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Brain Correlates of Suicide Attempt in 18,925 Participants Across 18 International Cohorts

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ABSTRACT

BACKGROUND: Neuroimaging studies of suicidal behavior have so far been conducted in small samples, prone to biases and false-positive associations, yielding inconsistent results. The ENIGMA-MDD Working Group aims to address the issues of poor replicability and comparability by coordinating harmonized analyses across neuroimaging studies of major depressive disorder and related phenotypes, including suicidal behavior.

METHODS: Here, we pooled data from 18 international cohorts with neuroimaging and clinical measurements in 18,925 participants (12,477 healthy control subjects and 6448 people with depression, of whom 694 had attempted suicide). We compared regional cortical thickness and surface area and measures of subcortical, lateral ventricular, and intracranial volumes between suicide attempters, clinical control subjects (nonattempters with depression), and healthy control subjects.

RESULTS: We identified 25 regions of interest with statistically significant (false discovery rate , .05) differences between groups. Post hoc examinations identified neuroimaging markers associated with suicide attempt including smaller volumes of the left and right thalamus and the right pallidum and lower surface area of the left inferior parietal lobe.

CONCLUSIONS: This study addresses the lack of replicability and consistency in several previously published neuroimaging studies of suicide attempt and further demonstrates the need for well-powered samples and collaborative efforts. Our results highlight the potential involvement of the thalamus, a structure viewed historically as a passive gateway in the brain, and the pallidum, a region linked to reward response and positive affect. Future functional and connectivity studies of suicidal behaviors may focus on understanding how these regions relate to the neurobiological mechanisms of suicide attempt risk.
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Suicide is a leading cause of death worldwide and is a considerable health concern in both developed and developing countries (1). While region- and country-specific estimates vary, the global average prevalence for suicide is estimated to be about 10.6 deaths per 100,000 (2). Suicide attempts outnumber actual suicides by 20- to 30-fold (3,4), which further increases the economic and social burden of suicidal behavior (5). Suicidal behavior is more common in people living with mental illness (6–8). For a long time, suicidal behaviors were conceptualized as a symptom inherent to certain conditions, in particular, major depressive disorder (MDD). It is increasingly clear that suicidal behavior is complex (9). On the whole, a better understanding of suicidality, in terms of its underlying mechanisms, could help identify individuals at increased risk of engaging in suicidal behaviors and inform better interventions (10).

Noninvasive neuroimaging technologies, such as magnetic resonance imaging (MRI), allow brain structure and function to be studied in vivo (11,12). The analysis of brain orphometry and neuroanatomical differences between individuals with mental illness and healthy control subjects has already proven useful in conditions such as MDD (13), bipolar disorder (14), and schizophrenia (15). Similar approaches have been used to study suicidal behaviors, albeit in small samples. Briefly, several studies have reported lower gray matter volume and cortical thickness in the frontal, prefrontal, orbitofrontal, dorsolateral, and temporal lobes and white matter hyperintensities associated with suicidal behaviors (16–29).

Nonetheless, small samples and heterogeneous analysis methods have led to a lack of replicability and inconsistent results (11,30). The ENIGMA-MDD Working Group aims to address issues of poor replicability and comparability in neuroimaging studies by coordinating harmonized analyses of MDD and related phenotypes, including suicidal behavior. In the most recent meta-analysis of subcortical brain volumes conducted by our working group, we did not detect any significant morphological differences associated with suicidal behavior independently of depression diagnosis (31). Identifying the neural substrates of suicide attempt is key to understanding the etiology of suicide. This in turn might lead to the development of novel therapeutic strategies based on behavioral neuroscience and brain stimulation (32).

Previous studies have pinpointed some of these associations, for example, alterations in the ventral and dorsal prefrontal cortex, the insula, and regions involved in temporal, striatal, and posterior circuits (11,30). However, studies have been performed on samples of small size and with several sources of potential bias, resulting in inconsistent findings across publications (11). Notably, subcortical associations did not replicate in our previous meta-analyses (31). Thus, we conclude that prior literature might not be sufficiently robust to support the role of specific brain structures in suicide attempt. For that reason, we decided to conduct a comprehensive exploratory investigation of neuroimaging correlates for suicide attempt in the largest participant sample to date. We performed a pooled mega-analysis of subcortical volumes and regional cortical surface area and thickness, using linear mixed-model regressions in a sample of 18,925 subjects from 18 cohorts from around the world. We aimed to shed light on the neural circuits that underlie suicidal behavior by comparing brain morphometry between MDD cases with a history of suicide attempt versus those without, as well as versus healthy control subjects.

