Structural MRI-Based Measures of Accelerated Brain Aging do not Moderate the Acute Antidepressant Response in Late-Life Depression

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Structural MRI-Based Measures of Accelerated Brain Aging do not Moderate the Acute Antidepressant Response in Late-Life Depression

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Highlights

- **What is the primary question addressed by this study?** Does accelerated brain aging in late-life depression, assessed with a machine learning algorithm using structural MRI data, moderate the clinical response to antidepressant medications?
- **What is the main finding of this study?** Accelerated brain aging, assessed either by machine learning or by established structural imaging markers, was not associated with a poorer response to antidepressant treatment.
- **What is the meaning of the finding?** Accelerated brain aging does not moderate the antidepressant response in late-life depression, so greater brain atrophy or structural pathology may not be a negative prognostic marker.

\textbf{ABSTRACT}

**Objective:** Late-life depression (LLD) is characterized by accelerated biological aging.

Accelerated brain aging, estimated from structural MRI (sMRI) data by a machine learning
algorithm, is associated with LLD diagnosis, poorer cognitive performance, and disability. We hypothesized that accelerated brain aging moderates the antidepressant response.

**Design and Interventions:** Following MRI, participants entered an 8-week randomized, controlled trial of escitalopram. Nonremitting participants then entered an open-label 8-week trial of bupropion.

**Participants:** 95 individuals with LLD.

**Measurements:** A machine learning algorithm estimated each participant’s brain age from sMRI data. This was used to calculate the brain-age gap (BAG), or how estimated age differed from chronological age. Secondary sMRI measures of aging pathology included white matter hyperintensity (WMH) volumes and hippocampal volumes. Mixed models examined the relationship between sMRI measures and change in depression severity. Initial analyses tested for a moderating effect of MRI measures on change in depression severity with escitalopram. Subsequent analyses tested for the effect of MRI measures on change in depression severity over time across trials.

**Results:** In the blinded initial phase, BAG was not significantly associated with a differential response to escitalopram over time. BAG was also not associated with a change in depression severity over time across both arms in the blinded phase or in the subsequent open-label bupropion phase. We similarly did not observe effects of WMH volume or hippocampal volume on change in depression severity over time.

**Conclusions:** sMRI markers of accelerated brain aging were not associated with treatment response in this sequential antidepressant trial.

**Keywords**
Biological changes that accompany the aging process are seen at cellular, organ, and organismal levels and are influenced by epigenetic, genetic, and environmental factors. These changes affect brain processes including cognitive, motor, and sensory functions. “Accelerated aging” describes when biological aging occurs more rapidly than expected. Individuals with the same chronological age may exhibit different biological ages, and the difference may have clinical implications. Accelerated aging, assessed using biological markers such as magnetic resonance imaging (MRI) measures, telomere length, epigenetic markers, or low-grade inflammation, occurs in a range of neuropsychiatric disorders, including schizophrenia, anxiety disorders, and depression. Markers of accelerated aging may have particular utility in older populations, including individuals with late-life depression (LLD). Yet it is unclear whether accelerated brain aging influences the clinical antidepressant response in LLD.

There is substantial work examining whether structural differences in brain morphology influence the treatment response in depression. In LLD, this work includes established structural magnetic resonance imaging (sMRI) markers of accelerated or pathological aging including white matter hyperintensity (WMH) volume and hippocampal volume loss. WMHs develop and worsen with aging and are typically more severe in LLD. Past work examined whether greater WMH severity influences the antidepressant treatment response in LLD, with studies both supporting and refuting this hypothesis. The reasons for these discrepancies are unclear, but could relate to heterogeneity in sample or study design, variability across samples in WMH location and what intrinsic functional networks are affected, or perhaps the overall effect of WMH is modest.
Evidence similarly supports a role of the hippocampus in depression across the lifespan,\textsuperscript{16} including individuals with LLD. The hippocampus exhibits volume loss with normal aging and accelerated hippocampus atrophy is a marker of Alzheimer disease.\textsuperscript{17} Similar to younger or midlife depression, LLD is associated with smaller hippocampal volumes \textsuperscript{18,19} and greater reductions in hippocampal volume over time.\textsuperscript{20-22} However, while LLD is associated with elevated dementia risk,\textsuperscript{23} smaller hippocampal volumes in LLD are not necessarily associated with underlying Alzheimer disease neuropathology.\textsuperscript{24} Smaller hippocampal volume is also associated with poorer acute response to antidepressant treatment in both midlife depression and LLD.\textsuperscript{25-27}

