

Subcortical shape alterations in major depressive disorder: Findings from the ENIGMA major depressive disorder working group

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Abstract

Alterations in regional subcortical brain volumes have been investigated as part of the efforts of an international consortium, ENIGMA, to identify reliable neural correlates of major depressive disorder (MDD). Given that subcortical structures are comprised of distinct subfields, we sought to build significantly from prior work by precisely mapping localized MDD-related differences in subcortical regions using shape analysis. In this meta-analysis of subcortical shape from the ENIGMA-MDD working group, we compared 1,781 patients with MDD and 2,953 healthy controls (CTL) on individual measures of shape metrics (thickness and surface area) on the surface of seven bilateral subcortical structures: nucleus accumbens, amygdala, caudate, hippocampus, pallidum, putamen, and thalamus. Harmonized data processing and statistical analyses were conducted locally at each site, and findings were aggregated by meta-analysis. Relative to CTL, patients with adolescent-onset MDD (≤ 21 years) had lower thickness and surface area of the subiculum, cornu ammonis (CA) 1 of the hippocampus and basolateral amygdala (Cohen's $d = -0.164$ to -0.180). Relative to first-episode MDD, recurrent MDD patients had lower thickness and surface area in the CA1 of the hippocampus and the basolateral amygdala (Cohen's $d = -0.173$ to -0.184). Our results suggest that previously reported MDD-associated volumetric differences may be localized to specific subfields of these structures that have been shown to be sensitive to the effects of stress, with important implications for mapping treatments to patients based on specific neural targets and key clinical features.

KEY WORDS

amygdala, ENIGMA, hippocampus, major depressive disorder (MDD), nucleus accumbens, shape analysis

1 | INTRODUCTION

Major depressive disorder (MDD) is one of the leading causes of disability worldwide, with relatively high rates of lifetime prevalence and recurrence (World Health Organization, 2017). MDD is often triggered by stressful experiences and is commonly associated with various affective symptoms (e.g., abnormalities in emotion regulation, reduced motivation

in the face of positive incentives, sustained experiences of negative affect; Davidson, Pizzagalli, Nitschke, & Putnam, 2002; Woody & Gibb, 2015), as well as with cognitive deficits (e.g., attention, learning, working memory, processing speed, motor functioning; McIntyre et al., 2013). Several subcortical regions—particularly the hippocampus, amygdala, and structures of the striatum—through their connections with one another and with cortical structures, are important for supporting a

number of these cognitive and affective processes that are disturbed in MDD (Davidson et al., 2002). In a recent multisite effort, we examined morphological alterations at the level of subcortical gray matter volumes in MDD (Schmaal et al., 2016), and found lower total hippocampal volumes, mainly driven by patients with recurrent episodes and by patients with a relatively early age of onset (i.e., prior to age 21). Despite the large study sample size and homogeneous analysis protocols, no statistically significant group differences emerged for any of the other subcortical structures. It is possible, however, that such aggregate measures of volume are either insensitive to local volumetric effects or that they obscure heterogeneous local effects by averaging out more complex shape effects. In this respect, the analysis of shape parameters represents a complementary approach to volumetric analyses.

Indeed, MDD is most likely characterized by specific associations with functionally distinct subregions within the hippocampus, amygdala, striatum, and other subcortical structures (e.g., thalamus). It is important to note, however, that characterizing local patterns in subcortical surfaces has traditionally been challenging due to the lack of identifiable surface landmarks that are more common in cortical surfaces (e.g., deep sulcal patterns). Thus, the lack of detectable volumetric differences in the amygdala, caudate, putamen, and NAcc between MDD and CTL in our previous meta-analytic study may be due to the fact that we did not use shape analyses to examine these important subdivisions (Schmaal et al., 2016). Furthermore, local variations in shape measures may provide critical insight into the anatomical relation between a subcortical structure and important clinical variables, such as illness onset and recurrence, as well as detect granular changes that may be particularly helpful in the context of monitoring intervention targets with more specificity.

To address these knowledge gaps, we conducted a multisite meta-analytic investigation to test whether MDD patients, and whether specific subgroups of MDD based on important clinical characteristics, show differences from controls in subcortical shape. Specifically, we applied meta-analytic models on effect sizes generated from 10 study cohorts from six different countries participating in the MDD Working Group of the international ENIGMA consortium. Each study site applied a well-validated harmonized preprocessing pipeline and conducted statistical models on high-resolution T1-weighted MRIs, yielding site-level summary statistics of volume and shape for seven bilateral subcortical regions from 1,781 patients diagnosed with MDD and 2,953 healthy controls (CTL).

