated segmentation methods reduce the likelihood that rater bias or inconsistent application of landmarks may influence volumetric data, such methods may prove less accurate than manual segmentation performed by an experienced neuroanatomist. However, our group (Nugent et al., 2012) and others (Morey et al., 2009) have found that the method used herein, at least in the hippocampus, yields volumetric data consistent with those obtained using manual segmentation. Another limitation of the methods was our inclusion of images acquired on different scanners. We do not believe, however, that this significantly affected our results, given that we have previously established reliability across the same scanners, and that we carefully matched the diagnostic groups so that similar proportions were scanned on each scanner. A final limitation is that these scans were acquired over a long (nine-year) period of time. However, we do not believe that time trends in the data (e.g., associated with scanner drift) introduced bias in the volumetric measures between groups, given that both controls and MDD subjects were imaged across the same interval.

One unexpected result of this study was the nominally (although non-significantly) larger subcortical volumes measured in the MDD-R group compared to the HC group before TIV correction. Because many of these subjects maintained remission from MDD for extended periods of time without maintenance doses of antidepressants, they may represent a subset of people particularly resilient to relapse, which could conceivably be reflected in larger subcortical volumes, although this is purely speculative. In contrast, this observation may solely be due to systematic differences in TIV. Following correction for TIV, the MDD-R subjects did not significantly differ from either the MDD-D or the healthy subjects, although this negative result may represent a lack of power to detect subtle differences rather than the absence of an effect. For example, the difference in right thalamic volume between MDD-D and MDD-R subjects was 1.23%, comparable to the significant 1.82% difference between the much larger MDD-D and HC groups.

In summary, in a large sample of patients with MDD-D (N=142) and healthy controls (N=159), we found significant reductions in the bilateral thalamus and bilateral hippocampus. The reduction in the bilateral thalamus remained significant after controlling for TIV, and there was a trend towards a significant reduction in right hippocampal volume after TIV correction. In contrast, subcortical volumes in MDD-R subjects did not differ significantly from HC in any region; however, before correction for TIV, MDD-R subjects showed larger volumes than MDD-D subjects in the bilateral thalamus and right lateralized putamen, hippocampus, and pallidum. The volumetric reduction in the thalamus and hippocampus may be associated with dysfunction within subcortical-cortical networks, consistent with previous findings of functional imaging abnormalities in these regions. Elucidating the etiology of these abnormalities may contribute to the development of new targets for antidepressant treatment.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.

Volumes for a) left and b) right thalamus adjusted for age and TIV in MDD-D and HC subjects. Error bars indicate mean and standard deviation.

MDD: major depressive disorder; HC: healthy controls.

Table 1

Demographic characteristics of subject samples.

	N	Age (years)	Female N(%)	Scanner A N(%)	Scanner B N(%)	Scanner C N(%)
HC (all)	169	34 (9.3)	98 (58%)	56 (33%)	22 (13%)	91 (54%)
HC matched to MDD-D	159	35 (9.1)	89 (56%)	46 (29%)	22 (14%)	91 (57%)
MDD-D	141	36 (11.1)	76 (54%)	43 (31%)	18 (13%)	80 (57%)
HC matched to MDD-R	122	36 (9.6)	84 (69%)	43 (35%)	N/A	79 (65%)
MDD-D matched to MDD-R	99	36 (11.1)	66 (67%)	37 (37%)	N/A	62 (63%)
MDD-R	71	38 (12.1)	50 (70%)	26 (37%)	N/A	45 (63%)

HC: healthy controls; MDD: major depressive disorder; MDD-D: major depressive disorder-depressed; MDD-R: major depressive disorder-remitted.

Estimated marginal mean volumes from the ANCOVA model for each structure tested, both for the absolute volumes and with the total intracranial volume (TIV) modeled as a covariate.