While these focused, hypothesis-testing studies are informative, modern techniques allow for data-driven sMRI analyses that can generate new insights into markers of antidepressant response. The Brain Age Gap Estimation (BrainAGE) algorithm \textsuperscript{28} is a machine learning technique that estimates an individual's age based solely on sMRI data. The difference between estimated brain age and actual chronological age can thus serve as a marker of resilience, if a brain appears younger than anticipated. Alternatively, it may be a marker of vulnerability and accelerated aging if a brain appears older than anticipated. We previously reported that older depressed adults exhibit older estimated brain ages than never-depressed elders.\textsuperscript{4} Further, the difference between the estimated brain age and an individual's chronological age (the brain-age gap, or BAG) is cross-sectionally associated with poorer cognitive performance and greater disability.\textsuperscript{5}

The purpose of this study was to extend this past work and determine whether this sMRI-based marker of accelerated brain aging moderates the clinical response to antidepressant treatment. We hypothesized that calculated brain age estimations older than participants' chronological age would be associated with less change in depression severity over time. To understand our findings in the context of past work, in exploratory analyses we
examined whether greater WMH volume and smaller hippocampal volumes were associated with a poorer antidepressant response.

**METHODS**

**Participants**

Participants were outpatients recruited from clinical referrals and community advertisements at Vanderbilt University Medical Center who enrolled in the CAARe study (Connectivity Affecting the Antidepressant Response). They were age 60 years or older without a diagnosis of dementia or significant cognitive impairment, as assessed by a review of medical records and with a Mini Mental State Exam (MMSE) score greater than 24. Participants were required to have a current diagnosis of Major Depressive Disorder (MDD; DSM-IV-TR) and a Montgomery-Asberg Depression Rating Scale (MADRS) score of 15 or greater. Further exclusion criteria included presence of acute suicidality, current or past primary Axis I disorder diagnoses except for anxiety symptoms occurring during a depressive episode, current or prior psychosis, history of substance abuse or dependence over the prior three years, primary neurological disorders including Parkinson’s disease or dementia, current psychotherapy, electroconvulsive therapy in the previous 6 months, contraindications to MRI, and acute grief.

The Vanderbilt University Institutional Review Board approved this study. All study participants provided written informed consent. The study was registered with ClinicalTrials.gov (NCT02332291). We have previously reported data from this cohort on the relationship between brain aging and the clinical presentation of LLD. Data from a subset of participants in this trial were also included in a preliminary report assessing the influence of amyloid deposition on the antidepressant response.
Clinical Assessments and Study Intervention

The DSM-IV-TR diagnosis of MDD was made using the Mini-International Neuropsychiatric Interview (MINI, version 5.0)\textsuperscript{32} and confirmed by interview with a study psychiatrist. Depression severity was quantified using the MADRS and medical burden quantified with the geriatric Cumulative Illness Rating Scale (CIRS).

Participants taking antidepressants at enrollment had those medications tapered and discontinued over several weeks, with at least two weeks between discontinuation of medication and MRI. Participants then entered the phase 1 double-blinded trial. They were randomized, in a 2:1 drug-to-placebo ratio, to receive escitalopram or placebo. Due to reports that white matter hyperintensity (WMH) severity may influence response to antidepressant medications,\textsuperscript{9,12,13} randomization was stratified by WMH severity. This was operationalized as "high" or "low" WMH severity based on a median WMH volume initially derived from earlier datasets in LLD and adjusted over the course of the study with a final cutoff of 2.0 mL. The study statistician (HK) created a sequential predetermined assignment managed by the Vanderbilt Investigational Drug Service to assign participants to the treatment arms. Participants and study staff were blinded to treatment allocation.

Phase 1 study drug was started at one tablet daily (either 10 mg of over-encapsulated escitalopram or matching placebo), with the option to increase to two tablets daily as early as week 2 based on clinical judgment and patient preference. Depression severity was assessed every two weeks using the MADRS, by telephone at weeks 2 and 6, and in clinic at weeks 4 and 8. Participants who did not remit after 8 weeks or could not tolerate blinded study medication had their phase 1 drug stopped and progressed to phase 2, an 8-week open-label trial of bupropion XL. Dosage started at 150 mg daily and increased to 300 mg daily within 1-2 weeks.
as tolerated. Dosage could further increase to a maximum 450 mg daily on week 4. Study assessments and depression severity scoring through MADRS followed the same protocol as phase 1.

