Brain Aging in Major Depressive Disorder: Results from the ENIGMA Major Depressive Disorder working group

Running title: Brain Aging in MDD: results from ENIGMA

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Abstract

Background: Major depressive disorder (MDD) is associated with an increased risk of brain atrophy, aging-related diseases, and mortality. We examined potential advanced brain aging in MDD patients, and whether this process is associated with clinical characteristics in a large multi-center international dataset.

Methods: We performed a mega-analysis by pooling brain measures derived from T1-weighted MRI scans from 29 samples worldwide. Normative brain aging was estimated by predicting chronological age (10-75 years) from 7 subcortical volumes, 34 cortical thickness and 34 surface area, lateral ventricles and total intracranial volume measures separately in 1,147 male and 1,386 female controls from the ENIGMA MDD working group. The learned model parameters were applied to 1,089 male controls and 1,167 depressed males, and 1,326 female controls and 2,044 depressed females to obtain independent unbiased brain-based age predictions. The difference between predicted "brain age" and chronological age was calculated to indicate brain predicted age difference (brain-PAD).

Findings: On average, MDD patients showed a higher brain-PAD of +0.90 (SE 0.21) years (Cohen's d=0.12, 95% CI 0.06-0.17) compared to controls. Relative to controls, first-episode and currently depressed patients showed higher brain-PAD (+1.2 [0.3] years), and the largest effect was observed in those with late-onset depression (+1.7 [0.7] years). In addition, higher brain-PAD was associated with higher self-reported depressive symptomatology (b=0.05, p=0.004).

Interpretation: This highly powered collaborative effort showed subtle patterns of abnormal structural brain aging in MDD. Substantial within-group variance and overlap between groups were observed. Longitudinal studies of MDD and somatic health outcomes are needed to further assess the predictive value of these brain-PAD estimates.

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Research in context

Evidence before this study

Accumulating evidence from studies suggests that, at the group level, MDD patients follow advanced aging trajectories, as their functional (e.g. walking speed, hand grip strength) and biological state (e.g. telomeres, epigenetics, mitochondria) reflects what is normally expected at an older age (i.e. biological age "outpaces" chronological age). While subtle structural brain abnormalities have been identified in MDD, it remains to be elucidated whether patients also deviate from the normal aging process at the brain level (brain predicted age difference [brain-PAD]) and whether this deviation is associated with clinical characteristics. We searched PubMed for relevant literature published in English [Language] before January 25, 2019. In this search we used (('brain age' OR 'brainAGE' OR 'brain-PAD' OR 'predicted brain ag*') AND 'depression' [Title/Abstract]), which revealed only two papers. One study found that MDD patients (N=104) were estimated to be +4.0 years older using brain-based age prediction models. A second study reported a non-significant relationship between brain-PAD and a short self-report scale of depressive symptoms in male veterans (N=359) who served in the United States military. Thus, whether a diagnosis of MDD is associated with the multivariate metric of brain aging in a large dataset, and which clinical characteristics further impact this metric, remains elusive.

Added value of this study

To our knowledge, this is the first study to examine deviations of normative brain aging in MDD and associated clinical heterogeneity in a large international and multi-center dataset, by pooling data from >8,000 subjects from 29 research samples worldwide. The current study shows that chronological age can be predicted from gray matter features in a large heterogeneous dataset with an age range covering almost the entire lifespan (10-75 years). Moreover, we show that our brain age prediction model generalizes to unseen hold-out samples, as well as to completely independent samples from different scanning sites. We found that, at the group level, patients had, on average, a +0.90 years greater discrepancy between their predicted and actual age compared to control participants and there was a subtle relationship between self-reported symptom severity and advanced brain aging in the MDD group. Finally, the strongest effects were observed in patients with a late onset of depression (>55 years old;

277 +1.7 years), currently depressed (+1.2 years), and in their first episode (+1.2 years), compared to
278 controls.
279
280 **Implications of all the available evidence**
281 This study confirms previously observed advanced biological aging in MDD at the group and brain level of
282 analysis. However, it is important to mention the large within-group and small between-group variance,
283 demonstrating that many patients did not show advanced brain aging. Our work contributes to the
284 maturation of brain age models in terms of generalizability, deployability, and shareability, in pursuance of
285 a canonical brain age algorithm. Further, other research groups with deep clinical phenotyping and
286 longitudinal information on mental and somatic health outcomes may use our model to promote continued
287 growth of knowledge for greater clinical application.
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Introduction

Major Depressive Disorder (MDD) is associated with an increased risk of cognitive decline,[1] brain atrophy,[2] aging-related diseases,[2] and importantly, overall mortality.[3,4] While normal aging is associated with significant loss of gray matter,[5] growing evidence suggests that neuropsychiatric disorders such as depression may have an accelerating effect on age-related brain atrophy.[6] Simultaneously, the aging population is increasing, and both depression and aging have been linked to poor somatic health and quality of life, and increased costs for society and healthcare.[7,8] This underscores the importance of identifying brain aging patterns in MDD patients to determine whether and how they deviate from healthy patterns of aging.