METHODS AND MATERIALS

Samples

We analyzed pooled data (mega-analysis) across 17 ENIGMAMDD Working Group cohorts with clinical and neuroimaging data available for participants fulfilling MDD criteria (33) (n = 2533) and healthy control subjects (n = 4066) and participants from the UK Biobank (n = 12,366). We defined three groups: suicide attempters; clinical control subjects, that is, participants with depression and no history of suicide attempt; and healthy control subjects. Descriptive statistics for each sample are listed in Table 1 and Table S1. Each cohort assessed depression status and history of a suicide attempt based on available clinical information. In the UK Biobank, lifetime depression status (n = 3633) and lifetime suicide attempt (n = 322) were ascertained using the Composite International Diagnostic Interview. Participants with no history of depression or suicide attempt (n = 8411) were defined as healthy control subjects. A psychiatric diagnostic interview was used to diagnose participants across the ENIGMA-MDD groups. Information on the instruments used to determine suicide attempt and exclusion criteria per site are available in Tables S2 and S3, respectively. The combined sample comprised 12,477 healthy control subjects and 6448 participants with a lifetime depression diagnosis. Within the depression group, 694 participants reported at least one suicide attempt. All sites obtained approval from their local institutional ethics committees and review boards to participate in this study, and all participants provided informed consent at their local recruitment institution.

Image Processing and Analysis

T1-weighted MRI structural brain scans were acquired and analyzed locally at each site using the validated and automated segmentation software FreeSurfer (34) (http://surfer.nmr.mgh.harvard.edu/). Image acquisition parameters and software versions and descriptions are detailed in Table S2. The segmentation of cortical and subcortical phenotypes was visually inspected for accuracy following standardized protocols designed to facilitate harmonized image analysis across multiple sites (http://enigma.ini.usc.edu/protocols/imagingprotocols/). Within each cohort, measures were visually verified for accuracy and excluded if they were not properly segmented. Within-cohort outliers (defined as measurement greater than 3 standard deviations away from the mean) were excluded from the analysis. We examined five global brain measures, including intracranial volume (ICV), total surface area of the left and right hemispheres and mean cortical thickness of the left and right hemispheres, 16 subcortical brain volume measures, and cortical surface area and thickness measures for 68 brain regions of interest (ROIs) as defined by the Desikan-Killiany atlas (35).

Ascertainment of Suicide Attempt History

In this study, a suicide attempt was defined as any self-harm act with the intent to die. In this study, we focused on lifetime suicide attempt, as opposed to other suicidal behaviors, to reduce potential heterogeneity arising from different suicide risk assessment instruments used across cohorts. Attempt severity was not assessed because of a lack of information in individual studies. A description of instruments used to measure suicide attempt in each site is available in Table S2. Cohorts also provided (where available) information on 1) whether participants have used antidepressants; 2) depression severity, coded either as the Hamilton Depression Rating Scale score excluding the suicide item, or as the number of DSM-IV MDD criteria endorsed (ranging from 0 to 9); 3) age of depression onset; and 4) whether depression was recurrent or a single episode.

Statistical Analyses

Linear Mixed-Effects Models. Statistical analyses were performed in R version 3.6.1 (R Foundation for Statistical Computing, Vienna, Austria) using the statistical package nlme. Linear mixed-effects models were used to account for site variation (with a random intercept for scan site) while correcting for desired covariates as fixed effects. We modeled each regional measure as an outcome while using an indicator variable per group of interest: healthy control subjects, patients with MDD with no suicide attempt history (clinical control subjects), and patients with MDD with attempt history (suicide attempters). All models were adjusted for age and sex, while surface area and volumetric analyses were also adjusted for ICV (except when ICV was the measure of interest). Main effects of groups (i.e., differences between groups of healthy control subjects, clinical control subjects, and suicide attempters) were identified by performing a type II analysis of variance (F test) over the fitted linear mixed-effects model described above. We conducted follow-up (post hoc) analyses to assess whether the effects were driven by suicide attempt. ROIs were compared between suicide attempters and clinical control subjects, between suicide attempters and healthy control subjects, and between clinical control subjects and healthy control subjects. Finally, we conducted several sensitivity analyses. First, to assess the effects of severity, recurrence, and age of onset of depression and history of antidepressant use on the observed associations, we repeated the post hoc analyses of the four regions showing evidence of association with suicide attempt, including additional covariates one at a time. Then, to evaluate the contribution of the largest cohort in the analysis to the observed results on the four ROIs mentioned above, we conducted the analyses excluding the UK Biobank cohort.