**MRI Acquisition and Brain Age Analyses**

Participants competed MRI on a research-dedicated 3.0T Philips Achieva whole-body scanner using a 32-channel head coil. The MPRAGE images were obtained using TR = 8.75 ms, TE = 4.6 ms, flip angle = 9 degrees, and spatial resolution = 0.89 x 0.89 x 1.2 mm³ plus a FLAIR T2-weighted imaging conducted with TR = 10,000 ms, TE = 125 ms, TI = 2700 ms, flip angle = 90 degrees, and spatial resolution = 0.7 x 0.7 x 2.0 mm³. As previously described,⁴,²⁸ the brain age estimator is an automated deep learning tool used to estimate age from a T1-weighted brain MRI. The first step in the brain age biomarker pipeline is to use affine registration³³ to align the subject T1-weighted brain MRI to a standard template.³⁴ Images undergo N4 bias field correction³⁵ to alleviate bias from acquisition. The input to the brain age estimation algorithm includes this preprocessed brain MRI and the volume of 132 distinct brain regions obtained from a whole-brain segmentation using a multi-atlas technique.³⁶ The “brain age” algorithm then uses a deep convolutional neural network regression model trained on over 5,000 healthy controls ages 4 to 96 years to predict age with high accuracy.²⁸ As such models may have a bias towards the average age of the original sample,³⁷ the nonlinear deep learning approach used to train the brain age estimator includes intercept terms at every stage of the learning process to compensate for potential structural biases. Additionally, we applied cross validation in the brain-age validation process to reduce over training. For this study, we conducted model inference using the brain age algorithm without any further model optimization or changes. Brain age calculations were performed on an
NVIDIA GeForce Titan GPU with 12 GB memory and all deep learning algorithms were implemented and tested using Tensorflow v1.4 with a Keras backend v2.2.

The output from the algorithm is the subject’s estimated age, with the brain-age gap (BAG) measure calculated as algorithm-estimated age less true chronological age. Thus, a higher positive BAG indicates a brain is estimated as older than its chronological age while a negative BAG indicates a brain is estimated as younger than chronological age.

**Alternative Structural Image Analyses**

WMH volumes, used for stratification during randomization, were measured on FLAIR-weighted MRI scans using the Lesion Segmentation Toolbox. These analyses, as previously described, were implemented through the VBM8 toolbox in SPM8 using the threshold of 0.3. We previously reported that cerebral WMH volume was significantly positively associated with BAG.

Hippocampal volumes were calculated using FreeSurfer (version 6). The FreeSurfer methods have been previously described. Parcellation used an anatomical mask derived from the Desikan-Killiany Atlas that identified cortical and subcortical regions, including the hippocampus. Intracranial volume was assessed using the method implemented in FreeSurfer. We visually inspected the data by overlaying the surfaces and subcortical segmentations over the T1 data. Individual slices in each orientation were assessed for errors. No manual corrections were needed.

**Analytic Plan**
Statistical analyses were conducted in R version 4.0.3 (https://rstudio.com). Summary statistics were used to characterize the sample. The primary depression outcome was change in MADRS score. Participants were removed from analyses in either phase if they did not have at least one follow-up assessment while on study medication.

The primary imaging measure was the “brain-age gap” or “BAG”, calculated as the difference between the algorithm-determined estimated age and the chronological age. A negative BAG indicated that the estimated brain age appeared younger than the chronological age, while a positive BAG indicated an older estimated brain age. To better contextualize the relationship between BAG and treatment response, in exploratory analyses we examined total cerebral WMH volume and left and right hippocampal volume. WMH volumes underwent log base 10+1 transformation prior to analyses to adjust for positive skew.