Guided by findings from our prior meta-analysis in which we reported that the most robust difference between individuals with MDD and CTL was smaller hippocampal volume (Schmaal et al., 2016), and from recent work indicating that the cornu ammonis subfields (CA) 1–4, dentate gyrus (DG), and the subiculum (SUB) are associated with exposure to aversive stressful experiences (Teicher, Anderson, & Polcari, 2012; Treadway et al., 2015) and MDD (Cao et al., 2017; Cole et al., 2010; Han, Won, Sim, & Tae, 2016; Huang et al., 2013; Roddy et al., 2018; Treadway et al., 2015), we hypothesized that patients with MDD would exhibit reductions in these hippocampal subregions. Given previously documented effects of age of illness onset and recurrence of illness on subcortical volumes (primarily the amygdala and hippocampus; Hamilton, Siemer, & Gotlib, 2008; Schmaal et al., 2016),

we also sought to stratify groups according to these clinical characteristics: early (prior to age 21) versus later (after age 21) onset MDD and first-episode versus recurrent-episode. We also report results from additional exploratory analyses of medicated and nonmedicated patients (each compared separately to CTL) and of dimensional associations between subcortical shape and depression severity (clinician-rated as well as self-reported) among patients with MDD.

2 | MATERIALS AND METHODS

2.1 | Samples

Ten participating sites in the MDD Working Group of ENIGMA consortium (Schmaal et al., 2016, 2017; Thompson et al., 2014) applied harmonized preprocessing and statistical models on structural T1-weighted MRIs, yielding site-level summary statistics of subcortical volume and shape from a total of 4,734 participants (1,781 patients with MDD and 2,953 CTL). Detailed demographics, clinical characteristics, and exclusion criteria for study enrollment for each site are presented in Supporting Information Table S1. All participating sites obtained approval from their respective local institutional review boards and ethics committees. All study participants provided written consent at their local site.

2.2 | Clinical variables of interest

We selected specific clinical variables of interest based on prior work demonstrating their effects on aggregate subcortical volumes in MDD (Hamilton et al., 2008; Schmaal et al., 2016). Specifically, we considered participants with earlier or adolescent onset (EO) to be those who developed their first episode at or before age 21, and participants with later or adult onset (LO) to be those who developed their first episode after age 21 (Schmaal et al., 2016). We defined recurrent-episode MDD (RECUR) to be those who experienced more than one major depressive episode (Schmaal et al., 2016).

Because not all sites used the same depression severity scales, as a supplemental analysis we assessed the severity of depressive symptoms at the time of scan as measured by the clinician-rated 17-item Hamilton Depression Rating Scale (HDRS-17; Hamilton, 1960) or the 21-item self-report Beck's Depression Inventory (BDI; Beck, Ward, Mendelson, Mock, & Erbaugh, 1961) and their linear associations with subcortical shape metrics for the subset of sites that had this information. Similarly, because the majority of sites did not include detailed information on lifetime medication usage, dosage, or adherence, as a supplemental analysis we also compared MDD groups on the basis of antidepressant medication usage at the time of scan.

2.3 | Image processing and analysis

All participating sites collected anatomical T1-weighted MRI brain scans locally at each site, where they were analyzed using the fully-

automated and validated segmentation software FreeSurfer version 5.3 (Fischl, 2002), with the exception of three sites which used version 5.0 or 5.1 (see Table S1). A subset of these subcortical measures has been previously published (Frodl et al., 2016; Renteria et al., 2017; Schmaal et al., 2016); however, none of these prior meta-analyses from the ENIGMA MDD Working Group conducted shape analyses. Detailed information on the number of sites that overlap between the present investigation and the subcortical paper ENIGMA MDD (Schmaal et al., 2016) is presented in Table S2. Image acquisition parameters and software descriptions for each sample are presented in Supporting Information Table S1. The seven bilateral subcortical segmentations were: the nucleus accumbens, amygdala, caudate, hippocampus, pallidum, putamen, and thalamus (as well as lateral ventricles and total intracranial volume, ICV). All segmentations were visually inspected for accuracy following standardized protocols (<http://enigma.ini.usc.edu/protocols/imaging-protocols/>).