Emerging evidence indicates that chronological age and biological age may be distinct processes that can diverge. Current multivariate pattern methods can predict chronological age from biological data (i.e., epigenetics, transcriptomics, proteomics, metabolomics, see Jylhava, Pedersen, and Hagg for a review)[9] with high accuracy. Similarly, chronological age can be predicted from brain images, resulting in an estimate known as "brain age".[10] Importantly, by calculating the difference between a person's estimated brain age and their chronological age, one can translate a complex aging pattern across the brain into a single outcome:[11] brain-predicted age difference (brain-PAD).[12] A positive brain-PAD represents having an 'older' brain than expected for a person of their chronological age, whereas a negative brain-PAD signals a 'younger' brain than expected at the given chronological age. Higher brain-PAD scores have been associated with greater cognitive impairment,[13] increased morbidity,[10] and exposure to cumulative negative fateful life events (e.g., death of a close family member, financial hardship, or divorce).[14]

Prior studies from the Enhancing NeuroImaging Genetics through Meta-analysis (ENIGMA)-MDD consortium with sample sizes over 9,000 participants have shown subtle reductions in subcortical structure volumes in major depression that were robustly detected across many samples worldwide. Specifically, smaller hippocampal volumes were found in individuals with earlier age of onset and recurrent episode status.[15] In addition, different patterns of cortical alterations were found in adolescents

versus adults with MDD, suggesting that MDD may affect brain morphology (or vice versa) in a way that depends on the developmental stage of the individual.[16] Likewise, brain development and aging likely differ by sex.[17] The different neural and clinical presentations of depression and aging across sex emphasize the need to stratify populations studied into groups of females and males to better understand sex-dependent or sex-specific effects.

Given that prior studies suggest advanced biological aging in MDD (e.g., shorter telomere length,[18] greater epigenetic aging,[19,20] and advanced brain aging),[6] it is important to examine whether biological aging findings in depression can be confirmed in a large heterogeneous dataset consisting of many independent samples worldwide, based on commonly derived gray matter measures. Only a handful of studies have investigated brain-PAD in people with psychiatric disorders,[21] showing older brain-PAD in schizophrenia,[6,22,23] borderline personality disorder, and first-episode and at-risk mental state for psychosis,[6,24] yet findings were less consistent in bipolar disorder.[23,25]

Only two studies to date specifically investigated premature brain aging in MDD - using relatively small samples of 104 and 211 patients, respectively, with inconsistent findings of a brain-PAD of +4.0 years versus no significant difference.[6,26] The current study is the first to examine brain aging in over 8,000 individuals from the ENIGMA MDD consortium (29 cohorts, 11 countries worldwide), covering almost the entire lifespan (10-75 years). We hypothesized higher brain-PAD in MDD patients compared to controls. We also conducted exploratory analyses to investigate whether higher brain-PAD in MDD patients was associated with demographic (age, sex) and clinical characteristics such as disease recurrence, antidepressant use, remission status, depression severity, and age of onset of depression.

Methods

Samples

Twenty-nine cohorts from the ENIGMA-MDD working group with neuroimaging and clinical data from MDD patients and controls participated in this study (**appendix**). The combined sample covered almost

the entire lifespan (10-75 years of age). Details regarding demographics, clinical characteristics, and exclusion criteria for each cohort may be found in the **appendix**. Because the literature suggests differential brain development and maturation by sex,[17] we estimated brain age models separately for male and female samples. Sites with less than ten healthy males or females were excluded from the training dataset and subsequent analyses (for exclusions see **appendix**). In total, we included data from N=8,159 (93.5%) participants, including N=4,948 (56.7%) control individuals (N=2,236 [45.2%] males; N=2,712 [54.8%] females) and N=3,211 (36.8%) individuals with MDD (N=1,167 [36.3%] males; N=2,044 [63.7%] females). All participating sites obtained approval from the appropriate local institutional review boards and ethics committees, and all study participants or their parents/guardians provided written informed consent.

Training and test samples

An overview of the data partition is shown in **figure 1A** and described in more detail in the **appendix**. Structural brain measures from 1,147 male obtained from 28 scanners and 1,386 female controls obtained from 34 scanners were included in the training sample. The top panel in **figure 1B** shows the chronological age distribution in the training sample. A hold-out dataset comprised of controls served as test sample to validate the accuracy of brain age prediction model; 1,089 male and 1,326 female controls from the same scanning sites were included. Likewise, 1,167 male and 2,044 female MDD patients from the corresponding neuroimaging sites were included in the MDD test sample. The bottom panel in **figure 1B** shows the chronological age distributions across the test samples. More details on data partitioning are shown in the **appendix**.