Mixed-effect models were used to examine the association between BAG, treatment arm, and time with change in depression severity. The model included fixed and random effects of the time-invariant primary variables (i.e., BAG and treatment arm), interactions between primary variables, and covariates as predictors of MADRS across all five time points. Specifically, the interaction term estimating the combined effect of the three variables of interest (i.e., BAG x treatment x time) was used to evaluate whether the imaging measure moderated the effect of treatment on MADRS score over time. Primary analyses examined MADRS over the blinded initial 8-week trial and included covariates of sex and chronological age, as well as relevant two-way interaction and main effect terms. If the three-way interaction term did not reach statistical significance, it was removed, and the remaining two-way interaction terms were examined. Specifically, the interaction between BAG and time was evaluated to determine a nonspecific, treatment-independent effect of BAG on change in MADRS over time. The interaction between treatment and time was evaluated to determine whether treatment differentially affected MADRS score. Secondary analyses examined change in MADRS over
the second open-label 8-week trial, examining covariates of chronological age and sex and including the interaction between time and BAG and relevant main effect terms. Exploratory analysis assessed similar interaction effects but replaced BAG estimates with hippocampal volume and included intracranial volume as a covariate. Variables were log-transformed to account for negative skew.

In final secondary analyses, we used logistic regression models to examine the effect of BAG on remission status, defined as a final MADRS score of less than 8. These models were conducted for both the first blinded trial and the second open-label trial and included covariates of chronological age, sex, treatment, and baseline MADRS score. As only a small number of individuals receiving placebo achieved remission (Table 1), due to this limitation on statistical power we did not test for a differential effect of BAG on remission between the two treatment arms in the blinded phase 1 trial.

RESULTS

After screening, we enrolled 162 depressed elders (Figure 1). Of those enrolled, 67 individuals were subsequently withdrawn due to not meeting entry criteria, withdrawal of consent, or loss to follow-up. Ninety-five depressed elders completed baseline procedures and randomization, however one participant withdrew from the study prior to receiving study drug. The remaining 94 participants were included in primary analyses (Table 1), with 38 participants remitting over the course of the study (40.4%) and 56 not remitting (59.6%), defined as a final MADRS score of 7 or less. There were no statistically significant differences in baseline demographic or MRI variables between groups who received escitalopram or placebo, but the escitalopram group exhibited significantly lower final MADRS scores (Table 1). Calculated brain age and chronological age were highly correlated, with a mean absolute error of 6.26 years
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(Pearson’s R = 0.58, p <0.001). In analyses of Phase 1 data, when compared to individuals who remitted, those who did not remit exhibited comparable calculated ages and brain age gaps (Supplemental Table 1). Nonremitting participants also exhibited significantly higher mean baseline MADRS scores (Remit: 23.87, SD=5.02; Nonremit: 27.65, SD=5.22; t=3.54, df =92, p <0.01) and higher mean dose of study drug received (Remit: 16.22mg, SD=4.92; Nonremit: 18.70mg, SD=3.39; t=2.67, df =92, p=0.01)

**Primary analyses of initial blinded, controlled trial of escitalopram**

After adjusting for covariates, BAG did not significantly moderate the effects of escitalopram on change in depression severity (MADRS) over time as evaluated by a three-way interaction model (Fig 2; BAG x treatment x time: estimate (b) = -0.0724, standard error (SE)=0.04, t =-1.76, df =342, p = 0.0794). After removing the three-way interaction term from the model, we then examined the remaining two-way interactions. BAG also did not moderate the change in depression severity over time (BAG x time: b = 0.0024, SE=0.02, t = 0.12, df =343, p = 0.9053). We did observe a statistically significant effect of treatment allocation on MADRS score over time, favoring escitalopram (treatment x time: b = -1.0702, SE=0.27, t = -3.89, df =343, p = 0.0001).

**Secondary analyses of subsequent open-label trial of bupropion**

Forty-one participants progressed from the blinded phase 1 trial to the subsequent phase 2 trial of open-label bupropion (Figure 1). One was removed from analyses due to stopping bupropion prior to any follow-up assessment. Administration of bupropion improved depressive symptoms, with a mean MADRS decrease of 15.60 (SD = 5.43) over the trial period.
After adjusting for covariates, BAG did not significantly moderate change in depression severity (MADRS) over time (BAG x time: $b = -0.0178$, SE = 0.03, $t = -0.67$, $df = 132$, $p = 0.5023$). After removing the interaction term, BAG did not exhibit a primary effect on MADRS ($b = -0.0412$, SE = 0.13, $t = -0.31$, $df = 36$, $p = 0.7594$), however MADRS score significantly decreased over time ($b = -1.3095$, SE = 0.18, $t = -7.28$, $df = 133$, $p < 0.0001$).

