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Title:
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Date:
2025-12-01

Citation:
Serrarens, C., Toenders, Y. J., Pozzi, E., Aleman, A., Alexander, N., Başgöze, Z., Belov, V., Berger, K., Brosch, K., Bülow, R., Busatto, G. F., Capitão, L. P., Connolly, C. G., Couvy-Duchesne, B., Cullen, K. R., Dannlowski, U., Davey, C. G., de Zubicaray, G. I., Dima, D. ,... Yang, T. T. (2025). Regional brain morphology and current antidepressant use: findings from 32 international cohorts from the ENIGMA major depressive disorder working group. Molecular Psychiatry, 30 (12), pp.5625-5636. https://doi.org/10.1038/s41380-025-03310-8.

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Regional brain morphology and current antidepressant use: findings from 32 international cohorts from the ENIGMA major depressive disorder working group

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The understanding of how antidepressant (AD) use is associated with brain structure in individuals with major depressive disorder (MDD) remains incomplete. We aimed to examine the association between AD medication use and brain morphology in relation to age and sex by pooling structural neuroimaging and clinical data from 32 cohorts within the ENIGMA-MDD working group. Interaction effects of group (2076 cases with current AD use (AD), 1495 cases not currently taking AD (nAD) and 5125 healthy controls (HC)) with age and sex, and main effects of group on regional brain structure (cortical surface area and thickness, and subcortical volume) were examined. Additionally, we examined the effect of AD type (SSRI, SNRI or mirtazapine) and duration of use on brain morphology. Younger individuals in the AD group showed lower bilateral middle temporal gyrus thickness compared to nAD and HC, but this was not seen in older individuals (crossover around 50 years). Lower hippocampal volume and thinner inferior temporal gyrus were shown in AD compared to nAD. These effects were independent of group differences in disease-course-related measures, but were driven by depressive symptom severity. Greater bilateral rostral anterior cingulate thickness was found in individuals older than approximately 40 years taking mirtazapine compared to individuals taking SSRIs or SNRIs. Evidence for subtle structural brain differences in temporal and limbic regions in individuals with MDD who currently use AD medication were found compared to those not currently taking AD medication. Future longitudinal studies are needed to determine the causality of these associations.

Molecular Psychiatry (2025) 30:5625–5636; https://doi.org/10.1038/s41380-025-03310-8

INTRODUCTION

Over 300 million people suffer from major depressive disorder (MDD), a leading cause of disability worldwide [1]. Antidepressant (AD) medication is the most used pharmacological therapeutic treatment for MDD [2], and the number of people who are prescribed AD continues to increase [3]. Randomized controlled clinical trials have demonstrated a modest effect of AD treatment on response and remission rates [4–6]. Despite the high rate of use, our understanding of the neurobiological mechanisms through which AD may improve mood remains limited.

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Received: 18 March 2024 Revised: 5 August 2025 Accepted: 15 October 2025
Published online: 3 November 2025

Animal studies have suggested that antidepressants, in particular selective serotonin reuptake inhibitors (SSRIs), upregulate brain-derived neurotrophic factor (BDNF), enhance dendritic arborization and total dendritic length of hippocampal neurons and stimulate hippocampal proliferation and neurogenesis, thereby reversing neuronal atrophy and cell loss [7–11]. Magnetic resonance imaging (MRI) has been used to examine the association between AD medication use and brain structure in humans [12, 13]. Previous cross-sectional neuroimaging studies have shown larger hippocampal and orbitofrontal cortex (OFC) volumes in MDD patients currently taking AD (i.e. MDD patients using antidepressants at time of scanning) compared to medication-naive MDD patients, but smaller than those in healthy controls [14, 15]. This suggests a potential neuroprotective effect of AD medication on brain morphology in MDD patients. Longitudinal studies showed significant increases in hippocampal volume [16, 17], dorsolateral prefrontal cortex (DLPFC) volume [18], medial orbitofrontal cortex (mOFC) thickness [19] and thickness of other regions in prefrontal, parietal, and temporal lobes [20] in MDD patients following AD medication treatment. Given previous findings of brain structure alterations in unmedicated MDD patients [21, 22], these findings may suggest (partial) normalization of brain structure of MDD patients after AD medication treatment. Conversely, other studies found no significant longitudinal changes in hippocampal volume [23–26], amygdala volume [24], anterior cingulate cortex (ACC) volume [24] or whole-brain cortical thickness [27] in MDD patients following AD treatment.

Clinical and preclinical evidence suggests that AD medication may have different behavioral and biological effects across the lifespan [10, 28, 29], although the underlying mechanisms remain elusive. AD use might have a stronger impact on the developing brain through increased plasticity and dendritic spine density, mechanisms that have been associated with AD use [11, 30, 31]. However, our understanding of the association between AD medication use and brain structure across the lifespan in MDD patients based on neuroimaging studies remains incomplete, mainly due to heterogeneous findings across previous neuroimaging studies and limited power to detect small effects (which may result from variance in underlying mechanisms) in previous studies [32, 33].

Meta-analysis of the existing literature may increase power and address limitations related to small sample sizes, but it is hampered by heterogeneity in methods used to process neuroimaging data and limited by publication bias. The MDD Working Group within the Enhancing Neuro Imaging Genetics through Meta-Analysis (ENIGMA; http://enigma.usc.edu/) consortium aims to address these issues by performing individual participant data (IPD)-based meta-analyses or mega-analysis of pooled neuroimaging data from MDD patients across many samples, processed with harmonized protocols. In the first ENIGMA-MDD meta-analysis, we identified subcortical brain volume changes in MDD patients when compared to healthy controls [34]. In a supplementary meta-regression analysis the results revealed a trend towards lower hippocampal volume in samples with a higher percentage of patients with MDD taking AD medication [34]. A second ENIGMA-MDD meta-analysis, focusing on cortical structural abnormalities in MDD patients relative to healthy controls, revealed lower cortical thickness in adult patients, with the highest effect sizes and most widespread alterations in thickness in patients using antidepressants (effect size Cohen's d ranging between −0.08 to −0.13 [35];). These findings seem to contradict part of the previous literature on associations between brain structure and AD use as well as evidence from animal studies which suggested normalization of brain structure with antidepressant use. However, in our prior research on the combined ENIGMA-MDD sample, the strongest subcortical and cortical brain alterations were shown in adults with MDD that were using AD medication at time of scanning compared to those who were not. Our previous ENIGMA-MDD results in adults were interpreted as a potential confounding effect of severity; i.e., patients with more severe or recurrent/chronic depression are more likely to show the strongest reduction in cortical thickness, surface area and subcortical brain volumes and are also more likely to use AD. However, this was not examined directly.

In contrast to findings in adults, an ENIGMA-MDD meta-analysis in adolescent patients showed no differences in brain measures between individuals with MDD who were on AD medication at time of scanning and healthy controls, while adolescents who were not taking AD medication at time of scanning showed lower surface area in various regions compared to healthy controls [35]. Moreover, adolescents taking antidepressants showed larger regional cortical surface area compared to adolescent cases that were not taking AD medication at time of scanning. These findings are more in line with the animal literature and potentially suggest neuroprotective effects of AD medication on surface area in adolescents.