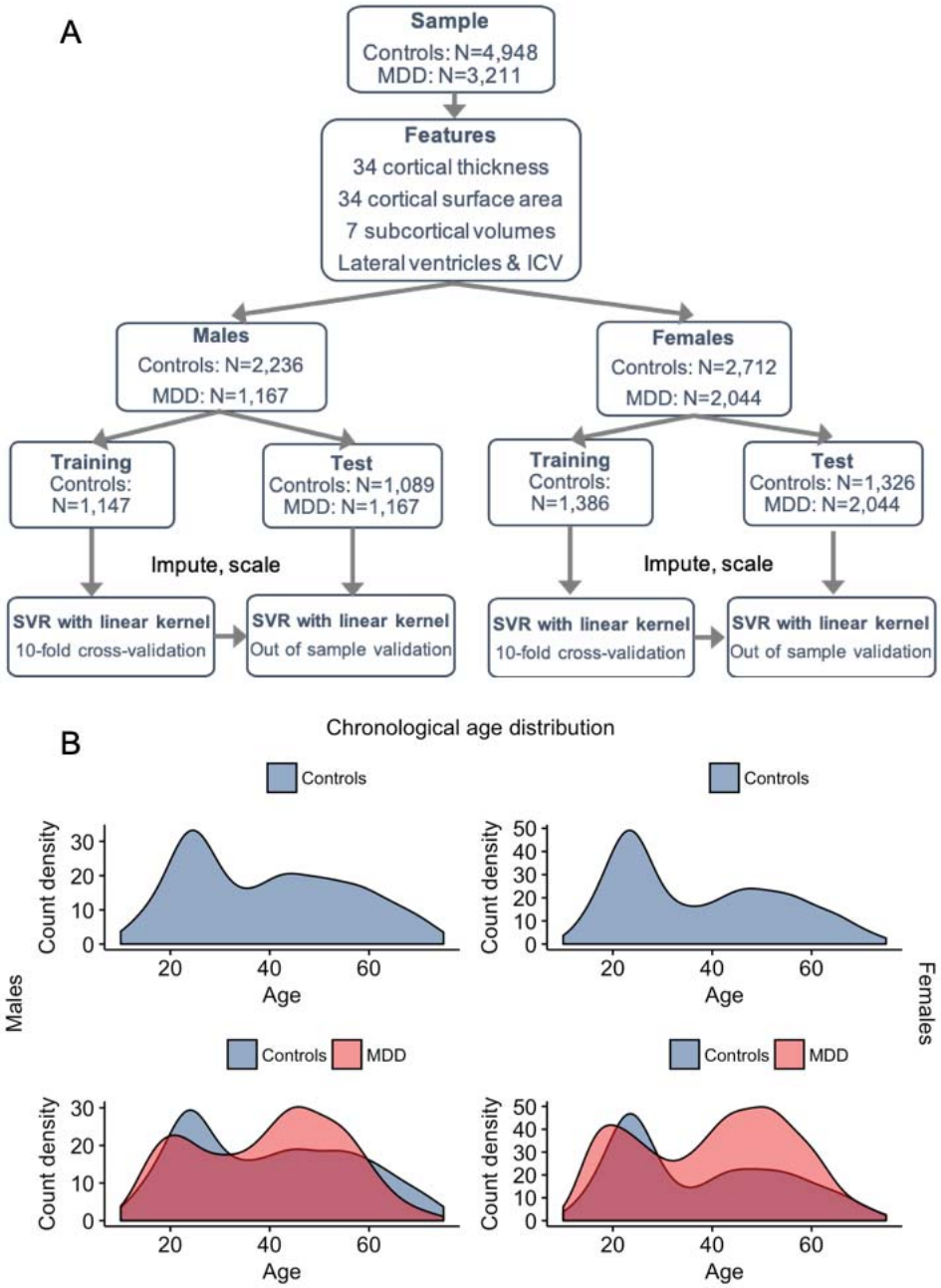

***Figure* 1: (A) Schematic illustration of features used and data partition into training and test samples, separately for males and females. (B)** Data from control groups (*blue*) were partitioned within scanning sites preserving chronological age distribution. Major depressive disorder (MDD) groups are shown in *red*. The *top panel* illustrates the male and female training samples. The *bottom panels* show the male (controls: mean [SD] in years, 40.0 [16.5]; MDD: 39.6 [14.8]) and female test samples (controls: 37.6 [16.2]; MDD: 40.0 [15.5]). ICV, intracranial volume; SVR, support vector regression.

Image processing and analysis

Structural T1-weighted scans of each subject were acquired at each site and analyzed locally using standardized protocols to facilitate harmonized image analysis across multiple sites (http://enigma.ini.usc.edu/protocols/imaging-protocols/). Briefly, the fully automated and validated segmentation software, FreeSurfer 5.1 or 5.3 was used to segment seven subcortical gray matter regions (nucleus accumbens, amygdala, caudate, hippocampus, pallidum, putamen, and thalamus), lateral ventricles, 34 cortical thickness and 34 surface area measures, and total intracranial volume (ICV). Segmentations were visually inspected and statistically examined for outliers. Further details on cohort type, image acquisition parameters, software descriptions, and quality control may be found in the **appendix**. Individual-level structural brain measures and clinical and demographic measures from each cohort were pooled at a central site to perform the mega-analysis.

Brain age prediction model

To estimate the normative brain age models, we combined the FreeSurfer measures from the left and right hemispheres by calculating the mean ((left+right)/2) of volumes for subcortical regions and lateral ventricles, and thickness and surface area for cortical regions. Using a mega-analytic approach, we first estimated normative models of the association between the 77 average structural brain measures and chronological age in the training sample of controls (separately for males and females) using a support vector regression (SVR) with a linear kernel, from the python-based *sklearn* package.[27] All measures were combined as predictors in a single multivariate model.

To assess model performance and optimize the regularization parameter, C, we performed 10-fold cross-validation. To quantify model performance, we calculated the mean absolute error (MAE) between predicted brain age and chronological age. Both male and female brain age models will be made public upon publication (https://www.photon-ai.com/); for guidelines and instructions, see **appendix**. Of note, we also estimated a model including left and right hemisphere measures, that did not result in significantly superior prediction accuracy, which allowed us to reduce the feature space to average left/right values as described (data not shown). We also compared the SVR to other machine learning methods, including

ridge regression, Gaussian process regression, and generalized additive models. Results of these comparisons are provided in the **appendix**; briefly, the different approaches all showed similar performance to the model presented here.

Model validation

Model performance was further validated in the test sample of controls. The parameters learned from the trained model in controls were applied to the test sample of controls and to the MDD test samples to obtain brain-based age estimates for these individuals. To assess model performance in these test samples, we calculated: a) MAE; b) Pearson correlation coefficients between predicted brain age and chronological age; and c) the proportion of the variance explained by the model (R^2). To evaluate generalization power to completely independent test samples, we also applied the training model parameters to healthy control subjects (males, N=646; females, N=757) from the ENIGMA Bipolar Disorder (BD) working group (**appendix)**.