We analyzed shape using the ENIGMA-Shape protocol (<http://enigma.usc.edu/ongoing/enigma-shape-analysis/>), for which test-retest reliability has been previously validated (Hibar et al., 2015). Briefly, shapes were extracted using the FreeSurfer 5.3 parcellation, followed by a topological correction and mild smoothing based on the topology-preserving level set algorithm (Gutman et al., 2015). As in prior work, after registering shapes to standardized templates, we then defined two vertex-wise measures of space morphometry which facilitated comparisons of subcortical shape: *radial distance*, as derived from the medial model (Gutman et al., 2015; Gutman, Wang, Rajagopalan, Toga, & Thompson, 2012), which yields a measure of "shape thickness," and the *Jacobian determinant*, as derived from tensor-based morphometry (TBM; Gutman et al., 2015; Wang et al., 2011), which yields a metric of localized tissue reduction or enlargement of surface area (relative to the respective template shape). Because the Jacobian represents the ratio of the area in the individual shape relative to the area in the template at the corresponding vertex, and is not Gaussian in distribution, we used the logarithm of the Jacobian in all analyses examining shape surface area. A useful feature of the ENIGMA-Shape pipeline is that results are based on bilateral shape measures (i.e., templates for corresponding left and right regions are vertex-wise registered after reflecting one of them, and summed vertex-wise). Importantly, our registration algorithm provides a unique and stable matching between datasets, allowing us to efficiently meta-analyze the effects of MDD across datasets (as in Roshchupkin et al., 2016). See "Image processing and analysis" under the Supporting Information for more details on the pipeline for subcortical shape analysis and on quality control procedures.

Each of the 10 study sites applied the subcortical shape pipeline and ran *a priori* statistical models (for details, see "Statistical framework for meta-analyses", below) that were guided by discussions with ENIGMA-MDD members and previous work (Schmaal et al., 2016, 2017) to generate summary statistics for inclusion in our meta-analyses.

2.4 | Site-specific statistical models

To harmonize analyses across sites, a set of standardized scripts to compute mass univariate statistics was distributed to all participating sites

via the ENIGMA-Git page (<https://github.com/ENIGMA-git/ENIGMA/tree/master/WorkingGroups>). Each study site performed mass univariate (per-vertex, per-measure) analysis for all the linear models proposed in the present study (see Table 1). Specifically, for our primary statistical models of interest, subcortical shape measures of thickness (radial distance) and surface area (log of the Jacobian determinant) were the outcome variables, and a binary group indicator variable (e.g., 0 = CTL, 1 = MDD) was the predictor of interest, with age, sex (as a factor), and total ICV as covariates. Our planned comparisons included the following: MDD versus CTL; early-onset MDD (EO) versus CTL; later-onset MDD (LO) versus CTL; EO versus LO; recurrent episode MDD (RECUR) versus CTL; first episode MDD (FIRST) versus CTL; RECUR versus FIRST. We also tested whether sex and age significantly interacted with diagnostic group. Although demographic variables for MDD versus CTL were matched at the site-level, such matching was not necessarily preserved for subgroup comparisons (e.g., EO vs. CTL). Thus, in all analyses, age, sex (as a binary factor), and total ICV were included as covariates.

Finally, we conducted exploratory analyses testing for the associations (i.e., linear correlations) with HDRS-17 and BDI scores (separately) within the MDD group only, as well as comparing groups based on antidepressant usage at the time of scan (MED vs. CTL, and NON vs. CTL) to explain variation in subcortical shape measurements. These analyses were exploratory as only a subset of sites collected the relevant information that permitted us to conduct these analyses.

2.5 | Meta-analytic framework and correction for multiple comparisons

The resulting group-level maps of effect sizes (i.e., Cohen's *d* for the group comparisons and Pearson's *r* for the dimensional analyses), regression parameters, and confidence intervals, as well as basic site information, were aggregated for mass univariate meta-analysis. As performed in Schmaal et al. (2017, 2016), we conducted meta-analyses which pooled each site's effect sizes, for each region, using an inverse variance-weighted random-effects model as implemented in the R package *metafor* (version 1.9-1) and fit with REML (<https://cran.r-project.org/>). One advantage of random effects models is that they allow effect sizes to vary across studies due to study-specific differences (e.g., mean age); random effects models therefore weight within-study as well as between-study variance in the pooled effect size estimates to mitigate bias or undue influence from the largest samples in the meta-analysis (Borenstein, Hedges, Higgins, & Rothstein, 2010).

Maps of *p*-values resulting from the meta-analysis were corrected for multiple comparisons using a modified searchlight false discovery rate (FDR) procedure set to $p < .05$ (for details on procedures and code, see Langers, Jansen, & Backes, 2007). We applied this correction globally across all seven bilateral subcortical regions and measures (thickness, surface area) for each linear model. See "Meta-analytic framework and correction for multiple comparisons" in the Supporting Information for more details. For comprehensiveness, we also conducted and report local FDR-corrected results for each of the seven bilateral subcortical structures (i.e., corrected independently in each subcortical region and for each shape metric) in the Supporting Information. Finally, we also report I^2 values for