In summary, many conflicting findings exist with regard to the association between AD medication use and brain structure alterations in MDD and it remains unclear what the influence of age and sex is on this association. To examine the association between AD use and cortical and subcortical morphology in more depth and in a larger sample with more detailed and comprehensive information (regarding type and duration) on AD use compared to the previous ENIGMA-MDD meta-analyses, we employed a large sample from the ENIGMA-MDD working group and conducted a mega-analysis to investigate the relationship between AD medication use and brain morphology in relation to age and sex. This mega-analytic approach allowed us to examine the interaction with age and sex across all cohorts and the total age range, in comparison to our previous meta-analytic approach where these interactions could only be examined within cohorts.

Patients and methods

Samples. The ENIGMA-MDD Working Group is a collaboration between more than 40 international research groups, from 14 different countries worldwide, that have collected neuroimaging and clinical data from MDD patients and healthy controls. Thirty-two of these groups have collected detailed information about current AD use and agreed to participate in this study. In total, we pooled and analyzed data from 8696 individuals, including 3571 MDD patients and 5125 healthy controls (HC). MDD patients were further grouped into either: 1) cases with current AD use (AD group) (i.e., MDD patients using AD medication at the time of scanning; $n = 2076$) or 2) cases not currently taking AD (nAD group) (i.e., MDD patients not using AD medication at the time of scanning; $n = 1495$). Demographic and clinical characteristics for the AD group, nAD group and HC are presented in Table 1. A detailed summary of demographic and clinical characteristics of each sample is presented in Supplementary Table S1. Diagnostic assessment instruments and exclusion criteria for every site are listed in Supplementary Table S2. All sites obtained ethics approval from their local institutional review boards and ethics committees for the original studies and sharing of the data for this project. All participants provided informed consent at their local recruitment institution.

Image acquisition and processing

Structural T1-weighted images were acquired locally at each site. Image acquisition parameters and processing software of each sample are listed in Supplementary Table S3. T1-weighted images were analyzed using the fully automated and validated segmentation software FreeSurfer [36], following standardized protocols to facilitate harmonized image analysis and quality control procedures across sites (see http://enigma.ini.usc.edu/protocols/

Table 1. Group differences in demographic and clinical measures between HC, the AD group and nAD group.

	HC N = 5125	AD N = 2076	nAD N = 1495	ANOVA/T-test	Chi-square	Direction of effect
Age (SD)	38.02 (15.45)	42.82 (12.78)	34.88 (15.65)	F = 133.9, p < 0.05		AD > HC>nAD
Sex (% female)	56.25	60.45	67.83		$X^2 = 65.84$, p < 0.05	nAD>AD>HC
Age of onset (SD)	NA	31.97 (13.36)	25.90 (13.33)	T = 12.76, p < 0.05		AD>nAD
HDRS-17 score (SD)	NA	15.52 (7.81)	11.30 (8.56)	T = 10.11, p < 0.05		AD>nAD
BDI-II score (SD)	NA	25.81 (11.51)	16.76 (12.08)	T = 13.40, p < 0.05		AD>nAD
Number of episodes (SD)	NA	4.03 (5.61)	3.36 (6.29)	T = 2.65, p < 0.05		AD>nAD
% in remission	NA	7.94	18.00		$X^2 = 62.92$; p < 0.05	nAD>AD
% recurrent MDD	NA	73.61	55.98		$X^2 = 91.42$, p < 0.05	AD>nAD

NB: HC Healthy controls, AD cases with current AD use, nAD cases not currently taking AD.

imaging-protocols/). Mean (across left and right hemisphere) cortical thickness and surface area measures of 34 cortical gray matter regions and average thickness and surface area were obtained based on the Desikan-Kiliany atlas, as well as mean volume segmentations of 7 subcortical gray matter structures together with lateral ventricles and total intracranial volume (ICV). Segmentations were visually inspected and statistically reviewed for outliers. Regions that were not properly segmented according to visual inspection, were excluded from the analyses. Despite the standardized segmentation and QC protocols for FreeSurfer, there remain site differences in the extracted brain imaging features because of the different scanner types and T1-weighted sequences, and these site differences can be a potentially strong confound in multisite analysis [37]. In order to correct the neuroimaging measures for this residual heterogeneity due to scan site, we used ComBat harmonization [37] in R (version 3.3.1) (R Core Team). ComBat adjusts for the variability between sites using an empirical Bayes approach, whereas variability associated with the included covariates (age, sex and diagnosis) is preserved. Within-site outliers (defined as measures greater than three standard deviations away from the mean of a region) were excluded from the analyses.

Statistical framework

Group (AD group, nAD group and HC) differences in demographic and clinical characteristics were examined using analysis of variance and chi-square tests in R (version 3.3.1) [38]. To examine group differences in subcortical volumes, and cortical thickness and surface areas, multiple regression analyses were performed separately for every region of interest (ROI). The subcortical volume, cortical thickness and surface area of each ROI was introduced as the dependent variable in separate univariate models. The regression models included group (AD group, nAD group and HC), age and sex. Furthermore, in analyses with cortical surface area and subcortical volume, ICV was included as an additional covariate. Given that head size does not scale with cortical thickness, ICV was not included as a covariate in the cortical thickness analyses [39]. We first assessed the significance of group-by-age and group-by-sex interactions on regional brain structure (cortical thickness and surface area, and subcortical volume). In the case of a significant group-by-age interaction effect, the data was plotted and visual inspection was used to examine a crossover point. If no significant interaction effects were detected (false-discovery rate; FDR p-value > 0.05), these interaction terms were removed from the model to investigate the main effect of group, while including age and sex as covariates. If a significant group effect was present (FDR p-value < 0.05), we performed pairwise comparisons between each pair of groups in post-hoc tests. Effect size estimates of group-by-age and group-by-sex interactions, as well as the main effect of group were calculated using the effectsize package in R [40]. For interaction effects and the main effect of group, we calculated partial η-square as effect size. In two-group comparisons following a significant main effect of group, we calculated the Cohen's d metric. In interaction analyses, to correct for the number of brain regions, FDR multiple comparison corrections were applied for the total number of ROIs (N = 78) including 7 subcortical volume structures, lateral ventricle volume, 34 cortical thickness regions, 34 cortical surface area regions, average thickness, and average surface area. In main effect of group analyses, to correct for the number of brain regions, FDR multiple comparison corrections were applied for the total number of ROIs showing no significant interaction effects. Lastly, in post-hoc tests, to correct for the number of brain regions, FDR multiple comparison corrections were applied for the total number of ROIs showing a significant main effect of group. Results were considered significant if the FDR corrected p-value was lower than 0.05.