**Secondary analyses of remission status**

To examine whether BAG contributed to alternative markers of treatment resistance, we additionally examined whether BAG was associated with remission status, defined as a final MADRS of less than 8. In models controlling for chronological age, sex, treatment, and baseline MADRS score, BAG was not associated with remission status in either the phase 1 controlled escitalopram trial (z-value = 0.50, 88 df, $p = 0.6183$) or the phase 2 open-label bupropion trial (z-value = 1.35, 36 df, $p = 0.1776$).

**Exploratory analyses of established structural neuroimaging markers of brain aging**

To better contextualize these findings, we conducted exploratory analyses examining established structural markers of brain aging. After adjusting for covariates, log-transformed WMH volume did not significantly moderate escitalopram’s effects on change in MADRS score over time as evaluated by a three-way interaction model (WMH x treatment x time: $b = 0.0866$, SE = 0.1612, $t = 0.54$, $df = 342$, $p = 0.5916$). When the three-way interaction term was removed, log-transformed WMH volume also did not moderate change in MADRS over the first trial (WMH x time: $b = -0.0214$; SE = 0.0771; $t = -0.28$; $df = 343$; $p = 0.7818$) or during the subsequent open-label bupropion trial (WMH x time: $b = 0.0222$; SE = 0.1074; $t = 0.21$; $df = 132$; $p = 0.8368$).
In analyses examining the effect of hippocampal volume on change in depression severity, neither left nor right hippocampal volume significantly moderated escitalopram’s effects on change in MADRS score over time as evaluated by a three-way interaction model (hippocampal volume x treatment x time; Left: $b = 0.0001$, SE=0.0006, $t = 0.15$, $df = 342$, $p = 0.8812$; Right: $b = 0.0002$, SE=0.0006, $t = 0.28$, $df = 342$, $p = 0.7779$). When the three-way interaction term was removed, hippocampal volume did not significantly moderate change in MADRS over time (hippocampal volume x time; Left: $b = -0.0003$, SE=0.0003, $t = -0.97$, $df = 343$, $p = 0.3309$; Right: $b = -0.0005$, SE=0.0003, $t = -1.68$, $df = 343$, $p = 0.0940$). Similarly, hippocampal volume did not significantly moderate change in MADRS score over time during the open-label bupropion trial (hippocampal volume x time; Left: $b = -0.0007$, SE=0.0005, $t = -1.30$, $df = 132$, $p = 0.1945$; Right: $b = -0.0002$, SE=0.0005, $t = -0.37$, $df = 132$, $p = 0.7086$).

**DISCUSSION**

In this sequential antidepressant trial in LLD, accelerated brain aging assessed using an algorithm-guided estimation of brain age did not moderate clinical antidepressant response. Neither our primary nor secondary analyses supported our hypothesis that individuals with an estimated brain age older than their chronological age would exhibit a poorer response to treatment or be less likely to achieve remission. Similar negative findings were observed in this sample with more established structural imaging markers of brain aging, total cerebral WMH volume and hippocampal volume. These data support that age-related structural biomarkers are not a robust moderator of antidepressant medication response in LLD.

Broadly, the search for a clinically-accessible biomarker that reliably predicts differential responses to antidepressant treatments has been frustrating, despite extensive study over decades.45 This suggests that any potential markers of response to conventional
antidepressant medications, particularly sMRI markers, may not have large effect sizes. As antidepressant medications typically exhibit small-to-medium effect sizes over placebo, finding subtler within-group differences of smaller magnitude is likely to require greater power and require larger samples. With modest effect size, such markers are less likely to be clinically relevant or clearly prognostic at the individual level.

While LLD is more heterogeneous than depression occurring earlier in life, this heterogeneity may provide a better opportunity to identify such a biomarker. Structural or functional brain differences that could adversely affect treatment response may be affected by aging or by allostatic effects of recurrent depressive episodes across the lifespan, thus magnifying their effect. Supporting this theory, past studies have suggested an association between other markers of accelerated or pathological aging and antidepressant treatment response, including leukocyte telomere length and cortical amyloid deposition. However, clear, replicable results can be difficult to identify.

While our BAG measure has a relationship with cognitive performance and disability in LLD, it raises the question of whether brain-age gap is too broad or not well-suited to capture mechanisms relevant to antidepressant response. As the BAG is a sMRI-based measure that reduces brain differences to a single number, it does not capture functional intrinsic network connectivity measures that change over the course of achieving remission on antidepressant medications. Focal structural changes that may negatively affect network function may be more closely related to treatment response than such global sMRI measures. Functional MRI measures may be stronger moderators of the antidepressant response, but such measures are currently not integrated into clinical neuroimaging.