TABLE 1 Summary of results

| Statistical model | # of first group/# of second group/total sample size | # of sites | Global-FDR correction results for thickness (Cohen's d /% affected/ I^2) | Global-FDR correction results for surface area (Cohen's d /% affected/ I^2) |
|-----------------------------|--|------------|---|---|
| MDD versus CTL ^a | 1,781/2,953/4,734 | 10 | n.s. | n.s. |
| EO versus CTL | 476/2,879/3,355 | 9 | Hipp: -0.172/4.51%/1.41 Amyg: -0.164/4.23%/0.04 | Hipp: -0.180/22.52%/2.79 Amyg: -0.168/6.01%/1.36 |
| LO versus CTL | 1,028/2,879/3,907 | 9 | n.s. | n.s. |
| EO versus LO | 476/1,028/1,504 | 9 | n.s. | n.s. |
| RECUR versus CTL | 1,273/2,953/4,226 | 10 | n.s. | n.s. |
| FIRST versus CTL | 500/2,879/3,379 | 9 | n.s. | n.s. |
| RECUR versus FIRST | 1,174/500/1,674 | 9 | Hipp: -0.173/1.61%/6.27 Amyg: -0.174/3.45%/7.21 Thal: 0.177/6.79%/0.90 | Hipp: -0.174/1.94%/0.47 Amyg: -0.183/0.52%/0 Thal: 0.176/7.68%/5.78 |
| MED versus CTL | 976/2,879/3,855 | 9 | Hipp: -0.139/2.99%/7.92 Caudate: -0.133/9.73%/8.24 | Hipp: -0.136/9.32%/7.87 Caudate: -0.140/2.31%/2.72 NAcc: -0.143/22.10%/13.1 |
| NON versus CTL | 797/2,933/3,730 | 9 | n.s. | n.s. |
| HDRS-17 ^b | 720 | 4 | n.s. | n.s. |
| BDI ^b | 760 | 6 | n.s. | n.s. |

Note: Statistical models in bold indicate primary analyses. All site-specific analyses included age, sex (as a factor), and intracranial volume (ICV) as covariates and all meta-analytic models pooled each sample's effect sizes (i.e., d or r) using an inverse variance-weighted random effects model. For more information on each study site, please see Table S1. Thickness is measured by radial distance and surface area is measured using tensor-based morphometry. See Figures 1 and 2 for more details on results from the primary analyses surviving global-FDR correction, Figures S3–S7 for more details of results from the primary analyses surviving local-FDR correction, and Figures S8–S10 for results on the supplemental analyses involving medication usage.

Abbreviations: BDI, Beck's Depression Inventory; CTL, healthy controls; EO, early-onset MDD (≤ 21 years old); FIRST, first-episode MDD; HDRS-17, Hamilton Depression Rating Scale (17 items); LO, later-onset MDD (> 22 years old); MDD, major depressive disorder; MED, medicated at time of scan; n.s., no significant effects; NON, not medicated at time of scan; RECUR, recurrent-episode MDD.

^aInteractions between age and sex (separately) were also tested.

^bDimensional analyses conducted within MDD only.

each of our significant effects, which reflect the amount of heterogeneity relative to the total amount of variance in the observed effects.

Figure S1 for a map of I^2 values for the surface area results for EO versus CTL.

3 | RESULTS

3.1 | Global FDR-corrected effects

3.1.1 | MDD versus CTL (and interaction effects with age and sex)

There were no significant differences between MDD and CTL, and no significant interactions between diagnostic group and age or sex.

3.1.2 | Age of onset groups

There were no significant differences between LO and CTL, and no significant differences between EO and LO. Relative to CTL, EO had lower thickness in the hippocampus (Cohen's d = -0.17) and amygdala (Cohen's d = -0.16), and smaller surface area in the hippocampus (Cohen's d = -0.18) and amygdala (Cohen's d = -0.17). The strongest effects were primarily in the surface area of the SUB, CA1, and BLA. See Table 1 and Figure 1 for more details. Please see

3.1.3 | Recurrence status

There were no significant differences between RECUR and CTL, and no significant differences between FIRST and CTL. Relative to FIRST, RECUR had lower thickness in the hippocampus (Cohen's d = -0.17) and amygdala (Cohen's d = -0.17), and smaller surface area in the hippocampus (Cohen's d = -0.17) and amygdala (Cohen's d = -0.18). These effects were primarily in the surface area of the CA1 and BLA. Relative to FIRST, RECUR also had both greater thickness (Cohen's d = 0.18) and greater surface area (Cohen's d = 0.18) in the medial posterior thalamus. See Table 1 and Figure 2 for more details. Please see Figure S2 for a map of I^2 values for the surface area results for RECUR versus FIRST.