Statistical analyses

All statistical analyses were conducted in the test samples only. Brain-PAD (predicted brain-based age - chronological age) was calculated for each individual and used as the outcome variable. While different prediction models were built for males and females separately, the generated brain-PAD estimates were pooled for statistical analyses. For our main analysis, we investigated three linear mixed models (LMM) of brain-PAD: a) main effects of age, sex, and diagnosis, b) all main effects and all second order interactions of age, sex, and diagnosis, and c) main effects and all second and third order interactions of age, sex, and diagnosis. To calculate the association between each FreeSurfer feature and brain-PAD, we used univariate regressions corrected for multiple comparisons (false discovery rate; FDR). Surface area and subcortical measures were additionally corrected for ICV.

Within MDD patients, we also used LMM to examine associations of brain-PAD with clinical characteristics, including recurrence status (first vs. recurrent episode), antidepressant use at time of scanning (yes/no), remission status (currently depressed vs. remitted), depression severity at study

inclusion (the 17-item Hamilton Depression Rating Scale (HDRS-17) and the Beck Depression Inventory (BDI-II)), and age of onset of depression (categorized as: early, <26 years; adult, >25 & <56 years; and late onset, >55 years). All analyses included scanning site as a random intercept to account for scanner and FreeSurfer version differences and were corrected for chronological age, age^2, age^3, and sex, tested two-sided. Findings were considered statistically significant at $p<0.05$.

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The study design, data collection, analysis, interpretation, writing, and submission of this report were performed independently from any funding source. The corresponding author had full access to the complete dataset in the study. All authors had the final responsibility for the decision to submit for publication.

Results

Brain age can be predicted from regional brain measures

Within the training set of controls, under cross-validation the structural brain measures predicted chronological age with a MAE of 6.86 (SD 5.32) years in males and 6.91 (5.34) years in females. Correlations between chronological and predicted brain age were r=0.85, p<0.001 in males, and r=0.84, p<0.001 in females, with R^2=0.72 and R^2=0.71, respectively. When applying the model parameters to the test samples of controls, the MAE was 6.35 (4.92) and 6.63 (5.08) years for males and females, respectively. Similarly, within the MDD group, the MAE was 6.86 (5.58) and 7.22 (5.42) years for males and females, respectively. **Figure 2** shows the correlation between chronological age (y-axis) and predicted brain age (x-axis)[28] in the out-of-sample control (males r=0.87, p<0.001; R^2=0.76 and females r=0.86, p<0.001; R^2=0.74), and MDD test samples (males r=0.81, p<0.001; R^2=0.66 and females r=0.82, p<0.001; R^2=0.68). The model also showed relatively good generalization to completely independent healthy control samples of the ENIGMA Bipolar Disorder working group (MAE=7.24 [SD 5.82]; r=0.76, p<0.001; R^2=0.57 for males and MAE=7.45 [5.44]; r=0.75, p<0.001; R^2=0.56, for females), **appendix.**