Importantly, we also did not observe a relationship between secondary markers of brain aging on the antidepressant response. Despite a large body of work examining the relationship...
between WMH and depression, studies examining WMH influences on the response to antidepressant medications are not consistent and report both positive and negative findings. Hippocampal volumes are more consistently reported as being associated with antidepressant response, but there is the possibility of a publication bias in this literature. The negative findings in this report raise the possibility that our cohort may have had relatively lower levels of pathological brain aging than comparable LLD studies, reducing our ability to detect an effect on any of the sMRI measures. This possibility is supported by the observation that the WMH volumes observed in this sample (Table 1) were lower than we have reported in past studies using different acquisition and WMH quantification methods.

Practically, it was encouraging to see that individuals with older-appearing brains did not show a worse treatment response to treatment. This contrasts with disappointing preliminary findings that conventional antidepressants may be less effective in LLD patients with greater amyloid burden. Clinicians often make clinical appraisals of their patients’ MRI results based on atrophy or vascular pathology. This study’s findings suggest they should not be overly discouraged about the prognosis of a patient where neuroimaging suggests accelerated aging. However, such clinical appraisals should consider concomitant cognitive difficulties, which may be a better predictor of poor antidepressant response.

Although this study utilized a rigorous randomized, placebo-controlled design, limitations include the study being conducted at a single site with a relatively modest sample size, particularly in the placebo arm. Fundamentally, BAG is a cross-sectional measure which captures apparent brain age at a single point in time. Studies of accelerating aging and late-life depression often benefit from longitudinal measures which can assess change over time. Like all machine-learning tools, BAG has a complex methodology so we cannot exclude the possibility that focal structural findings could be predictive of clinical response.
In conclusion, our study does not support that the BAG as a measure of accelerated aging can predict response to antidepressant treatment. However, our past work suggests that BAG is related to functional measures, including cognitive performance and disability. This study should not be considered as evidence that accelerated brain aging is unrelated to the likelihood of responding to antidepressant treatment. It only supports that this specific method of measuring brain aging is unrelated to clinical outcomes. Future work should continue to examine the relationship between brain aging and depression outcomes but examine other markers of aging and consider more focal changes rather than solitary, global metrics such as the BAG.

DISCLOSURES AND CONFLICTS OF INTEREST
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The authors have no disclosures to report.

Parts of this work have been previously presented at the 2021 Annual Meeting of the American Association for Geriatric Psychiatry.

AUTHOR CONTRIBUTIONS
Drs. Taylor, Kang, and Landman contributed to the design of the study and acquisition of study data. Dr. Bermudez, Mr. Boyd, Mr. Elson, and Dr. Kang contributed to direct analyses of study data. Dr. Landman, Dr. Szymkowicz, and Ms. Ryan guided and informed analyses of study data and, along with Dr. Taylor, Mr. Ahmed, and Dr. Christman, contributed to interpretation of study data. Mr. Ahmed, Ms. Ryan, Dr. Christman and Dr. Taylor drafted the initial versions of the manuscript. All authors approved of the final version to be published and are accountable for the accuracy and integrity of the study.