3.2 | Supplemental results assessing associations with depression severity

There were no significant associations with depressive symptom severity using HDRS-17 or BDI scores in any subcortical structural outcome measures.

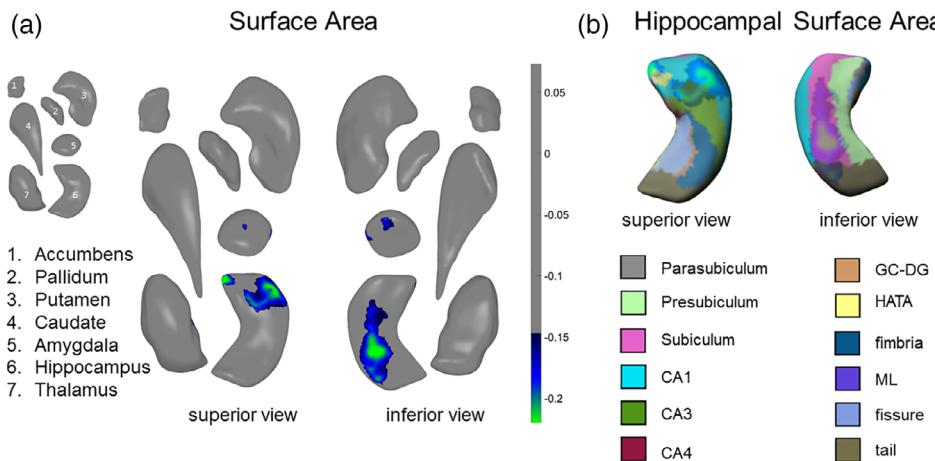


FIGURE 1 Global-FDR corrected results for EO versus CTL. (a) Surface area effects in subregions of the amygdala and hippocampus from a superior view (left) and an inferior view (right). (b) Surface area effects overlaid on the FreeSurfer v. 6.0 hippocampal subfield atlas (mirrored). Colored bars correspond to range of effect sizes (Cohen's d). All results are based on bilateral shape measures (i.e., templates for corresponding left and right regions are vertex-wise registered after reflecting one of them, and summed vertex-wise). See Table 1 for more information

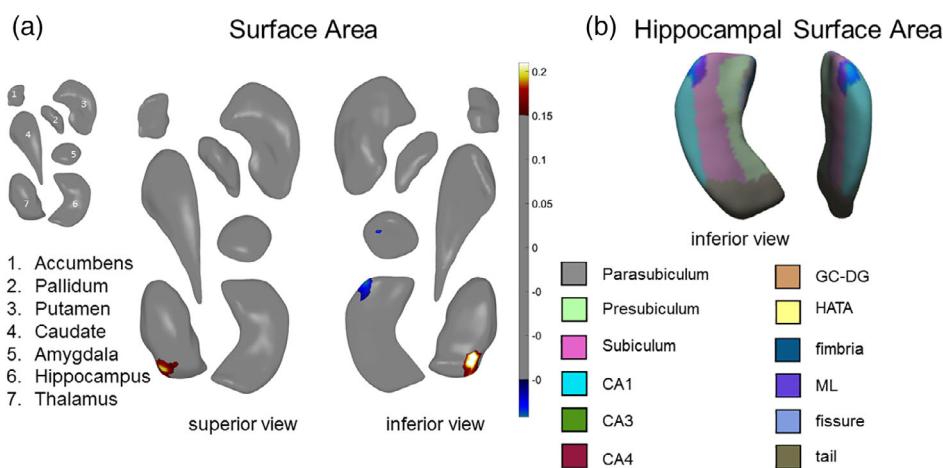


FIGURE 2 Global-FDR corrected results for RECUR versus FIRST. (a) Surface area effects in subregions of the amygdala, hippocampus, and thalamus from a superior view (left) and an inferior view (right). (b) Surface area effects overlaid on the FreeSurfer v. 5.3 hippocampal subfield atlas. Color bars correspond to range of effect sizes (Cohen's d). All results are based on bilateral shape measures (i.e., templates for corresponding left and right regions are vertex-wise registered after reflecting one of them, and summed vertex-wise). See Table 1 for more information

3.3 | Supplemental results of group comparisons based on local-FDR correction

Overall, the results from the local-FDR corrected results were consistent with the global-FDR corrected results, including smaller thickness and surface area of the SUB and BLA in EO relative to CTL and smaller BLA thickness in RECUR relative to FIRST. Not surprisingly, we observed more significant results with the local-FDR correction. Notably, MDD relative to CTL exhibited smaller surface area in SUB, BLA, and NAcc shell. Please see Table S2 for a summary of local FDR-corrected thresholds and Figures S3–S7 in the Supporting Information for more details.