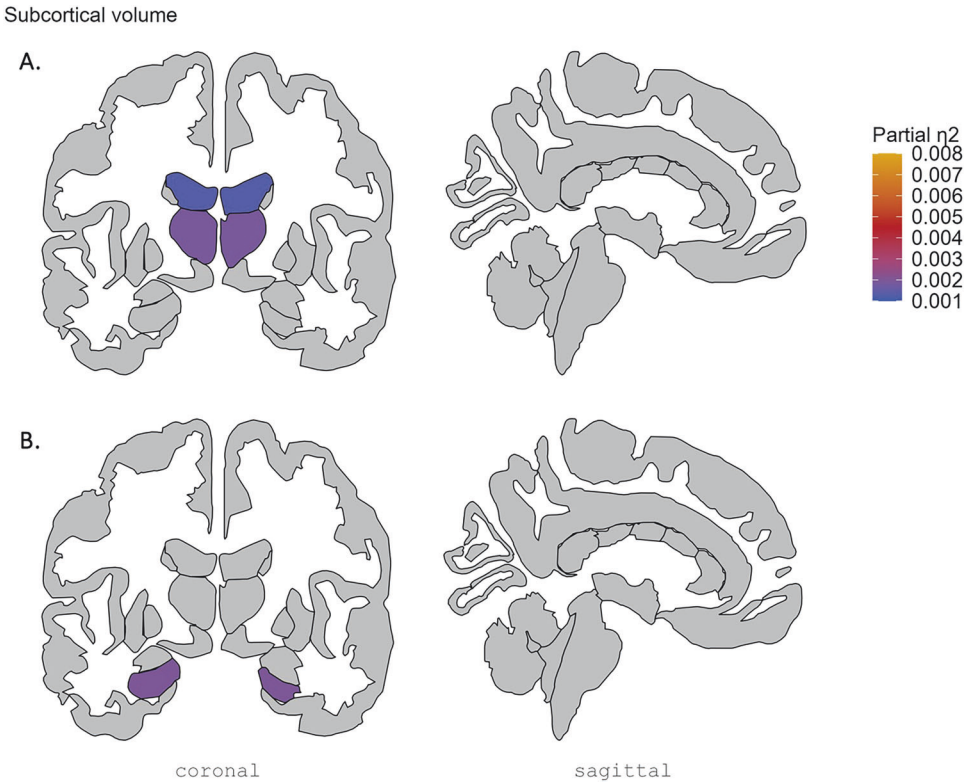

Fig. 1 Effect sizes for subcortical volume regions showing significant group-by-age interaction effects and main effect of group. Effect sizes for volume of the (**A**) thalamus and lateral ventricles showing a significant group-by-age (AD, nAD and HC group) interaction effect and of the (**B**) hippocampus showing a significant main effect of group. AD: cases with current AD use; nAD: cases not currently taking AD; HC: healthy controls.

Secondary analyses

For ROIs that showed a significant interaction or main effect of group in the primary analyses, we performed additional sensitivity analyses to examine whether they remained significant after correcting for symptom severity or disease course. In these secondary analyses we performed the analyses described above with the following additional secondary covariates in separate analyses: total Beck Depression Inventory (BDI-II [41];) or the total 17-item Hamilton Depression Rating Scale (HDRS-17 [42];) score, number of depressive episodes (subdivided into 3 categories, either 1, 2 or 3 or higher number of depressive episodes), stage of illness (first episode vs recurrent) and remission status (acutely depressed or remitted patients). As these variables were not available in HC, we performed the secondary analyses in a sample consisting of only the AD and nAD group.

In exploratory analyses we investigated effects of duration and type of AD medication use in the AD group on all ROIs. These analyses were done in a subset of the total sample that had information on duration of use and type of AD. The analyses were performed with either 1) type of AD medication (i.e., SSRI; $n = 405$, serotonin-norepinephrine reuptake inhibitor: SNRI; $n = 383$; mirtazapine; $n = 120$) or 2) duration of current AD medication use in months ($n = 303$) included in the regression model. First, significance of interactions between either 1) type of AD medication or 2) duration of current AD medication use with age and sex was assessed. If no significant interaction effects were detected (FDR p-value > 0.05), these terms were removed from the model to investigate the main effect of type of AD medication or duration of current AD medication use. When a significant group-by-sex or group-by-age interaction or main effect of AD group was found for either duration or type of AD medication use, we performed the analyses using the additional secondary covariates as described above.

RESULTS

Demographic and clinical characteristics

Demographic and clinical characteristics for the AD, nAD and HC group are presented in Table 1. The groups significantly differed in 1) age, with higher mean age in the AD group compared to the other groups, and higher age in HC compared to the nAD group, 2) sex, with more females in the nAD group compared to the other groups, and more females in the AD group compared to HC, 3) age of MDD onset, with an older age of onset in the AD group compared to the nAD group, 4) HDRS-17 and BDI-II scores, with higher current symptom severity in the AD group compared to the nAD group, 5) number of depressive episodes, with more depressive episodes in the AD group compared to the nAD group, 6) percentage in remission, with more patients in remission in the nAD group compared to the AD group, and 7) stage of illness with a higher ratio of recurrent episodes versus first episode in the AD group compared to the nAD group.

Interaction and main effects on brain morphology

While there were no significant group-by-sex interaction effects on brain morphology (see Supplementary Tables S4-6), significant group-by-age interaction effects were found for volume of two subcortical regions (thalamus and lateral ventricle; see Fig. 1A, Supplemental Fig. 1, Supplementary Table S4; partial η^2 0.0019 and 0.0013 respectively), 13 out of 35 cortical thickness regions (see Fig. 2A, Supplemental Fig. 2, Supplementary Table S5; partial η^2 between 0.0039 and 0.0011) and surface area of the lateral occipital cortex and insula (see Fig. 3A, Supplemental Fig. 3, Supplementary Table S6; partial η^2 0.0012 and 0.0015 respectively). In addition, we observed significant main effects of group on the volume of the hippocampus (see Fig. 1B, Supplementary Table S4; partial η^2 0.0020), thickness of 17 cortical regions (see Fig. 2B, Supplementary Table S5; partial η^2 between 0.0079 and

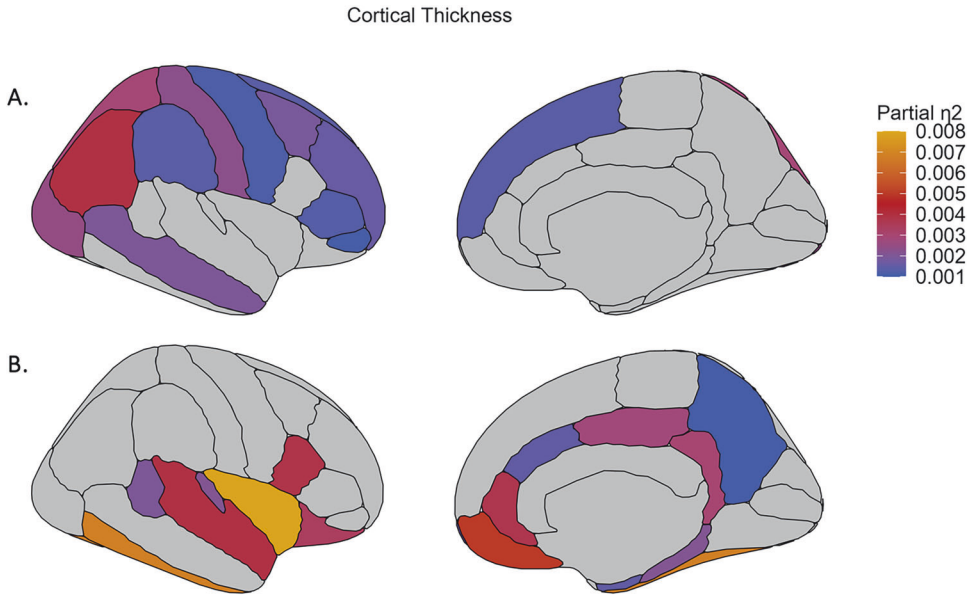

Fig. 2 Effect sizes for cortical thickness regions showing significant group-by-age interaction effects and main effect of group. Effect sizes for (**A**) significant group-by-age (AD, nAD and HC group) interaction effects and (**B**) significant main effect of group on cortical thickness regions, plotted on the right hemisphere. AD: cases with current AD use; nAD: cases not currently taking AD; HC: healthy controls.