REFERENCES


Table 1. Demographic characteristics
<table>
<thead>
<tr>
<th></th>
<th>All Subjects (N = 94)</th>
<th>Placebo (N = 32)</th>
<th>Escitalopram (N = 62)</th>
<th>Test Value</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years (chronologic)</td>
<td>66.22 (4.53)</td>
<td>66.44 (4.81)</td>
<td>66.11 (4.41)</td>
<td>t = 0.32</td>
<td>0.75</td>
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<tr>
<td>Age, years (calculated)</td>
<td>70.58 (7.47)</td>
<td>69.07 (8.46)</td>
<td>71.36 (6.85)</td>
<td>t = 1.33</td>
<td>0.19</td>
</tr>
<tr>
<td>Brain age gap (BAG)</td>
<td>4.36 (6.43)</td>
<td>2.63 (6.95)</td>
<td>5.25 (6.01)</td>
<td>t = 1.81</td>
<td>0.08</td>
</tr>
<tr>
<td>Sex, % female (N)</td>
<td>59.57% (56)</td>
<td>62.5% (20)</td>
<td>58.06% (36)</td>
<td>x² = 0.17</td>
<td>0.68</td>
</tr>
<tr>
<td>Education, years</td>
<td>16.67 (2.10)</td>
<td>15.22 (2.04)</td>
<td>15.31 (2.27)</td>
<td>t = 0.19</td>
<td>0.85</td>
</tr>
<tr>
<td>MMSE</td>
<td>29.38 (0.97)</td>
<td>29.22 (1.21)</td>
<td>29.47 (0.82)</td>
<td>t = 1.04</td>
<td>0.30</td>
</tr>
<tr>
<td>CIRS</td>
<td>5.77 (3.48)</td>
<td>6.28 (3.28)</td>
<td>5.5 (3.30)</td>
<td>t = 0.98</td>
<td>0.33</td>
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<tr>
<td>Baseline MADRS score</td>
<td>26.18 (5.45)</td>
<td>25.78 (6.29)</td>
<td>26.39 (5.01)</td>
<td>t = 0.47</td>
<td>0.64</td>
</tr>
<tr>
<td>Final MADRS score</td>
<td>14.79 (11.32)</td>
<td>19.69 (11.67)</td>
<td>12.26 (10.34)</td>
<td>t = 3.04</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>Remission at final evaluation</td>
<td>38 (40.4%)</td>
<td>9 (28.1%)</td>
<td>29 (46.8%)</td>
<td>x² = 3.05</td>
<td>0.08</td>
</tr>
<tr>
<td>Final Dose (mg)</td>
<td>17.69 (4.24)</td>
<td>18.06 (4.02)</td>
<td>17.50 (4.37)</td>
<td>t = 0.62</td>
<td>0.54</td>
</tr>
<tr>
<td>WMH volume</td>
<td>2.54 (3.57)</td>
<td>2.77 (3.20)</td>
<td>2.42 (3.77)</td>
<td>t = 0.47</td>
<td>0.64</td>
</tr>
</tbody>
</table>
Hippocampal volume, left

<table>
<thead>
<tr>
<th></th>
<th>Mean (SD)</th>
<th>Mean (SD)</th>
<th>Mean (SD)</th>
<th>t = 1.31</th>
<th>p = 0.19</th>
</tr>
</thead>
<tbody>
<tr>
<td>Left</td>
<td>3.88 (0.42)</td>
<td>3.78 (0.47)</td>
<td>3.91 (0.38)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Hippocampal volume, right

<table>
<thead>
<tr>
<th></th>
<th>Mean (SD)</th>
<th>Mean (SD)</th>
<th>Mean (SD)</th>
<th>t = 1.26</th>
<th>p = 0.21</th>
</tr>
</thead>
<tbody>
<tr>
<td>Right</td>
<td>4.00 (0.41)</td>
<td>3.91 (0.51)</td>
<td>4.04 (0.35)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Data for continuous variables presented as mean (standard deviation), and for categorical variables as percentage (N). Volumes presented in milliliters. Analyses do not include one subject allocated to receive escitalopram who never took study drug nor completed any follow-up assessment. For continuous variables, analyses were conducted using two-tailed t-tests with 92 degrees of freedom. Categorical variables were analyzed using the chi-square test with 1 degree of freedom. Remission was defined as a final MADRS score of less than 8.

CIRS = Cumulative Illness Rating Scale; MADRS = Montgomery-Asberg Depression Rating Scale; MMSE = Mini-Mental State Exam; WMH = white matter hyperintensity

Fig. 1 Study CONSORT diagram
The majority of people who were not eligible at the screening visit were due to MRI safety concerns, not meeting the depression severity criterion, or having other neurological or psychiatric disorders. Most placebo arm withdrawals were for worsening symptoms. Most drug arm withdrawals were for medication intolerance. Participants who withdrew were included in analyses unless they did not complete at least one follow-up assessment while on study drug.

Fig. 2 Brain-Age Gap predicting change in MADRS over time.
Figure displays MADRS (y-axis), BAG (x-axis), and the relationship between these two variables at each study time point. The brain-age gap (BAG) was not statistically associated with treatment-specific differences in change in depression severity (Montgomery-Asberg Depression Rating Scale score) over time, evaluated by a three-way interaction model (BAG x treatment x time; $t = -1.76, p = 0.0794$). Brain-age gap (BAG) is in years, calculated as the difference between the calculated estimated age and the chronological age.