Statistical Significance Definition.

We corrected for multiple comparisons using a false discovery rate procedure (36) for each set of morphometry measures separately. The significance threshold to define ROIs for post hoc analyses was set at false discovery rate p value , .05. For the post hoc tests of the ROIs identified above, we used a matrix spectral decomposition to identify the number of effective variables (37,38) coupled with Bonferroni correction to keep the type I error rate at 5%. In this review, a significant result survived post hoc multiple testing corrections (p , Bonferroni corrected threshold), whereas a nominally significant result was only significant before correction (p , .05).

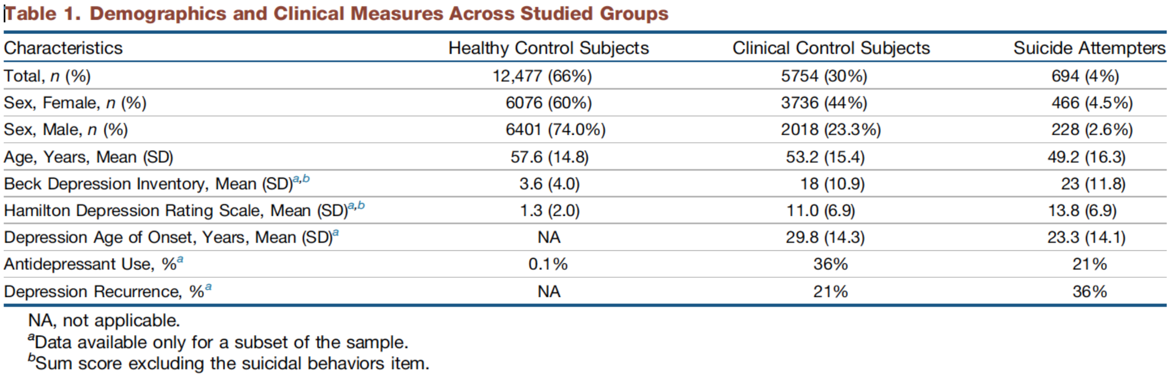

Table 1. Demographics and Clinical Measures Across Studied Groups

Characteristics	Healthy Control Subjects	Clinical Control Subjects	Suicide Attempters
Total, *n* (%)	12,477 (66%)	5754 (30%)	694 (4%)
Sex, Female, *n* (%)	6076 (60%)	3736 (44%)	466 (4.5%)
Sex, Male, *n* (%)	6401 (74.0%)	2018 (23.3%)	228 (2.6%)
Age, Years, Mean (SD)	57.6 (14.8)	53.2 (15.4)	49.2 (16.3)
Beck Depression Inventory, Mean (SD)[a,b]	3.6 (4.0)	18 (10.9)	23 (11.8)
Hamilton Depression Rating Scale, Mean (SD)[a,b]	1.3 (2.0)	11.0 (6.9)	13.8 (6.9)
Depression Age of Onset, Years, Mean (SD)[a]	NA	29.8 (14.3)	23.3 (14.1)
Antidepressant Use, %[a]	0.1%	36%	21%
Depression Recurrence, %[a]	NA	21%	36%

NA, not applicable.

[a] Data available only for a subset of the sample.

[b] Sum score excluding the suicidal behaviors item.

RESULTS

Suicide Attempt Prevalence and Sample Demographics

Details on the sample of each cohort included in this analysis are summarized in Table 1 and Table S1. Notably, not all cohorts had cases of suicide attempt, but still contributed data to the healthy or clinical control groups. The pooled mean age (SD) was 56.22 (15.17) years. Differences in age and sex composition across cohorts were detected (Table S1) and used as covariates for all the analyses. The total sample size comprised 18,925 subjects, of which 3.67% (n = 694) had at least one past suicide attempt. Furthermore, 30.40% (n = 5754) of the total sample was diagnosed with depression but did not report a previous suicide attempt. Methodological differences (e.g., scanner used or different parameters for the scan) between participating cohorts are listed in Table S2.