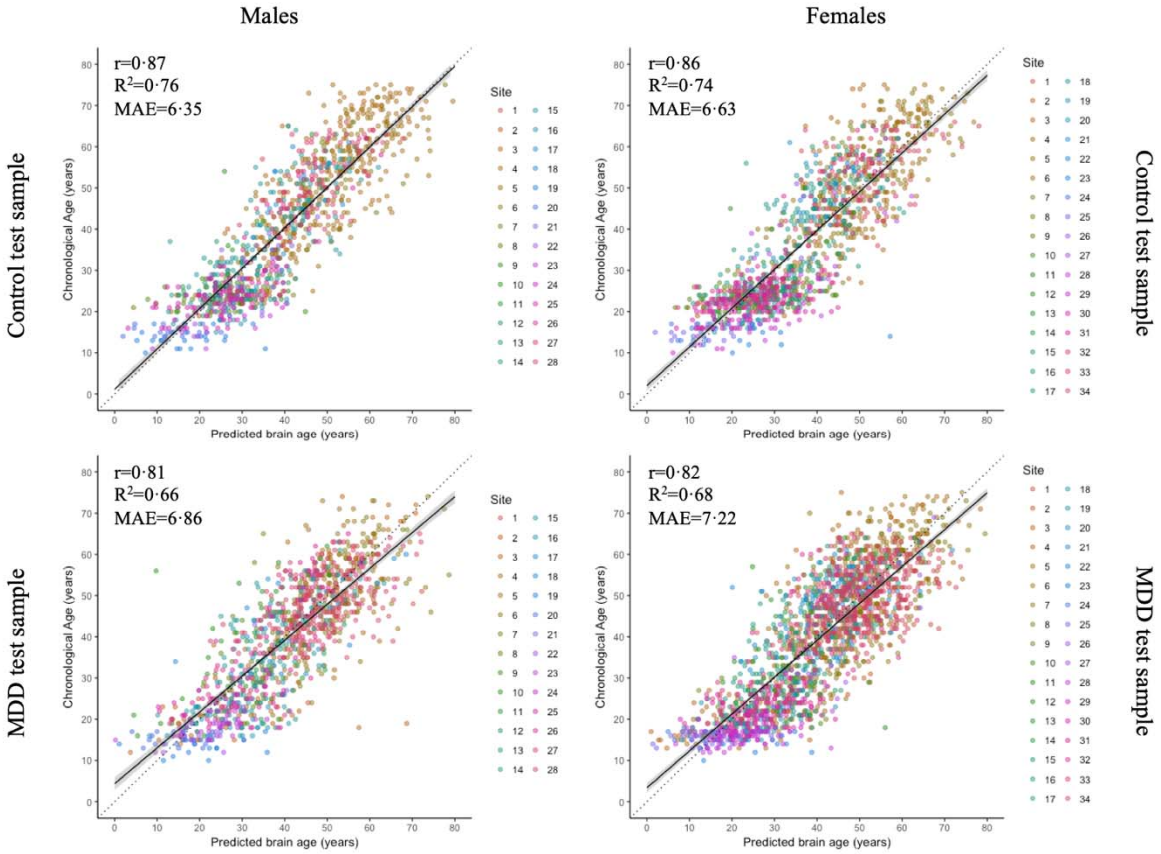

***Figure 2*: Brain age prediction based on 7 FreeSurfer subcortical volumes, lateral ventricles, 34 cortical thickness and 34 surface area measures, and total intracranial volume.** The plots show the correlation between chronological age and predicted brain age in the test samples, derived from the 10-fold cross-validation of the Support Vector Regression model in the training samples, separately for males (*left*) and females (*right*). The colors indicate scanning sites and each circle represents an individual subject: the *upper panels* display controls and the *lower panels* MDD patients. Diagonal dashed line reflects the line of identity (x=y).

MDD patients show increased brain-PAD compared to controls

There was a main effect of diagnostic group. Specifically, individuals with MDD showed +0.90 (SE 0.21) years higher brain-PAD than controls ($p<0.0001$, Cohen's $d=0.12$, 95% CI 0.06-0.17), **figure 3**. Additionally, we found significant main effects for age, age^2, and age^3 ($b=-0.02$-0.72, all p's<0.0001), and a trend for a main effect of sex, with higher brain-PAD in females ($b=0.39$, $p=0.0501$). Our analyses revealed no significant three-way interaction between diagnosis-by-age-by-sex, nor significant two-way interactions. Of note, there were no significant interactions with age, age^2, or age^3 and MDD status; thus, the residual age effects in the brain-PAD estimates did not influence the case-control difference. Further, all nonlinear age effects were accounted for in analyses. All FreeSurfer features, except the entorhinal and temporal pole average thickness, showed a significant ($P_{FDR}<0.05$) association with brain-PAD. All features, except the mean lateral ventricles, yielded negative associations, and are visualized in **figure 4**.

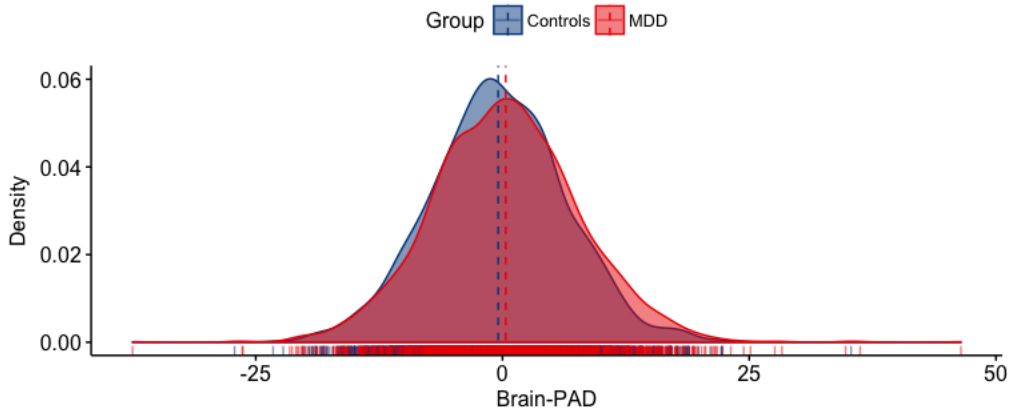

***Figure 3*: Case-control differences in brain aging.** Brain-PAD (predicted brain age - chronological age) in patients with major depressive disorder (MDD) and controls. Group level analyses showed that MDD patients exhibited significantly higher brain-PAD than controls ($b=0.90$, $p<0.0001$), although large within-group variation and between-group overlap is observed. The brain-PAD estimates are adjusted for chronological age, age^2, age^3, sex and scanning site.