3.4 | Supplemental results of group comparisons based on antidepressant usage

Please see Table S1 for a summary of results comparing MED, NON, and CTL, and Figures S8–S10 in the Supporting Information for more details.

4 | DISCUSSION

The present study is the largest investigation of subcortical shape in MDD to date with a total of 1,781 patients with MDD and 2,953 healthy controls. We identified reductions in the thickness and surface area of the subiculum (SUB) and the cornu ammonis (CA) one subfields of the hippocampus and the basolateral amygdala (BLA) in patients with an adolescent age of onset (i.e., prior to age 21 years) compared to healthy controls. Further, patients with recurrent depression (i.e., more than one episode of MDD) exhibited lower thickness and surface area primarily in CA1 and BLA compared to patients experiencing their first episode of depression.

Our findings build significantly from our initial study from the ENIGMA MDD Working Group (Schmaal et al., 2016). First, we report depression-related effects in the shape of structures—namely, the amygdala and thalamus—that did not yield statistically significant volumetric differences as a function of depression status (Schmaal et al., 2016). Second, we provide information on which aspects of gray matter morphology (thickness, surface area) are impacted by depression. Third, we report that the subiculum of the hippocampus and the

basolateral amygdala specifically are affected by early onset and recurrent depression. Thus, our results reveal depression-related differences that are manifested in nuanced changes in subcortical morphometry. Importantly, these patterns may offer insight into important clinical influences (e.g., early onset, recurrent episodes) on the brain basis of MDD.

In line with findings from our previous findings (Schmaal et al., 2016), we found significant reductions in hippocampal volume that were primarily driven by patients who had an age of onset of depression prior to 21 years and/or patients experiencing recurrent episodes of MDD. Our present finding that early-onset MDD is characterized by smaller surface area of the SUB and CA1 compared to healthy controls suggests that excessive or dysregulated stress responses play a key role in the development of MDD, consistent with broader theoretical literature (Hammen, 2005). Our results are theoretically consistent with preclinical and clinical models of MDD that posit that stress-induced increases in glucocorticoid levels shrink dendrites and reduce the number of spines in the hippocampus, resulting in atrophy (McEwen et al., 2015; Tata & Anderson, 2010). Postmortem data indicate that the human SUB may contain a higher density of glucocorticoid binding sites than CA1-4 or even the DG (Kim, Pellman, & Kim, 2015; Sarrieau et al., 1986). The SUB also receives input from other subfields of the hippocampus (especially CA1), has reciprocal connections with the hypothalamic nuclei, and sends projections to several subcortical and cortical targets, making it a key structure that regulates the HPA axis (Lowry, 2002; O'Mara, 2005). In light of the extant literature focused on hippocampal subfields in the context of stress and MDD (Bearden et al., 2009; Cao et al., 2017; Cole et al., 2010; Han et al., 2016; Huang et al., 2013; Roddy et al., 2018; Teicher et al., 2012; Treadway et al., 2015), at least two potentially complementary explanations emerge: first, stress-induced neurotoxicity due to HPA-axis dysregulation prior to disease onset may have led to the observed structural deficits. Second, in light of our findings that recurrent MDD is associated with lower thickness and smaller surface area in CA1, the hippocampal alterations we report may also be a consequence of the stress associated with experiencing multiple episodes of depression. Unfortunately, an insufficient number of sites provided information on the number and timing of depressive episodes, making it challenging to dissociate the effects of early onset from recurrent depression. Future longitudinal data are ultimately needed to disentangle these possibilities.

Patients with recurrent MDD also showed reduced basolateral amygdala (BLA) and enlarged medial posterior thalamus relative to those in their first episode. Our finding of reduced BLA in patients with recurrent MDD relative to those in their first episode clarifies conflicting data in the extant literature on the effects of MDD on amygdala volume and is consistent with the role of the BLA in responding to threats and stressors in the environment (Terburg et al., 2018). Indeed, previous studies have documented that age of onset, number of episodes, and antidepressant medication affect amygdala volume in people with MDD (Hamilton et al., 2008; Kronenberg et al., 2009; Rubinow et al., 2016; Schmaal et al.,

2016; van Eijndhoven et al., 2009). Interestingly, in our exploratory analyses examining patients who were medicated (at the time of scan) and also those who were not medicated versus CTL, we did not find evidence of enlarged amygdala volume, as was reported in a meta-analysis from a decade ago (Hamilton et al., 2008). Given the partial overlap in sites and samples (see Table S2), it is not surprising our results are more aligned with our prior meta-analysis of aggregate subcortical volumes, where we reported a trend that individuals with MDD exhibit reduced amygdala volume compared to healthy controls (Schmaal et al., 2016).