Subcortical Volumetric Measures

The thalamus (right and left), right pallidum, and total ICV exhibited a statistically significant group effect (i.e., any difference between healthy control subjects, clinical control subjects, or suicide attempters) after correcting for multiple comparisons. The left pallidum and the right nucleus accumbens showed a nominally significant difference but did not survive correction for multiple comparisons (Table S4). Depressed attempters exhibited smaller volumes in the left and right thalamus and right pallidum compared with both clinical (Cohen's d = 20.13, 20.14, and 20.12, respectively) and healthy control subjects (Figure 1). Depressed attempters also exhibited smaller ICV compared with healthy control subjects (Cohen's d = 20.13). This association did not reach significance, when comparing attempters and clinical control subjects, after accounting for multiple testing. None of the regions with a significant group effect showed a significant difference when comparing clinical control subjects with healthy control subjects (Table S5).

Cortical Surface Area

Eight of the 68 cortical regions under analysis displayed a significant group effect (Table S6). These regions included the left and right pericalcarine, left and right cuneus, left inferior parietal, left rostral middle frontal, right lingual, and right fusiform gyri. Depressed attempters exhibited, on average, a smaller surface area of the left cuneus, left inferior parietal, left rostral middle frontal, and right pericalcarine regions, compared with healthy control subjects. Furthermore, clinical control subjects exhibited smaller surface areas in the right pericalcarine and right fusiform gyri compared with healthy control subjects and clinical control subjects (Table S7). The left and right cuneus, left inferior parietal, right pericalcarine, and right lingual also exhibited nominally significant differences between attempters and clinical control subjects (p , .05, uncorrected). After correcting for post hoc multiple testing, only the left inferior parietal surface area was significantly different between attempters and clinical control subjects (Cohen’s d = 20.12) (Figure 2).

Cortical Thickness

Widespread cortical thickness differences between the three groups were observed (Table S8). Five of these regions showed a significant difference when comparing attempters with healthy control subjects, and three of those five (left fusiform, left insula, and left rostral middle frontal) showed nominally significant lower cortical thickness in depressed attempters compared with clinical control subjects. Only the left rostral middle frontal region displayed a statistically significant difference between attempters and healthy control subjects (Table S9). The left fusiform and the left insula also showed a nominally significant difference between clinical and healthy control subjects. Conversely, the left rostral middle frontal did not show a significant difference between clinical and healthy control subjects. All regions with a nominally significant difference between attempters and clinical control subjects were in the left hemisphere. After adjusting for multiple testing in the post hoc tests, none of the cortical thickness differences between attempters and clinical control subjects reached statistical significance (Figure 3, bottom, left panel).

Sensitivity Analyses

Finally, we performed sensitivity analyses to assess the effect of additional covariates on the associations discovered. Namely, we tested whether our results were robust to adjustment for previous antidepressant use, depression severity, age of onset, and recurrence. These analyses had lower statistical power because data on these variables were available in fewer cohorts. Participants with a history of suicide attempt continued to show a smaller volume of the right thalamus (p , .05) even after adjusting for history antidepressant use, depression severity, age of onset, and recurrence (Tables S10–S13). No other region remained significant after adjusting for any of these variables. A final sensitivity analysis was performed by excluding the UK Biobank cohort. While all of the effects were in the same direction, only the association between suicide attempt and lower right thalamus volume remained statistically significant (p = .004) (Table S14).