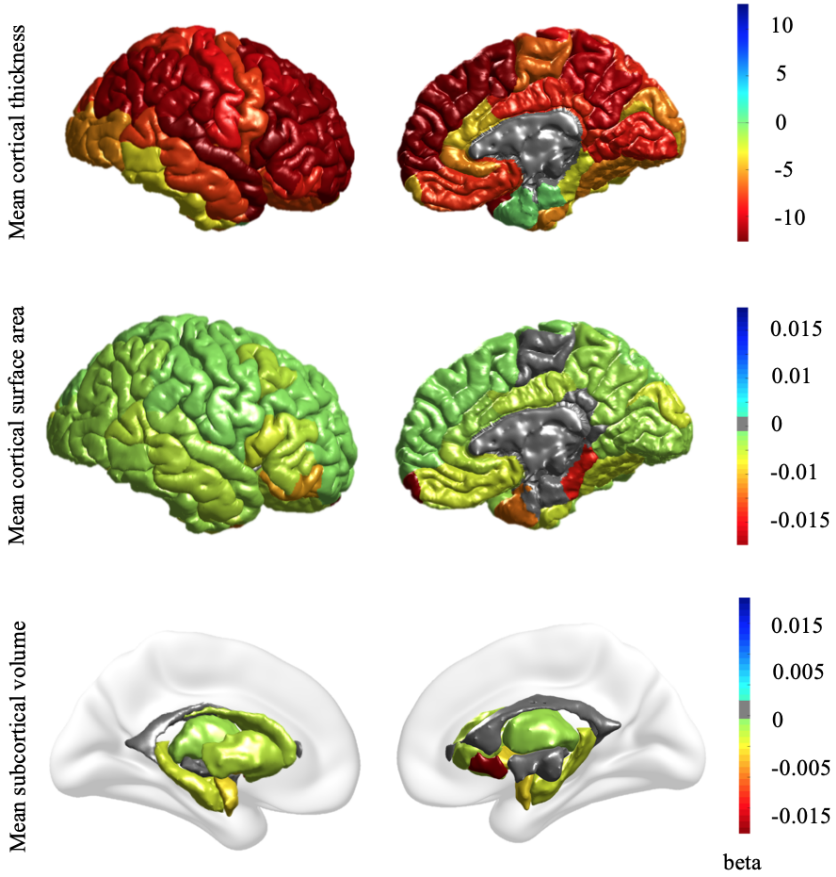

Figure 4: **Univariate associations between brain predicted age difference (predicted brain age - chronological age; brain-PAD) and FreeSurfer measures across controls and major depressive disorder (MDD) groups.** Effect sizes (regression coefficients) are shown for regions with a significant (P_{FDR}<0.05) negative association with brain-PAD, only the mean lateral ventricles yielded a significant positive association. The figure shows associations with cortical thickness measures (*top row*), cortical surface areas (*middle row*), and subcortical volumes (*bottom row*). The brain-PAD estimates are adjusted for chronological age, age^2, age^3, sex and scanning site. The significant negative association with ICV was excluded from this figure for display purposes.

Clinical characteristics and brain-PAD

Strongest effects of higher brain-PAD were observed in patients with late age of onset of depression (>55 years; +1.7 years, *p*=0.009, Cohen's *d*=0.17), currently depressed (+1.2y, *p*<0.0001, *d*=0.13), and first episode (+1.2y, *p*=0.0001, *d*=0.12) MDD patients, compared to controls. However, we observed relatively similar effects in remitted (+1.2y, p=0.01, d=0.11), both antidepressant users and antidepressant medication-free (both +0.9y, p's<0.002, d=0.09), early age of onset of depression (<26 years; +0.8y, p=0.0005, d=0.10), and recurrent depressed patients (+0.7y, p=0.003, d=0.08), as well as in those with an adult age of onset of MDD (+0.5y, p=0.02, d=0.06), compared to controls (**table 1**). Post-hoc comparisons between the MDD subgroups did not show any significant differences (i.e., first vs. recurrent episode, antidepressant medication-free vs. antidepressant users, remitted vs. currently depressed patients, or early vs. adult vs. late age of onset of depression). Brain-PAD was positive in all MDD subgroups, and there were no negative associations with any clinical characteristics.

MDD patients vs. Controls	N	b (p value)	SE	Cohen's d	SE	95% CI
First episode MDD	1,080	1.15 (0.0001)	0.28	0.12	0.04	0.05-0.19
Recurrent episode MDD	1,940	0.73 (0.0027)	0.24	0.08	0.03	0.02-0.14
Current MDD	2,179	1.23 (<0.0001)	0.26	0.13	0.03	0.07-0.19
Remitted MDD	344	1.24 (0.0146)	0.51	0.11	0.06	-0.006-0.22
AD medication-free	1,753	0.84 (0.0006)	0.25	0.09	0.03	0.03-0.15
AD user	1,366	0.85 (0.0020)	0.28	0.09	0.03	0.02-0.15
All MDD patients	3,211	0.90 (<0.0001)	0.21	0.12	0.03	0.06-0.17
Early onset MDD	1,400	0.85 (0.0005)	0.24	0.10	0.03	0.03-0.16
Adult onset MDD	1,420	0.54 (0.0244)	0.24	0.06	0.03	-0.002-0.13
Late onset MDD	125	1.73 (0.0091)	0.66	0.17	0.09	-0.01-0.35

Table 1: **Clinical characteristics and brain aging.** Positive brain-PAD scores (predicted brain age - chronological age) were found for all subgroups of patients with major depressive disorder (MDD) compared to controls (N=2,256). b=regression coefficient; this indicates the average brain-PAD difference between MDD patients and controls in years. AD, Antidepressant.

Increased brain-PAD is associated with greater depressive symptom severity

There was an association with depression severity at the time of scanning within the MDD sample, illustrated by higher brain-PAD in individuals with more severe self-reported depressive symptomatology (b=0.05, p=0.004) as measured in N=1,538 patients who completed the BDI-II. We were not able to confirm this, however, in N=1,905 depressed individuals who were assessed using the HDRS-17 clinician-based questionnaire (b=0.003, p=0.90).

Discussion

Using a brain age algorithm based on commonly used brain measures derived from T1-weighted scans from over 3,500 males and 4,900 females, we found subtle age-associated gray matter differences in major depressive disorder (MDD). At the group level, the brain age model predicted chronological age in controls and MDD patients from 77 brain morphometric features, and patients had, on average, a 0.90 years greater discrepancy between their predicted and actual age compared to control participants. Strongest effects were observed in late-life onset of depression (+1.7y, d=0.17), currently depressed (+1.2y, d=0.13), and first episode MDD (+1.2y, d=0.12) patients, compared to controls. Finally, each one-point increase in self-reported symptom severity score at study inclusion added, on average, 18 days of brain aging, potentially underscoring the importance of reducing the number of symptoms in the treatment of depression.