Table 2

	Raw		TIV covariate					
	MDD		HC		ANCOVA		MDD	
	Mean Vol (mm ³)	Standard Error	Mean Vol (mm ³)	Standard Error	F (p)		Mean Vol (mm ³)	Standard Error
Left Thalamus	8007.5	57.66	8297.7	55.01	15.96 (<0.001)**		8037.93	41.6
Right Thalamus	7781.1	57.70	8071.3	55.04	15.94(<0.001)**		7810.41	43.1
Left Caudate	3417.3	37.35	3518.7	35.63	4.638 (0.032)			
Right Caudate	3568.7	41.90	3708.0	39.98	6.96 (0.009)*			
Left Putamen	4993.1	49.49	5084.8	47.21	2.16 (0.142)			
Right Putamen	4855.1	47.87	4964.7	45.67	3.3 (0.07)			
Left Hippocampus	3694.9	42.69	3860.5	40.72	9.48 (0.002)**		3706.58	39.9
Right Hippocampus	3778.2	38.30	3944.7	36.54	11.9 (0.001)**		3789.84	35.2
Left Pallidum	1716.6	16.87	1766.2	16.09	5.45 (0.02)			
Right Pallidum	1753.7	16.29	1808.7	15.54	7.18 (0.008)*			

** Result significant after Bonferroni correction for multiple comparisons at p<0.05.

* Result trended towards significance after Bonferroni correction for multiple comparisons at p<0.10.

HC: healthy controls; MDD: major depressive disorder

Table 3

Estimated marginal mean volumes from the ANCOVA model between MDD-D, MDD-R, and HC for each structure tested, with and without TIV as a covariate.

	Raw		TIV covariate													
	MDD-D		MDD-R		HC		ANCOVA		MDD-D		MDD-R		HC		ANCOVA	
	Mean Vol (mm ³)	Standard Error	Mean Vol (mm ³)	Standard Error	Mean Vol (mm ³)	Standard Error	F (p)		Mean Vol (mm ³)	Standard Error	Mean Vol (mm ³)	Standard Error	Mean Vol (mm ³)	Standard Error	F (p)	
Left Thalamus	8015.6	64.55	8367.4	76.15	8281.5	59.44	7.93 (<0.001)	<i>***a,b</i>	7965.4	45.96	8034.8	57.62	8105.6	43.51	2.73(0.067)	
Right Thalamus	7780.1	66.95	8159.2	78.99	8047.1	61.65	8.16 (<0.001)	<i>***a,b</i>	7729.8	49.15	7825.5	61.62	7870.6	46.54	2.42 (0.091)	
Left Caudate	3449.7	43.18	3595.6	50.94	3565.5	39.76	3.17 (0.044)									
Right Caudate	3580.5	48.07	3839.4	56.71	3749.5	44.27	7.08 (0.001)	<i>***a,b</i>	3552.8	41.14	3655.8	51.57	3652.3	38.95	2.049 (0.131)	
Left Putamen	4987.0	53.50	5200.7	63.12	5082.8	49.27	3.56 (0.03)									
Right Putamen	4854.4	53.34	5099.4	62.93	4973.5	49.12	4.737 (0.009) <i>*b</i>									
Left Hippocampus	3668.1	47.39	3830.7	55.91	3850.6	43.64	4.87 (0.008) <i>*a</i>									
Right Hippocampus	3748.0	41.97	3945.5	49.51	3914.6	38.65	6.48 (0.002)	<i>***a,b</i>	3729.8	38.73	3824.8	48.56	3850.7	36.67	2.96 (0.053)	
Left Pallidum	1722.5	19.45	1779.6	22.95	1772.2	17.91	2.60 (0.076)									
Right Pallidum	1749.2	17.44	1840.6	20.57	1794.7	16.06	6.19 (0.002)	<i>***b</i>	1740.2	15.47	1780.9	19.39	1763.1	14.64	1.52(0.221)	

*** Survives Bonferroni correction for multiple comparisons at p<0.05

^aMDD and HC significantly different in post-hoc *t*-tests

^bMDD-D and MDD-R significantly different in post-hoc *t*-tests.

HC: healthy controls; MDD-D: major depressive disorder-depressed; MDD-R: major depressive disorder-remitted.