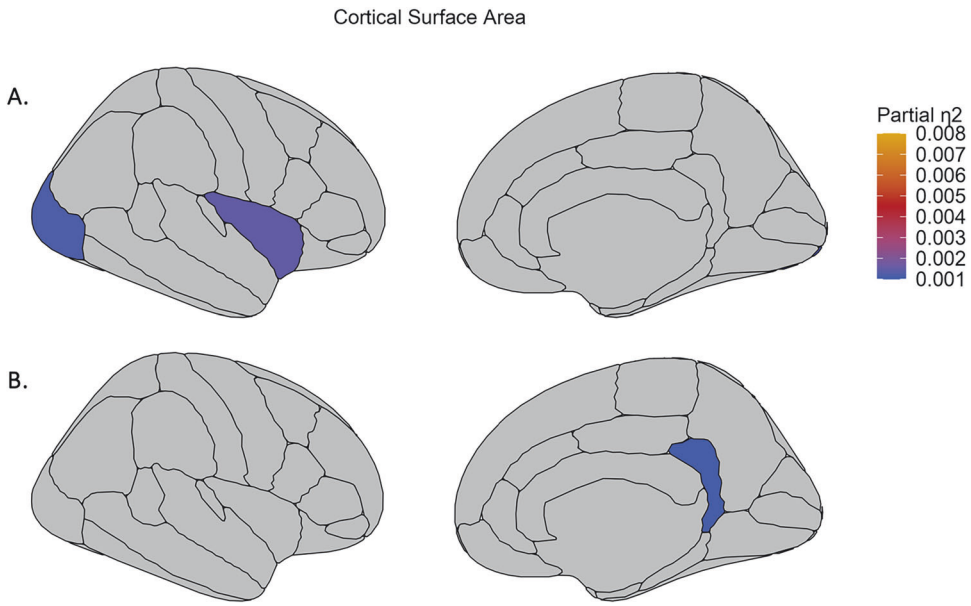

Fig. 3 Effect sizes for cortical surface area regions showing significant group-by-age interaction effects and main effect of group. Effect sizes for surface area of the (**A**) insula and lateral occipital cortex showing a significant group-by-age (AD, nAD and HC group) interaction effect and of the (**B**) isthmus cingulate cortex showing a significant main effect of group, plotted on the right hemisphere. AD: cases with current AD use; nAD: cases not currently taking AD; HC: healthy controls.

0.0011) and surface area of the isthmus cingulate cortex (see Fig. 3B, Supplementary Table S6; partial η^2 0.0011). These effects are further detailed below, reported separately for effects driven by AD use and effects driven by MDD diagnosis in general.

AD medication use and brain morphology

Two of the abovementioned significant group-by-age interaction effects showed that the association between age and regional cortical thickness were different in the AD group than both the nAD group and HC, suggesting an effect of current AD use, namely in the middle temporal gyrus and inferior frontal gyrus (pars triangularis). Upon visual inspection, these two regions showed a cross-over around the age of 50, with lower thickness in the AD group, compared to both the nAD group and HC in younger participants, while there was no difference in older participants (see Fig. 4). When correcting for additional clinical variables, including HDRS-17 score, number of depressive episodes, illness stage and remission status, the significant group-by-age interaction for cortical thickness of the middle temporal gyrus remained (Supplementary Table S7-S12), except for when including BDI-II score (Supplementary Table S9).

In terms of main effects of group, post-hoc tests showed lower hippocampal volume in the AD group compared to the nAD group (see Fig. 5A; Supplementary Table S13; Cohen's d −0.1300). This finding remained significant after correcting for the number of depressive episodes, stage of illness and remission but not after