The positive association between brain aging and symptom severity, measured with the self-report BDI-II questionnaire, was not confirmed using the clinician-based HDRS-17. Post-hoc analyses in overlapping samples with both scores (N=1,302) yielded a significant correlation between them (r=0.67, p<0.0001), yet the same discrepant association with brain-PAD. This could perhaps be explained by the differential proportion of items emphasizing cognitive and affective (BDI-II) or somatic and behavioral dimensions (HDRS-17).[29] Alternatively, brain age may be more sensitive to subjective (BDI) than to objectively (HDRS-17) rated experiences, consistent with the finding of Kwak and colleagues (2018) that the subjective experience of aging was closely related to predicted brain age.[30] However, it is important to

598 bear in mind the small effect size (b=0.05). Nonetheless, positive associations with current depressive
599 symptom severity have been previously reported with more advanced levels of biological aging, as
600 indicated by shorter telomere length[31] and increased epigenetic aging.[19]
601
602 This study showed relatively largest effect size of advanced brain aging in patients with a late-life onset of
603 depression (>55 years old) compared to controls. However, we did not find significant differences
604 between early vs. adult vs. late onset of depression groups. Additionally, no differences between remitted
605 (N=344) and acute patients (N=2,179) were found, leading to the speculation that an initial brain insult
606 during a first episode of depression or preceding clinical disease onset may leave a lasting impact even
607 after remission. To date, the reversibility of gray matter alterations in MDD over time remains rather
608 elusive due to the lack of reliable longitudinal studies.[32] Yet, cross-sectional studies show that "younger"
609 appearing brains are seen in groups of individuals with greater physical activity,[33] long-term meditation
610 practitioners,[11] and amateur musicians,[34] suggesting that brain age might be a modifiable metric.
611 Moreover, one study suggests dynamic potential by showing that in healthy individuals brain-PAD was
612 temporarily reduced by 1.1 years due to the probable acute anti-inflammatory effects of ibuprofen.[35] In
613 this study, there was no detectable effect of antidepressant use on brain aging within MDD individuals. As
614 antidepressants are suggested to exert a neuroprotective effect, for example by promoting brain-derived
615 neurotrophic factor (BDNF),[36] it remains to be elucidated how adaptable brain age is in response to
616 pharmacotherapy. However, the cross-sectional nature of the current study and the lack of detailed
617 information on lifetime use, dosage and duration of use of antidepressants, do not allow us to draw any
618 conclusions regarding direct effects of antidepressants on brain aging. Thus, longitudinal research and
619 randomized controlled intervention studies are needed to develop an understanding of how reversible
620 brain aging is after remission of MDD and how modifiable in response to pharmacology, but also to non-
621 pharmacological strategies (e.g., psychological, exercise and/or nutritional interventions), as seen in other
622 biological age indicators.[37–39]
623
624 Further, the currently observed effect size of Cohen's d=0.12 with regard to brain aging is consistent with
625 previously seen modest structural brain differences in MDD. Earlier work from the ENIGMA MDD working

group also showed small subcortical (hippocampus; d=-0.14), and small to moderate cortical reductions (e.g. left medial orbitofrontal cortex thickness in adults, d=-0.13 and right lingual gyrus surface area in adolescents, d=-0.42) in patients compared to controls.[15,16] Here, we particularly find strong widespread significant negative associations between brain aging and cortical thickness, and comparably weaker associations with surface area and subcortical volume measures (**figure 4**), consistent with literature on age-related structural brain changes in adolescents[40] and adults.[41] We also visualized these associations separately for controls and MDD patients, but findings were similar and suggest comparable spatial brain aging patterns in both groups (**appendix**). Notably, we did not include a spatial weight map of our brain age model, as the weights (although linear) are obtained from a multivariable model, and do not allow for a straightforward interpretation of the importance of the brain regions contributing to the aging pattern.

Our findings were in contrast to earlier work showing a +4.0 years of brain aging in a smaller sample of MDD patients (N=104; 18-65 years).[6] However, a recent preliminary study in 211 MDD patients (18-71 years) found a similar effect size to ours, albeit non-significant (d=0.10, p=0.33).[26] In the latter study, brain-PAD was derived using a brain age model trained on >12,000 healthy individuals (vs. the 800 in the Koutsouleris study[6] vs. >1,100 in this study), emphasizing the relevance of sample size for both training and test samples for sensitivity to detect reliable, yet subtle, effects. Similarly, with respect to reaching statistical significance, large sample sizes are needed to detect small effect sizes commonly found with biological age indicators,[18,19,31] but also other markers (e.g. BDNF, cortisol, oxidative stress)[42–44] in depression research. A major strength of this study is, therefore, the mega-analytic approach of pooling harmonized data from many heterogeneous sites, making predictive models less susceptible to overfitting[45] and more generalizable to other populations.[46]

Inflammation may be a common biological mechanism between MDD and brain aging. Neuroimmune mechanisms (e.g. pro-inflammatory cytokines) influence biological processes (e.g. synaptic plasticity), and inflammatory biomarkers are commonly dysregulated in depression.[47] Both cerebrospinal fluid and peripheral blood interleukin (IL)-6 levels are elevated in MDD,[48] and increased IL-6 expression may affect brain morphology through neurodegenerative processes.[49] Moreover, work by Kakeda and colleagues