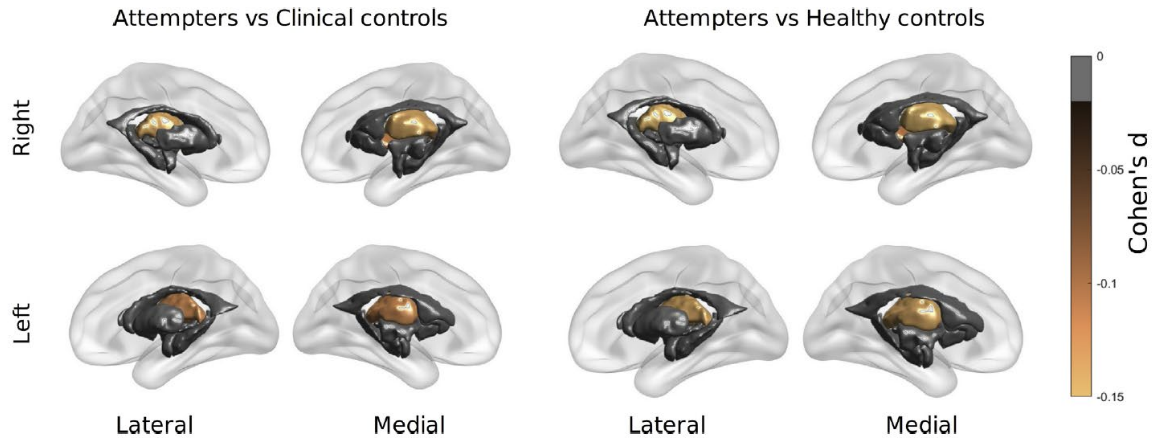

Figure 1. Group differences in subcortical volumes. Effect sizes are shown for regions that displayed a statistically significant difference in subcortical volumes between the groups: attempters compared with clinical control subjects (left panel) and attempters compared with healthy control subjects (right panel). No difference between clinical and healthy control subjects reached statistical significance after correction for multiple comparisons. Significant results are the bilateral thalamus and right pallidum.

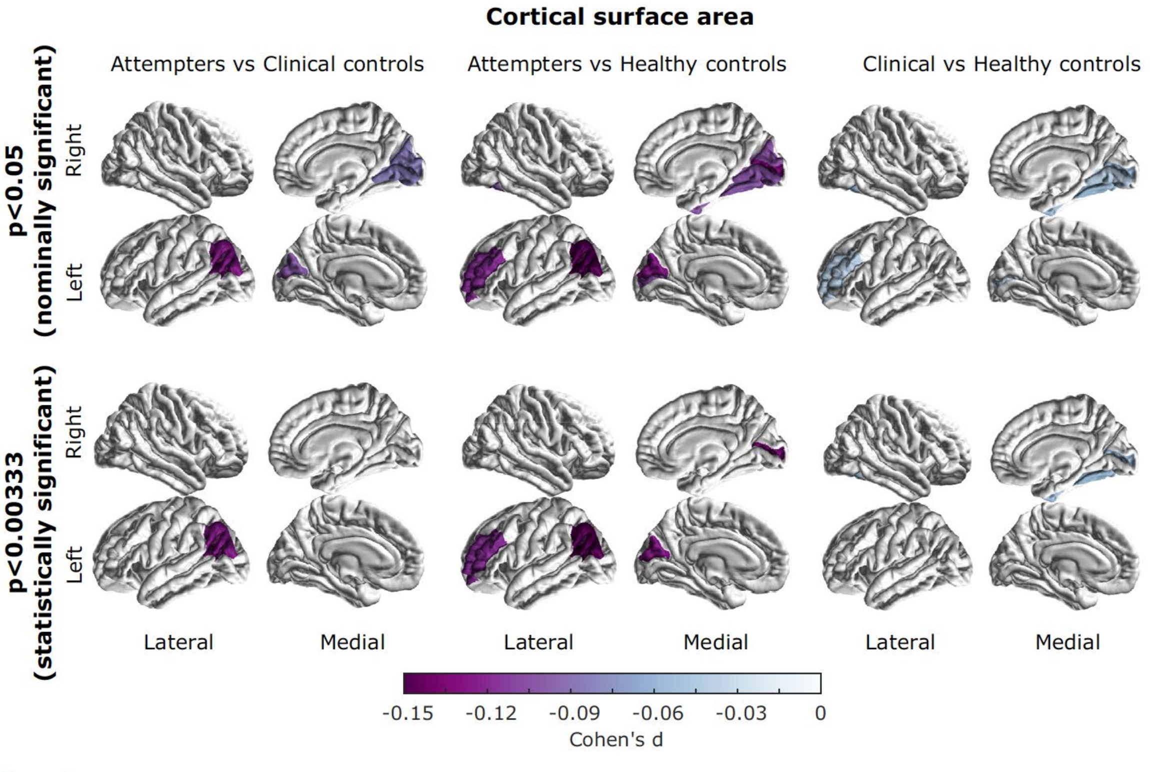

Figure 2. Group differences in cortical surface area. Effect sizes are shown for regions that displayed a (top) nominally significant ($p < .05$) or (bottom) a statistically significant ($p < .00333$ threshold after multiple test correction) post hoc difference between attempters and clinical control subjects (left panel), attempters and healthy control subjects (middle panel), and clinical control subjects compared with healthy control subjects (right panel). All of the colored regions showed a statistically significant group effect (false discovery rate < .05).