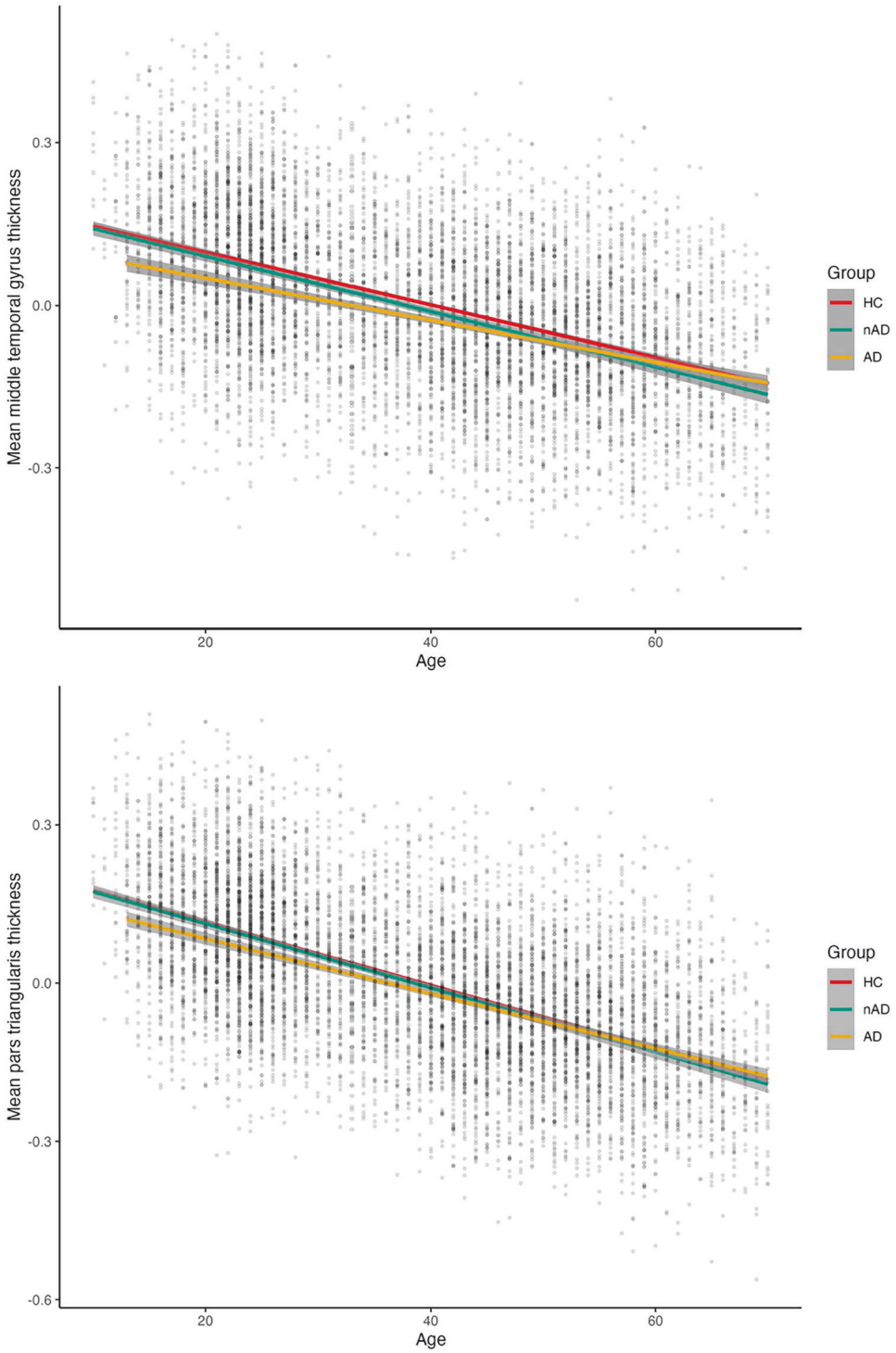

Fig. 4 Significant group-by-age interaction effects on mean thickness of the middle temporal gyrus and inferior frontal gyrus (pars triangularis). Mean cortical thickness for these regions is presented corrected for sex (estimated marginal means). HC: Healthy controls; nAD: cases not currently taking AD; AD: cases with current AD use.

correcting for current depression severity (HDRS-17 and BDI-II scores) (Supplemental Tables S14-S18). Cortical thickness of nine of the 17 significant regions showed lower cortical thickness in the AD group compared to the nAD group in the fusiform gyrus, inferior temporal gyrus, lateral orbitofrontal cortex, medial orbitofrontal cortex, parahippocampal gyrus, inferior frontal gyrus pars opercularis, superior temporal gyrus, frontal pole and insula (see Fig. 5A; Supplementary Table S19; Cohen's *d* between −0.0765 and −0.1349). Only the inferior temporal gyrus remained significantly lower in AD compared to nAD when correcting for number of depressive episodes, stage of illness and remission status, but not when correcting for current severity (HDRS-17 and BDI-II scores) (Supplementary Tables S20–24). Differences in surface area of the isthmus cingulate cortex were not present between the AD group and nAD group (see Fig. 5A; Supplementary Table S25; Cohen's *d* 0.0344).

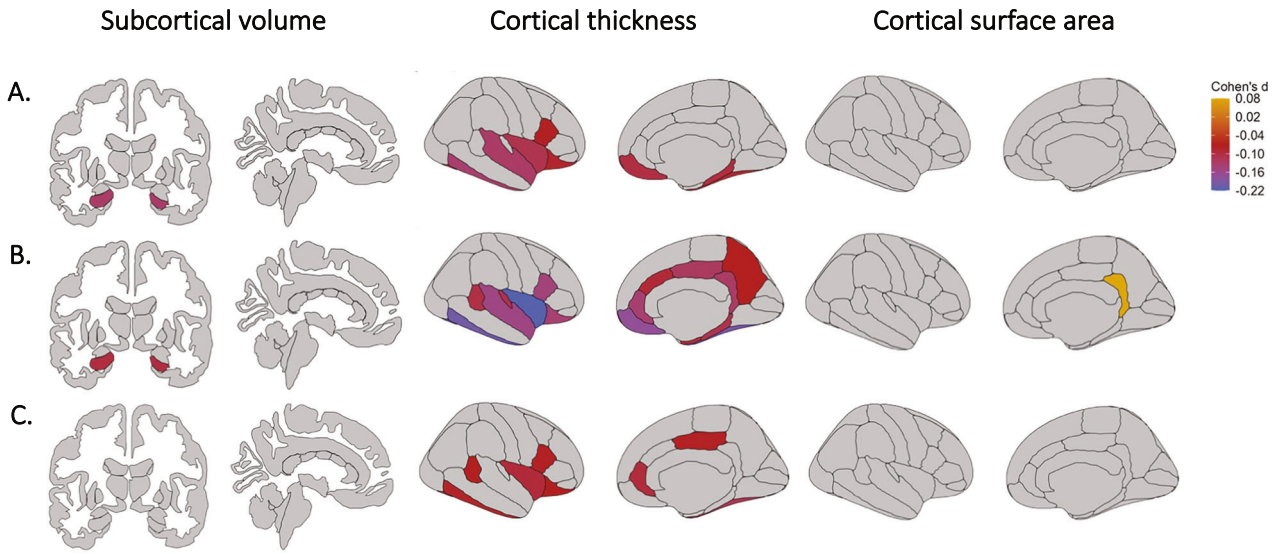

Fig. 5 Effects sizes for subcortical volume, cortical thickness, and cortical surface area regions showing a significant difference between groups. Effects sizes for subcortical volume, cortical thickness, and cortical surface area regions showing a significant difference between (**A**) AD-nAD individuals, (**B**) AD-HC individuals, and (**C**) nAD-HC individuals. Cortical thickness and cortical surface area regions showing a significant difference between groups are plotted on the right hemisphere. AD: cases with current AD use; nAD: cases not currently taking AD; HC: healthy controls.

MDD diagnosis and brain morphology

For other regions that showed a significant group-by-age interaction, results showed that the association between brain structure and age differed in either or both of the AD and nAD group compared to HC (but not between the AD and nAD group), suggesting that this may be an effect of MDD diagnosis, instead of an effect of AD use. For instance, volume of the thalamus showed upon visual inspection lower volume in both the AD and nAD group before age 40 compared to HC, while no differences were observed at older age (Supplementary Figure 1). For 13 out of the 35 cortical thickness regions that showed a significant group-by-age interaction (i.e., inferior parietal cortex, supramarginal gyrus, superior parietal cortex, lateral occipital gyrus), we observed upon visual inspection lower cortical thickness in younger (mostly before age 40–50) MDD patients (both in the AD and nAD group) compared to HC (Supplementary Figure 2). There were no significant findings to suggest that the association between sex and brain structure was different in the AD and nAD group compared to HC.

Similarly, there were significant main effects of group on brain morphology which showed that brain structure was altered in specific regions in either the AD or nAD group, but not both, compared to HC (Supplementary Table S26–31). Lower hippocampal volume was observed in the AD group compared to HC (see Fig. 5B; Supplementary Table S26; Cohen's *d* −0.0996). Lower cortical thickness was observed in 17 regions in the AD group compared to HC (see Fig. 5B; Supplementary Table S28; Cohen's *d* between −0.08 and −0.22). Lower cortical thickness of the banks of the superior temporal sulcus, fusiform gyrus, inferior temporal gyrus, lateral orbitofrontal cortex, pars opercularis of the inferior frontal gyrus, posterior cingulate cortex, rostral anterior cingulate cortex and insula was also shown in the nAD group compared to HC (see Fig. 5C; Cohen's *d* between −0.07 and −0.12; Supplementary Table S29). Higher surface area of the isthmus was observed in the AD group compared to HC (see Fig. 5B; Supplementary Table S30; Cohen's *d* 0.0807).