(2018) demonstrated a significant inverse relationship between IL-6 levels and surface-based cortical thickness and hippocampal subfields in medication-free, first-episode MDD patients.[50] This accords with the current observation of increased brain-PAD in medication-free and first-episode patients, compared to controls, perhaps suggesting that neuroimmune mechanisms may be chief candidates involved in the brain morphology alterations, also in the early stage of illness. Further, the age-related structural alterations in MDD may also be explained by shared underlying (epi)genetic mechanisms involved in brain development and plasticity (thereby influencing brain structure) and psychiatric illness.[51] For instance, Aberg and colleagues (2018) showed that a significant portion of the genes represented in overlapping blood-brain methylome-wide association findings for MDD were important for brain development, such as induction of synaptic plasticity by BDNF.[52]

Our current findings in MDD show lower brain aging than previously observed in schizophrenia (SCZ) (brain-PAD ranges from +2.6 - +5.5y, d=0.64)[6,22], even in early stages of first episode SCZ.[25] Inconsistent findings are reported in bipolar disorder (BD), with "younger" brain age[23] or no differences compared to controls.[25] However, more studies with larger sample sizes are needed to confirm brain aging in these psychiatric disorders - endeavors currently pursued by other ENIGMA psychiatric disease working groups using the same brain age models, which will allow future cross-disorder comparisons between brain-PAD in e.g. MDD, BD and SCZ.

While our results are generally consistent with existing literature on advanced or premature biological aging and major depression using other biological indicators,[18] it is important to critically consider the current findings and note their limitations. First, limited information was available on clinical characterization and brain-PAD could not be compared against somatic health outcomes here. Second, given the relatively crude and limited number of gray matter features, the best MAE that could be achieved was 6.9 years, compared to ~4.9 years accomplished by other brain age predictors (e.g., those based on spatial images with high dimensional features that may also include white matter).[12] However, an advantage to using FreeSurfer data over voxelwise methods is that the fewer dimensions render our models less prone to overfitting and more flexible in exploring the use of different machines and kernels

(**appendix**). Furthermore, pooling data from many scanning sites comes at the cost of increasing heterogeneity of MRI data and other sample specifics. However, withstanding the latter limitation, models are therefore consequently tested on "ecologically valid" samples, bolstering confidence in their deployability and shareability.[53] Finally, the large within-group variance regarding the brain-PAD outcome in both controls and MDD (**figure 3**), compared to the small between-group variance, renders the use of this brain aging indicator for discriminating patients and controls at the individual level difficult. As many of the MDD patients do not show advanced brain aging compared to controls, the clinical significance of the observed higher brain-PAD in MDD patients in this study may be limited. Yet, interindividual differences highlight the importance of studying the individual, rather than the average patient[54] and provide the opportunity to elucidate whether a subgroup of patients with high brain-PAD may be at risk for worse psychiatric, neurologic, and somatic health outcomes. Local sites that participated in this study with clinical phenotyping and longitudinal information on mental and somatic health outcomes (e.g., genomic variation, omics profiles, comorbidities, lifestyle, inflammation, oxidative stress, chronic diseases) will allow further evaluation of the predictive value of the brain-PAD estimates. This is expected to promote continued growth of knowledge in pursuance of useful clinical applications.

In conclusion, compared to controls, both male and female MDD patients show advanced brain aging, with a subtle association with current symptom severity. This is consistent with other studies of biological aging indicators in MDD at cellular and molecular levels of analysis (i.e., telomere length and epigenetic age). The deviation of brain metrics from normative aging trajectories in MDD may contribute to increased risk for mortality and aging-related diseases commonly seen in MDD. However, the substantial within-group variance and overlap between groups signify that more (longitudinal) work including in-depth clinical characterization and more precise biological age predictor systems are needed to elucidate whether brain age indicators can be clinically useful in MDD. Future studies may use our current ENIGMA brain age prediction model to associate brain-PAD with treatment response and other available information on longitudinal mental and somatic health outcomes, other aging indicators, and incidence and/or prevalence of other chronic diseases in their local samples in pursuance of greater clinical application.

Authors contributions

Concept and design: AFM, BP, JHC, LKMH, LS, LTE, NJ, PMT.

Acquisition, analysis or interpretation of data: AA, AC, AFM, AHS, AJ, AK, AMM, ANS, AS, AU, BAM, BCD, BG, BH, BJH, BJO, BK, BKD, BL, BP, BTB, CA, CC, CF, CGC, CGD, CH, CK, CM, CMB, CMD, DD, DG, DHW, DJS, DMC, EB, ECR, EF, EO,EPC, ES, EV, FLSD, FMH, FPM, GBF, GBH, GdZ, GM, GR, GT, GZ, HCW, HGR, HJG, HST, HV,HW, IB, IBH,IHG, IMV, JH, JHC,JL, JMF, JMG, JR, JR, JS, JS, JS, KB, KC, KLM, KS, KS, KW, LA, LKMH, LN, LR, LS, LTE, LTS, MA, MA, MA, MCGO,MDS, MGSS, MH, MHS, MI, MJP, MJvT, MJW, ML, MMR, MP, MVZ, NG, NH, NRW, NW, OAA, OG, OS, PBM, PF, PGPR, PGS, PMT, PRS, RD, RK, RL, RM, RS, RV, SF, SF, SIT, SNH, SSM, SW, TCH, TDS, TE, TF, TH, TH, TK, TMC, TTY, UD, UFM, VE, VZ, XC.

Drafting of the manuscript: LKMH, LS.

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Statistical analysis: AFM, JHC, LKMH, LS, RD.

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