DISCUSSION

This study addressed the lack of statistical power, which may have resulted in low replicability and consistency, in previous neuroimaging studies of suicide attempt. Our analyses revealed four regions associated explicitly with suicide attempt, above and beyond the effect of MDD, supporting the hypothesis of suicidality-associated neural differences (30). The relatively few regions identified and the overall small effect sizes should be taken as a warning for future studies attempting to perform these types of analyses in small samples. However, we have also identified a need for reducing heterogeneity across cohorts, for example, by including information on suicide attempt lethality; this is increasingly challenging as sample size increases. We observed statistically significant volume reductions of the left and right thalamus and the right pallidum, and a smaller surface area in the left inferior parietal cortex in participants with depression who had a history of suicide attempt compared with both clinical and healthy control subjects. Previous studies have suggested that these regions are associated with suicidal behaviors (17,21,39–41); however, the lack of evidence for associations in better-powered studies (31) and the lack of consensus in the field (11,13) made it challenging to reach definitive conclusions. A recent overview of a brain model for suicidal behavior identified at least four functional diathetic elements to suicide. These include subjective distress, impaired decision making, learning or memory deficits, and social distortion as part of a cognitive impairment (42). The regions identified here are involved in decision making behaviors such as impulsivity and planning, as well as attention and concept of self (see below). All of these factors are related to the four risk-increasing components discussed above.

The pallidum has been linked to reward response, social activity mediation, and positive affect (43,44). Furthermore, a recent structural MRI study has linked the pallidum to suicidal ideation severity and impulsivity in a small sample of Korean patients with MDD (45). Thus, alterations in the pallidum may reflect changes in affect and impulsivity known to be associated with suicidal behaviors (46,47). The thalamus, historically viewed as a passive gateway linking different brain regions, has been recently proposed to operate as an integrative hub of the brain (48), relaying signals between regions such as the basal ganglia and the cortex, but also frontal-subcortical connections that have been linked to suicide attempt through fractional anisotropy (42). A growing body of evidence suggests that the different nuclei within the thalamus are involved in high-order cognition (49). The thalamus serves as a region where the integration of cortico-striatal-thalamiccortical circuit takes place. These circuits modulate several behaviors including emotional drive and planning (50). Our results showing abnormalities in part of the basal ganglia (pallidum) and the thalamus would be consistent with implicating these circuits with suicide attempt. Furthermore, thalamic abnormalities and lesions have been linked to disorders such as addiction (51), bipolar disorder (52), and schizophrenia (53,54). Therefore, an impaired function in the thalamus and its related circuits with the basal ganglia and cortex might mediate suicide attempt through impaired affect, empathy, and processing of stimuli response relationships.

As previously reviewed (28), the parietal region is part of the executive control network, which exerts control over thought, emotion, and behavior. The inferior parietal lobe is further part of the posterior parietal cortex (55), known for its role in attention networks

(56) and processing of visual information. The inferior parietal lobe has been linked to schizophrenia through structural and functional differences including executive function and concept-of-self functions (57). It has further been linked to suicide attempt within bipolar disorder (58). Connectivity and functional studies are necessary to complement our results; however, studying suicidality using functional MRI carries important challenges such as the immediate need to reduce suicide risk and establishing a valid (i.e., relevant) time frame before or after a suicide attempt.

Conversely, no cortical thickness differences survived post hoc multiple testing correction. Some regions differed between attempters and healthy control subjects, but the lack of differences between clinical control subjects and suicide attempters suggests that these associations may be driven by depression status, rather than suicide attempt. The fact that subcortical volume and surface area associations had a stronger association with suicide attempt than with cortical thickness could be of interest in light of genetic analyses that identified substantial differences in the genetic etiology of cortical morphometry phenotypes (59–61). For example, surface area measurements were reported to have a higher heritability and to be more influenced by early developmental genetic influences than cortical thickness (60), suggesting that biomarkers associated with surface area are likely established earlier in life. In contrast, cortical thickness phenotypes may be more variable and more susceptible to adverse environmental effects later in life, such as substance use or having a psychiatric condition.