Type and duration of AD medication use

An age-by-type of AD medication use interaction effect was observed for thickness of the rostral anterior cingulate cortex (rACC) (Supplementary Table S33; partial η^2 0.0183). We observed upon visual inspection that older participants (after 40 years of age) who use mirtazapine showed higher thickness of the rACC than older participants taking SSRIs or SNRIs (see Fig. 6). After correcting for additional secondary covariates indicating severity of (the course) of depression, the interaction effect of age with type of AD medication use on thickness of the rACC remained significant, except when correcting for BDI-II severity (Supplementary Tables S38–42). In the AD group there were no significant interactions between sex and 1) type of AD medication or 2) duration of AD medication use on any brain measure (see Supplementary Tables S32–37).

For the regions that did not show significant interaction effects, we examined the main effect of type of AD medication use or duration of AD medication use. No significant findings were observed (Supplementary Tables S32–37).

DISCUSSION

In a large multi-study mega-analysis which included data from almost 9000 individuals, we examined whether there were interactions between age, sex and AD use group (AD, nAD and HC) on brain morphology (regional subcortical volume, and cortical thickness and surface area), while also examining main effects. In a subsample of the AD group, we examined the association between duration of AD use and brain structure, and examined interactions between brain structure and type of AD use (SSRI, SNRI, or mirtazapine). Our results reveal a complex association between AD use and MDD diagnosis on regional brain structure across the lifespan.

For two brain regions, the middle temporal gyrus and the triangular part of the inferior frontal gyrus, thickness was lower in younger participants in the AD group compared to both younger participants in the nAD group and HC (before age 50). In addition, lower hippocampal volume and inferior temporal gyrus thickness, as well as lower thickness in 8 other regions (in the frontal and temporal lobe) were shown in the AD group compared to the nAD group, suggesting an association between AD use (and not merely MDD) and brain morphology.

Our findings of lower middle and inferior temporal gyrus thickness, and hippocampal volume in the AD group compared to the nAD group could not be explained by clinical measures such as number of depressive episodes, recurrence of MDD (first episode

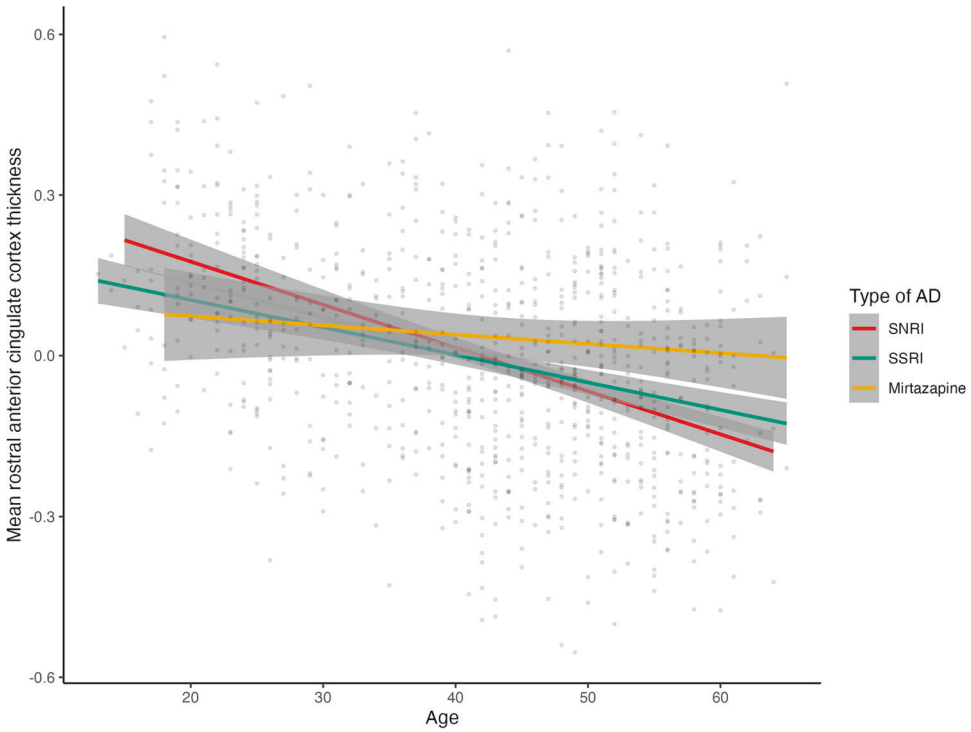

Fig. 6 Significant age-by-type of AD medication use interaction effect for mean cortical thickness of the rostral anterior cingulate cortex. Mean cortical thickness for this region is presented corrected for sex (estimated marginal means). SNRI: Selective serotonin and noradrenalin reuptake inhibitor; SSRI: Selective serotonin reuptake inhibitor.

or recurrent MDD) or remission status (current or remitted MDD), suggesting that these findings may be more specifically related to current AD use. However, these findings may have been driven by higher current depression symptom severity in the AD group compared to the nAD group, as findings were no longer significant after correcting for BDI-II and/or HDRS-17 scores. These findings may therefore, also reflect a state effect of depressed mood as opposed to, or in addition to, a direct effect of AD use. Interestingly, the differences between AD and nAD were mainly located in the temporal lobe (specifically thickness of the middle and inferior temporal gyrus and hippocampal volume). Temporal gyri, while classically thought to be involved in sensory information processing, are also important for emotional information processing and social cognition [43, 44]. In addition, the hippocampus is involved in both memory and emotional information processing [45]. Alterations of temporal lobe brain structure in individuals with MDD could therefore be related to impaired emotional and memory processing associated with MDD.

Findings from an animal study showed that antidepressant treatment was associated with reduced apoptosis in both the hippocampus and temporal cortex, suggesting that AD medication may act upon general cell survival enhancement in these regions [46]. Also, previous studies using positron emission tomography (PET) and single photon emission computed tomography (SPECT) suggest that AD medication may normalize fronto-temporal metabolism in MDD patients [12]. Moreover, prior studies in adult individuals with MDD showed that short-term use of SSRIs (e.g., paroxetine and citalopram) was associated with increased middle temporal gyrus and hippocampal volume [47]. Thus, AD medication use seems to predominantly impact the temporal cortex, which could potentially be explained by its role in emotional information processing, which shows a strong connection to MDD. However, while some studies across all age ranges also report increases in brain morphology following AD treatment, others report a decrease or find no differences (for a review please see [48]).

Specific genetic phenotypes of some individuals with MDD might have partly driven our findings of lower middle and inferior temporal gyrus thickness, and hippocampal volume in the AD group compared to the nAD group. A previous study investigating the association between the serotonin transporter promoter polymorphism (5-HTTLPR) and functional responses to citalopram in healthy controls, showed a greater decrease in glucose metabolism in temporal and frontal lobes in response to citalopram in specific 5-HTTLPR genotypes compared to other 5-HTTLPR genotypes [49]. Therefore, the 5-HTTLPR may be associated with reduced capacity for neuroplasticity in amongst others, the temporal lobe [50]. Exploring the effect of AD treatment on brain structure in individuals with MDD with various 5-HTTLPR genotypes might be interesting for future studies.