Our finding of greater medial posterior thalamic thickness and surface area in recurrent patients with MDD relative to first-episode patients is an intriguing result that requires more research. While one study of postmortem samples reported more neurons in the mediodorsal and anteromedial nuclei of the thalamus in people diagnosed with MDD relative to healthy controls (Young, Holcomb, Yazdani, Hicks, & German, 2004), others have reported larger thalamic volumes in first-episode treatment-naïve patients with MDD (Qiu et al., 2014; Zhao et al., 2014). Interestingly, in a meta-analysis by Bora et al., late-life depression was associated with smaller thalamic volume (Bora, Harrison, Davey, Yucel, & Pantelis, 2012). Lithium usage is associated with larger thalamic volumes in patients with bipolar disorder (Lopez-Jaramillo et al., 2017; Lyoo et al., 2010), but it is unclear from our data as well as in the current literature what the role of mood stabilizing medications are on brain structure in patients with MDD. As we report in the Supporting Information, patients receiving antidepressant treatment at the time of scan did not differ, on average, in thalamus thickness or surface area compared to healthy controls. It will be important for future research to carefully consider the role of subregions of the thalamus in MDD and determine how illness recurrence and/or medication usage affects morphometry of this structure.

Using a less stringent statistical threshold for significance (i.e., local-FDR correction only), we also report that patients with MDD show lower caudate thickness and smaller surface area in the shell of the nucleus accumbens (NAcc-s) compared to CTL (in addition to smaller surface area of SUB and BLA). As with the amygdala, while we did not detect overall statistically significant differences in nucleus accumbens volume between MDD and CTL (Schmaal et al., 2016), the use of shape analysis was more sensitive in identifying nuanced differences between groups. The NAcc-s enjoys robust connections with the orbitofrontal cortex (OFC), with prior research suggesting that both structures underlie disturbed reward processing and decision making in MDD (Drevets, 2007; Kumar et al., 2019). Similarly, extensive work has demonstrated that the caudate plays a critical role in reward-based reinforcement learning, with neurons in this structure relaying signals that code for expectation violation and reward prediction errors (Arulpragasam et al., 2018; Haber & Knutson, 2010; O'Doherty, 2004; Tricomi & Lempert, 2014). Smaller putamen and caudate volumes have been observed not only in adults with depression (Pizzagalli et al., 2009) but also in young adolescents with parental history of MDD (Pagliaccio et al., 2019), suggesting that these

morphological characteristics may represent risk markers. While more research in this area is clearly needed, our results are consistent with neurobiological models of anhedonia and melancholic MDD, which are characterized by more persistent episodes of depression (and indeed, we find smaller NAcc-s in recurrent patients relative to controls in our local-FDR corrected results), that implicate dopaminergic dysfunction specifically in mesolimbic pathways (Heller et al., 2009; Misaki, Suzuki, Savitz, Drevets, & Bodurka, 2016; Whitton, Treadway, & Pizzagalli, 2015).

Overall, our effect sizes are modest; nevertheless, they are comparable to what we have reported in prior meta-analytic investigations comparing MDD and CTL in subcortical and cortical regions (Schmaal et al., 2016, 2017). Given the heterogeneity of MDD as a disorder (e.g., atypical depression) and the likely clinical heterogeneity across the different study sites (e.g., illness duration, medication usage), it may be that several of the findings we report here represent nuanced variations in subcortical subregions as a function of specific clinical characteristics in MDD, and that combining across these distinct clinical subgroups resulted in smaller effect sizes. For instance, early-onset depression may affect the hippocampus specifically due to early and/or chronic exposure to stress (as well as experiencing recurrent episodes, which are themselves stressful experiences) whereas later-onset depression may affect the striatum due to experiences affecting reward-based circuitry specifically (e.g., anhedonia, motivational loss, etc.). Future research is needed to comprehensively parse subtypes of MDD and collect more detailed information on important clinical characteristics in order for us to link specific clinical profiles with their neurobiological substrates.