The substantial overlap between depression severity and suicide attempt (e.g., Table 1 shows that participants with a past suicide attempt also have higher Hamilton Depression Rating Scale and Beck Depression Inventory sum scores even after removing the suicide item) makes it difficult to differentiate whether an identified statistical effect is driven by depression severity or suicide attempt status. This is also supported by the fact that several cortical associations also displayed an effect when comparing clinical with healthy control subjects and that those results did not remain significant after sensitivity analyses that controlled for proxies of depression severity. Overall, effect sizes were smaller when comparing clinical with healthy control subjects than those when comparing suicide attempters with either control group. That might be due to the previously discussed collinearity between suicidal behaviors and depression severity. Many of the most severely depressed cases will be among the depressed suicidal group, thus reducing the strength of any signals associated with depression severity. In our previous study, we investigated intracranial and subcortical volumes for their association with suicidal behavior, ideation, plan, and attempt in a smaller sample (N = 3097). Notably, we did not detect any significant associations, and a post hoc power estimation analysis suggested that a sample size of .2290 cases (suicide attempters) would be required just for a subcortical volume study. In this study, the total sample size and the number of contributing cohorts more than doubled. Furthermore, we focused on suicide attempt only to reduce heterogeneity and expanded the number and type of brain morphology phenotypes under analysis (including cortical brain measures). Finally, we used a different methodology based on pooling individual-level data and using linear mixed models, in contrast to a classic meta-analysis as in our previous study. By using a mega-analytical approach instead of a meta-analytical approach, we could include more samples with a relatively small number of suicide attempt cases. Accordingly, we implemented a linear mixed-model framework, which allowed us to adjust for the differences across sites by modeling imaging site as a random effect without significantly compromising statistical power.

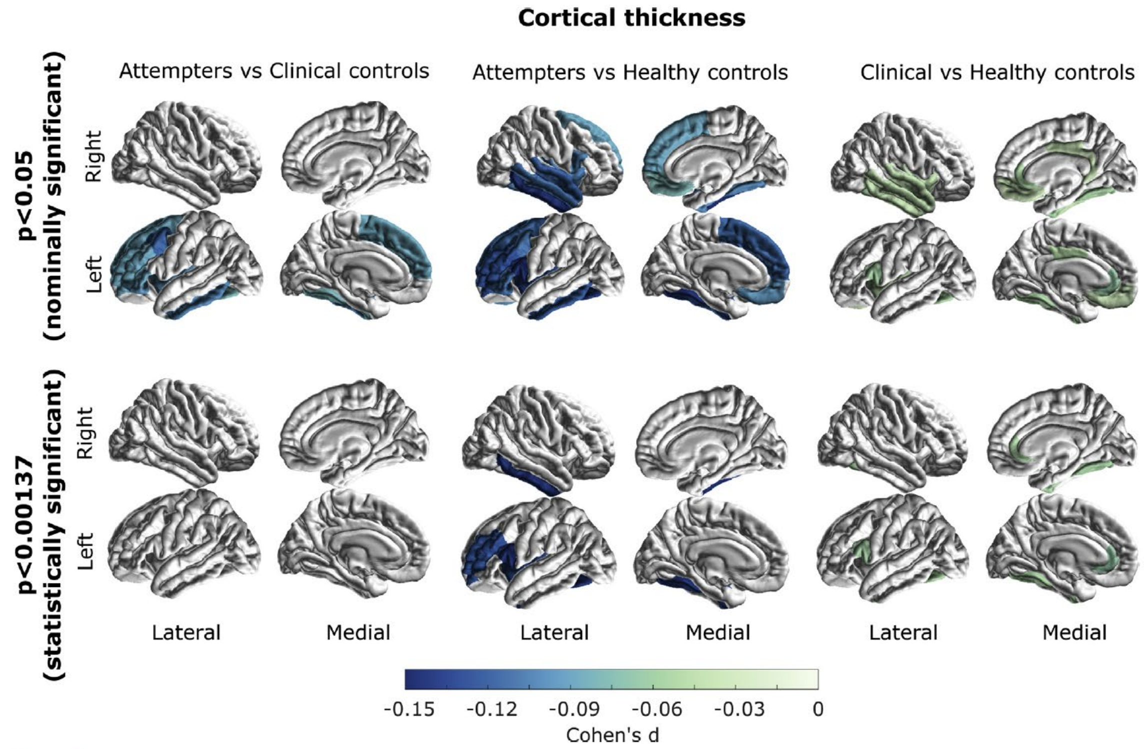

Figure 3. Group differences in cortical thickness. Effect sizes are shown for regions that displayed a (top) nominally significant ($p < .05$) or (bottom) a statistically significant ($p < .001373$ threshold after multiple test correction) post hoc difference between attempters and clinical control subjects (left panel), attempters and healthy control subjects (middle panel), and clinical control subjects compared with healthy control subjects (right panel). All of the colored regions showed a statistically significant group effect (false discovery rate $< .05$).