Results of interaction analyses with age showed altered regional brain morphology in younger MDD patients (i.e., before 40–50 years of age), for example lower thalamus volume, and lower thickness in frontal, occipital and parietal lobe regions, compared to HC, in both the AD and nAD groups. As this association was observed in both the AD and nAD groups, these effects seem driven by the diagnostic status of MDD rather than AD medication use per se. In older participants we did not observe a difference in brain morphology between these groups. We speculate that due to developmental neural changes (including structural, neurochemical and molecular changes) the brain of younger people might be more vulnerable to the effects of chronic stress associated with MDD and its underlying pathophysiology (e.g., inflammation, increased oxidative stress, increased cortisol) [51, 52]. Alternatively, physiological aging effects in older participants might obscure MDD-related changes in brain structure in this age group [53]. These findings extend our previous findings showing MDD associations with structural brain alterations that are modulated by age [35]. In previous meta-analyses we were not able to examine this question properly, as diagnosis-by-age interactions were done within each site separately (and thus limited to the age range of each specific sample) and then meta-analyzed.

Cortical thickness of multiple regions was lower in the AD group compared to HC, while these differences were not present when comparing AD to nAD. This may suggest a subtle AD effect, with cortical thickness of the nAD group being in between the AD and HC groups. This included cortical thickness of 9 regions, mainly located in the frontal, cingulate and temporal cortex. These regions are involved in integrating cognitive, emotional and social information [54–58] Evidence suggests that early changes in emotional information processing underlie subsequent mood improvement following AD medication treatment [59–61]. Thus, alterations of frontal, cingulate and temporal cortex brain structure in individuals with MDD could be related to changes in emotional information processing and mood improvement following AD medication treatment.

Our finding of altered brain structure in younger patients with MDD who are also using AD medication adds to the ongoing discussions about the implications of AD use in children, adolescents and young people [62, 63]. However, given the fact that the ENIGMA-MDD cohorts did not collect information on duration of *lifetime* AD use or other psychotropic medication and given the cross-sectional nature of this study, we cannot interpret these findings as direct effects of AD use in younger people.

Supplemental analyses in a subgroup of the AD group for whom this information was available revealed that there was a significant interaction between type of AD (SSRI, SNRI or mirtazapine) and age on brain structure. These results showed that in older people (after approximately 40 years), those using mirtazapine showed greater thickness of the rACC than older MDD patients using SSRIs or SNRIs. Similar to SNRIs, mirtazapine acts on both the serotonin and noradrenergic neurotransmitter systems. Mirtazapine blocks pre-synaptic noradrenergic α2 receptors, and thereby increases norepinephrine release, while also blocking heteroreceptors on serotonergic neurons and thereby increasing serotonin release [64]. In contrast to SNRIs such as venlafaxine, mirtazapine does not influence monoamine reuptake [64]. Mirtazapine may specifically influence the ACC, as it has a high binding potential in cortical regions [65], and the ACC is enriched with serotonin receptors [66]. Given that the rACC plays a crucial role in emotional regulation and reward processing [67–69], the observed greater rACC thickness in older MDD patients using mirtazapine may reflect a compensatory neuroplastic response. This could be driven by mirtazapine-induced serotonergic modulation, potentially enhancing synaptic plasticity and structural integrity in a region critical for emotional control and reward processing. Additionally, a previous randomized controlled trial has shown that a 4-week treatment with mirtazapine boosts serum levels of brain-derived neurotrophic factor (BDNF) while BNDF declined in patients treated with venlafaxine [70]. Given the important role of BDNF in neurogenesis and neuroplasticity, we speculate that mirtazapine, through this mechanism, may exert a protective effect against age-related decline in thickness of the rACC. However, we note that mirtazapine is not a first-line treatment for MDD and is often prescribed after insufficient response to more standard medication such as SSRIs or SNRIs. Hence, an alternative explanation may be that mirtazapine associated differences in brain morphology could be confounded by a longer and potentially more complex history of AD use. While in this study we did not observe associations between duration of current AD use and brain morphology, conclusions from this are limited in the view of a lack of information on lifetime duration of AD use. The observed association between mirtazapine use and greater rACC thickness in older MDD patients might partly reflect clinical characteristics of MDD patients for whom mirtazapine is prescribed, such as insomnia [71, 72], rather than a direct pharmacological effect of AD medication use itself.

While the clinical relevance of subtle effects remains to be fully elucidated, they may still reflect meaningful insights into the neural mechanisms underlying AD medication use in MDD, particularly in light of the large sample size and use of harmonized protocols to obtain brain morphology measures. However, the findings need to be interpreted in light of several limitations. First, this is a cross-sectional study, and future large and ideally randomized longitudinal studies are needed to precisely examine the interaction between age and AD use on brain structure. Importantly, such future longitudinal studies should not only examine the short-term but also long-term (over many years) effects of AD use on brain structure, while adequately correcting for potential confounders. Since depressive symptom severity influenced observed effects of AD use on temporal lobe structures, future longitudinal studies are needed to examine the long-term effects of AD use on brain structure while accounting for depression severity across different ages and at various time points before and following AD initiation. This approach could provide a more comprehensive understanding of the interplay between AD treatment, brain structure alterations, and depressive symptoms over time. Additionally, future longitudinal studies should investigate both short-term and long-term effects on AD use on brain structure in MDD patients, as well as the trajectories of brain changes in medication-naïve MDD patients and healthy individuals. The findings from the current study may help select brain regions of interest for future longitudinal studies on this topic. Following MDD patients who discontinue AD treatment during such a longitudinal study would be particularly valuable for assessing long-term effects of AD use. Second, while we have detailed clinical information available on MDD in this sample, we cannot rule out the presence of (pre-clinical) neurodegenerative diseases in older participants, which may have affected our results. Third, we were unable to take other factors into account which may play a role in changes in brain structure with age, and may differ between groups, including IQ, education level, lifestyle and metabolic factors [73–75]. Finally, we could not control for other psychotropic medication that participants may have been using or presence of comorbid anxiety disorders, as this information was not available for most participants.

To conclude, we report the first robust evidence for an association between current AD medication use and regional brain morphology in a mega-analysis of almost 9000 participants. Specifically, we observed lower middle temporal gyrus thickness in AD users (under ~50 years of age), and lower hippocampal volume and inferior temporal gyrus thickness in the AD group compared to the nAD group. In addition, we observed several brain alterations, which were likely driven by MDD diagnosis, and not AD use per se. Supplementary findings suggest mirtazapine may have a differential effect on brain structure in older participants compared SSRIs or SNRIs, however future research needs to replicate this finding and explore potential underlying mechanisms. In addition, it is recommended for future studies to take age into account when examining the association between AD medication use and the brain.

DATA AVAILABILITY

The datasets generated during and/or analysed during the current study are not publicly available due to privacy restrictions.