4.1 | Strengths, limitations, and future directions

As the first multisite meta-analytic study of subcortical shape in MDD, major strengths of our investigation include the large number of observations sampled from several sites across the world combined with the use of standardized quality control procedures across all of these sites. Despite the standardized preprocessing protocols and statistical analyses, one limitation of our meta-analytic investigation is that we combined pre-existing data across worldwide samples; thus, data collection protocols (e.g., scan sequences, depression measurements) were not harmonized. Therefore, there may be important sources of heterogeneity in both imaging acquisition protocols and in clinical assessments that will need to be considered in future investigations utilizing mega-analyses. Indeed, there are several advantages to mega-analyses over meta-analyses, including greater flexibility in model specifications (e.g., relaxation of model assumption such as within-study normality, inclusion of covariates at the level of individuals as well as at the level of sites, etc.) and potentially greater statistical power to detect certain effects (e.g., higher order interactions) (Boedhoe et al., 2019; Burke, Ensor, & Riley, 2017; Debray, Moons, Abo-Zaid, Koffijberg, & Da Riley, 2013). Nevertheless, there are several analytic advantages to meta-analyses over mega-analyses, including the ability to assess the robustness and generalizability of findings across cohorts (see Table 1, Figures S1 and S2), as

well as handling site-specific covariates to account for local population substructure (Burke et al., 2017; Schmaal et al., 2020).

Even though all sites performed quality control tests according to the ENIGMA-Shape Quality Control guide, a limitation of our study is the reliance on an automated segmentation tool (i.e., FreeSurfer) that has been shown to systematically overestimate the size of the hippocampus, amygdala, and other structures in comparison to manual tracing (Makowski et al., 2018; Schmidt et al., 2018; Schoemaker et al., 2016). However, a recent study reported that despite this bias, agreement between FreeSurfer and tracing methods, as well as measures of spatial overlap, were high ($r: 0.70\text{--}0.72$; Schmidt et al., 2018). Another recent study also reported high test-retest reliability for FreeSurfer estimates of the twelve subfields of the hippocampus, with the exception of the hippocampal fissure (ICC: 0.66–0.96; Whelan et al., 2016). Although this issue is outside of the scope of the present investigation, it is critical for the field to identify which subcortical (and cortical) regions may be adequately segmented by automated procedures and which may show systematic biases (or may only exhibit such biases with certain clinical conditions). Indeed, this is an explicit goal and active area of future research for the ENIGMA Consortium (Thompson et al., 2014, 2019).

It is important to note that with respect to hippocampal differences between MDD and CTL, the results of the present study differed from our previous study on subcortical volume, in that we identified group differences in subfields of this structure with local-FDR correction only whereas the most robust subcortical volumetric difference between groups was smaller hippocampal volume in MDD (Schmaal et al., 2016). One reason for this discrepancy is that the samples differed between the two studies, both in terms of total sample size (Schmaal et al. examined a total $N = 8,927$) and in the specific sites included. As detailed in Table S2, five of the sites ($n = 1909$) that were included in this study were not included in our previous study. Given the smaller sample size of the present study, statistical power is also likely an issue, particularly since we applied vertex-wise correction for determining significance thresholds, resulting in more stringent p -values. Despite these differences, the effect size for smaller hippocampal surface in MDD versus CTL in our study was $d = -0.11$, which is comparable to the effect size of our previous volumetric analyses ($d = -0.14$). Moreover, both studies report that early-onset depression robustly affected hippocampal morphology. Thus, despite the differing samples and distinct methodological approaches, the shape and volumetric analyses do broadly share consistent results with respect to MDD-related hippocampal effects.

While previous studies on overall volume in subcortical regions have identified important neurobiological correlates of MDD, investigating the shape of these structures may represent an important direction for future research focused on understanding structural abnormalities in psychiatric disease, as such findings are able to complement volumetric analyses that are unable to show surface abnormalities. Such an approach is particularly important for structures whereby distinct subfields or regions exhibit distinct functionality (e.g., BLA vs. CMA; Mosher et al., 2010) and promises to provide insight into circuit-level connections that can be investigated further with other imaging modalities

(e.g., diffusion-weighted MRI, resting-state MRI), as well as in preclinical animal models.

Finally, as we alluded to previously, investigating the effects of antidepressant medication was challenging in the present study, as the majority of sites did not collect detailed information on history, duration/adherence, type, and dosage of antidepressant treatment. Future research studies focused on collecting detailed information on lifetime medication usage in patients with MDD are needed to better understand how various antidepressants affect brain structure.

4.2 | Conclusions

We identified reductions in stress-sensitive subfields of the hippocampus, particularly in the subiculum and CA1, and in the basolateral amygdala in MDD patients with an earlier onset of depression and in MDD patients with recurrent episodes, compared to healthy controls and first-episode patients, respectively. Examining nuances in subcortical shape may help disentangle the complex clinical influences on the brain basis of MDD (e.g., structural correlates with important clinical variables, such as illness onset and recurrence), as well as provide the ability to detect fine-grained changes that show promise in the context of monitoring intervention targets with more specificity.

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DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available upon request from the investigators of each of the sites who have contributed data to this meta-analytic study. The data are not publicly available due to privacy or ethical restrictions.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

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