This study examined cohorts from the ENIGMA-MDD Working Group and a subset of participants fulfilling MDD diagnosis criteria from the UK Biobank. Heterogeneity across cohorts is a potential confounder of any large-scale collaboration. For example, the mechanisms underlying suicide have been shown to vary with age (62). Furthermore, different groups might have used different MRI scanners and acquisition parameters, studied treatment-naïve participants, or assessed suicide attempt using different instruments. To account for this, we used linear mixed models, which adjust for the effects of different sites, and relevant covariates such as age (and depression age of onset or antidepressant usage as sensitivity analyses), while preserving statistical power. All individuals with a history of suicide attempt also had an MDD diagnosis. Thus, we cannot conclude whether the associations observed in this study would also be correlated with suicide attempt history in other mental illnesses. While the direction of effects was highly consistent in the sensitivity analyses, only the right thalamus was associated with suicide attempt above and beyond potential covariates such as depression severity, recurrence, and history of antidepressant use. Furthermore, the right thalamus remained associated even after excluding the UK Biobank cohort, suggesting that it is a generalizable and robust association. The observation of other ROIs no longer showing an association with suicide attempt after correcting for these additional clinical variables was expected for several reasons. First, suicidality is highly collinear with depression severity, including recurrence of depressive episodes. Second, the lack of information on these variables in some of the contributing cohorts greatly reduced the sample size for the sensitivity analyses, resulting in reduced statistical power to detect the same small effect sizes observed for these brain measures across the whole sample.

It is important to acknowledge that a range of suicide risk assessment, MRI instruments, and acquisition parameters were used across cohorts. We have tackled this in two ways: 1) cohorts ascertained lifetime suicide attempt using standard instruments with help from a mental health expert, and 2) we used a statistical framework that corrects for heterogeneity and confounders arising from systematic cohort differences such as MRI scanner used. While we identified alterations associated with suicide attempt, the direction of causality was less clear. It is plausible that these alterations are a consequence of suicidal thoughts causing a brain rewiring. Suicide attempts may also affect brain morphometry. Longitudinal analyses are perhaps the best approach to help us understand whether these alterations are a cause or consequence of suicide attempt. Other limitations include the lack of detailed information on suicide attempt method and lethality, as well as detailed information for sensitivity analyses such as antidepressant type and prescription regime used. Furthermore, there is a known nondisclosure effect driven by suicide attempt being considered a taboo across several cultures. This would cause some actual cases to be reported as controls. Thus, our power to detect different neural mechanisms would be hindered by both the nondisclosure effect and a lack of detailed clinical information. Finally, this study was performed within participants with depression, and care should be taken when generalizing to other disorders.

This international collaboration has yielded valuable insights into the neurobiology of suicide. The number of associations discovered and their small effect sizes indicate that morphological differences between attempters and nonattempters will likely not be useful for clinical diagnosis or risk stratification.Even so, if several neural circuits underlie suicidal behaviors with relatively small effect sizes, the aggregation of them might still be useful for risk stratification. Heterogeneity, which can be increased by several factors including lack of information on the lethality of suicide attempt, also contributes to reduced power and might explain the small effect sizes. Thus, lowering heterogeneity, increasing sample size, examining more detailed suicide attempt–related phenotypes such as number of attempts, lethality, and age at first attempt and increasing the resolution of neuromaging studies (e.g., to the vertex level) as well as integrating neuroimaging measurements with other modalities (e.g., functional imaging data) will help advance the field.

In summary, our results suggest that suicide attempt is associated with volumetric reductions within the thalamus and right pallidum and surface area reductions in the left interior parietal lobe, over and above the effects of depression alone. Our findings suggest that several regions are associated with suicide attempt, albeit with relatively small effect sizes. This study addressed the lack of replicability and consistency in several previously published neuroimaging studies of suicide attempt and further demonstrated the need for well-powered samples and collaborative efforts to avoid reaching biased or misleading conclusions.

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MER and LS conceived and jointly supervised the study. Authors from all site cohorts were involved in data collection, processing, analysis, and funding for their samples. AIC implemented the analysis pipeline, performed all statistical analyses, and generated the tables and figures. AIC, MER, and LS drafted the first draft of the manuscript with feedback and input from all coauthors. All authors approved the content of this manuscript.

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