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ACKNOWLEDGEMENTS

ENIGMA MDD is supported by the National Institute of Mental Health grant numbers MH129832, MH117601 and MH129742. CS is supported by NIMH 5U01MH119740-05. LS is supported by an National Health and Medical Research Council (NHMRC) Investigator grant 2017962. The Goettingen site acknowledges funding from the University Medical Center Göttingen Starting Funds and the German Federal Ministry of Education and Research (BMBF: 01 ZX 1507, "PreNeSt - e:Med"). The work at DIP Groningen was funded by the Gratama Foundation, the Netherlands (2012/35 to Dr. Groenewold). SEM is supported by NHMRC grants APP1172917 and APP1158127. KLM is supported by funding from the National Institute of Child Health and Human Development (R01 HD050735), and the National Health and Medical Research Council (NHMRC 486682, 1009064), Australia. MDS acknowledges funding from the National Institute of Mental Health (Project Number R01MH125850), Brain and Behavior Research Foundation (Grant Number 28972). IHG is supported by the National Institute of Mental Health (R37MH101495). The University of Minnesota study is funded by the National Institute of Mental Health (K23MH090421), the National Alliance for Research on Schizophrenia and Depression, the University of Minnesota Graduate School, the Minnesota Medical Foundation, and the Biotechnology Research Center (P41 RR008079 to the Center for Magnetic Resonance Research), University of Minnesota, and the Deborah E. Powell Center for Women's Health Seed Grant, University of Minnesota. TCH is supported in part by the National Institutes of Health (K01MH117442, R01MH127176, R21MH130817). The Melbourne site was funded by National Health and Medical Research Council of Australia (NHMRC) Project Grants 1064643 (PI Harrison) and 1024570 (PI Davey). TTY acknowledges support from the National Center for Complementary and Integrative Health Grant numbers: R21AT009173, R61AT009864, R33AT009864; University of California San Francisco Weill Institute for Neurosciences; University of California San Francisco Weill Institute for Neurosciences Grant numbers: Award for Junior Investigators in the Neurosciences Impacted by COVID-19 Setbacks; National Center for Advancing Translational Sciences Grant numbers: CTSI UL1TR001872; American Foundation for Suicide Prevention Grant numbers: SRG-1-141-18; National Institute of Mental Health Grant R01MH085734 R01MH127176, K01MH117442. YO is supported by the Japan Agency for Medical Research and Development (AMED) under grant number JP18dm0307002. SHIP is part of the Community Medicine Research Network of the University Medicine Greifswald, which is supported by the German Federal State of Mecklenburg- West Pomerania. The Cardiff sample was supported by the Medical Research Council (UK) grant G 1100629. RR acknowledges support from grants from the German Research Foundation (grant RE4458/1-1 to R.R.) and the German Center for Mental Health (DZPG; BMBF grant 01EE2305C to R.R). TH was supported by the German Research Foundation (DFG grants HA7070/2-2, HA7070/3, HA7070/4). KD acknowledges support from the Innovative Medizinische Forschung (IMF; KO121806 to K.D.). This work was funded by the German Research Foundation (DFG), Udo Dannlowski (co-speaker FOR2107, DA 1151/5-1, DA 1151/5-2, grant DA1151/9-1, DA1151/10-1 and DA1151/11-1) and the Interdisciplinary Center for Clinical Research (IZKF) of the medical faculty of Münster (grant Dan3/022/22 to UD); This work was funded by the German Research Foundation (SFB-TRR58, Project C09 to UD). This work was supported by the German Research Foundation (DFG), grants NE2254/1-2, NE2254/3-1, and NE2254/4-1 to Igor Nenadić and DFG grant FOR2107, KI588/14-1 and FOR2107, KI588/14-2 to Tilo Kircher (coordinator of FOR2107). This work was supported by the Hessisches Ministerium für Wissenschaft und Kunst (HMWK; project "The Adaptive Mind") to TK and BS. BS was additionally supported by the German Research Foundation (DFG, STR1146/18-1). AW is supported by the German Research Foundation (DFG, STR1146/18-1; KI588/22-1). The FIDMAG group is grateful for support from CIBERSAM, AGAUR (2014-SGR-1573 and 2017-SGR-1271), Instituto de Salud Carlos III (Sara Borrell research contract CD19/00149). LPC was was funded by the NIHR Oxford Health Biomedical Research Centre (UK) at the University of Oxford as part of this work, and now works at the Psychology Research Centre (PSI/01662), School of Psychology, University of Minho. The centre is supported by the Foundation for Science and Technology (FCT) through the Portuguese State Budget (Ref.: UIDB/PSI/01662/2020). Liliana is also currently funded by FCT (Ref.: 2021.004515.CEECIND). The BiDirect study was funded by the German Ministry of Education and Research (01ER0816; 01ER1506). PMT and SIT are supported by NIH grants R01MH116147, P41EB015922, Milken Foundation/Baszucki Brain Research Fund, R01MH129742. NJ is supported by NIH grants R01MH117601, R01MH134004, R01MH116147 and P41EB015922. The IMH-MDD study was supported by National Healthcare Group Research Grant, Singapore (SIG/15012). BCD is supported by a CJ Martin Fellowship (NHMRC App 1161356). CHYF is supported by the Medical Research Council (G0802594), NIMH (R01MH134236). AJ was supported by DFG grants JA 1890/7-1 and JA 1890/7-2. IN was supported by DFG grants NE2255/1-2, NE2255/2-1, NE2255/3-1, NE2255/4-1. The Barcelona cohort was collected from studies funded by the Spanish Ministry of Health, Instituto Carlos III (PI10/00372; PI13/01057), by the CIBERSAM and by the CERCA programme of the Catalan Government (Generalitat de Catalunya). JCS was supported by NIMH (1R01MH085667-01A1), John S. Dunn Foundation (Houston, Texas), and Pat Rutherford Chair in Psychiatry (UTHealth Houston). Other funding source and potential conflict of interests include: ALKERMES (Advisory Board), BOEHRINGER Ingelheim (Consultant), COMPASS Pathways (Research Grant), JOHNSON & JOHNSON (Consultant), LIVANOVA (Consultant), RELMADA (Research Grant), SUNOVION (Research Grant),Mind Med (Research Grant).

AUTHOR CONTRIBUTIONS

CS, YJT, LS and LSvV contributed to the conception and design of the study, acquisition of data, analysis and interpretation of data, drafting and critically revising the manuscript, and approved the final version of the manuscript. EP, AA, NA, ZB, VB, KB, KB, RB, GFB, LPC, CGC, BCD, KRC, UD, CGD, GIdZ, DD, KD, VE, TEG, UE, CHYF, PFC, BRG, ASG, IHG, RGM, HJG, NAG, DG, OG, TH, GH, BJH, WH, MH, TCH, NI, EI, NJ, HJ, AJJ, AJ, TK, BKD, BK, AK, TML, EJL, ML, DEJL, FM, KLM, SEM, DMAM, SM, BM, IN, GO, YO, NO, JKP, EPC, MJP, RR, LR, JR, KR, ERC, PGPR, MDS, PGS, RS, AS, HS, KS, ES, JCS, DJS, FS, BS, LTS, FTO, SIT, PMT, MJvT, PU, AU, NvdW, SvdW, YVG, HV, MW, SW, KW, AW, MJW, TTY, GBZS, and DJV made substantial contributions to data acquisition, critically revised the manuscript for important intellectual content, and approved the final version of the manuscript.

COMPETING INTERESTS

PMT and NJ received partial grant support from Biogen, Inc., for research unrelated to this manuscript. DJS has received consultancy honoraria from Discovery Vitality, Johnson & Johnson, Kanna, L'Oreal, Lundbeck, Orion, Sanofi, Servier, Takeda and Vistagen. HJG has received travel grants and speaker honoraria from Fresenius Medical Care, Neuraxpharm, Servier, Indorsia, and Janssen Cilag as well as research funding from Fresenius Medical Care.

ADDITIONAL INFORMATION

Supplementary information The online version contains supplementary material available at https://doi.org/10.1038/s41380-025-03310-8.

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