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Preliminary evidence that cortical amyloid burden predicts poor response to antidepressant medication treatment in cognitively intact individuals with late-life depression

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Abstract

Objective: Amyloid accumulation, the pathological hallmark of Alzheimer's disease, may predispose some older adults to depression and cognitive decline. Deposition of amyloid may occur prior to the development of cognitive decline. It is unclear whether amyloid influences antidepressant outcomes in cognitively intact depressed elders.

Design: A pharmacoinaging trial utilizing florbetapir(18F) PET scanning followed by two sequential 8-week antidepressant medication trials.

Participants: Twenty-seven depressed elders who were cognitively intact on screening.

Measurements and Interventions: After screening, diagnostic testing, assessment of depression severity and neuropsychological assessment, participants completed florbetapir(18F) PET scanning. They were then randomized to receive escitalopram or placebo for 8 weeks in a double-blinded two-to-one allocation rate. Individuals who did not respond to initial treatment transitioned to a second open-label trial of bupropion for another 8 weeks.

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AUTHOR CONTRIBUTIONS

Drs. Taylor, Woodward, and Shokouhi contributed to the design of the study and acquisition of study data. Dr. Shokouhi, Mr. Boyd, Mr. Elson, and Dr. Kang contributed to direct analyses of study data. Dr. Andrews, Albert, Vega, and Newhouse guided and informed analyses of study data and, along with Drs. Taylor and Shokouhi, contributed to interpretation of study data. Drs. Taylor and Shokouhi 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.

The authors deny any conflicts of interest.

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Results: Compared with 22 amyloid-negative participants, 5 amyloid-positive participants exhibited significantly less change in depression severity and a lower likelihood of remission. In the initial blinded trial, 4 of 5 amyloid-positive participants were non-remitters (80%), while only 18% (4 of 22) of amyloid-negative participants did not remit ($p=0.017$; Fisher's Exact test). In separate models adjusting for key covariates, both positive amyloid status ($t=3.07$, 21 *df*, $p=0.003$) and higher cortical amyloid binding by standard uptake value ratio ($t=2.62$, 21 *df*, $p=0.010$) were associated with less improvement in depression severity. Similar findings were observed when examining change in depression status across both antidepressant trials.

Conclusions: In this preliminary study, amyloid status predicted poor antidepressant response to sequential antidepressant treatment. Alternative treatment approaches may be needed for amyloid-positive depressed elders.

INTRODUCTION

Amyloid beta (A β) accumulation may predispose some older adults to develop depressive episodes.¹ In cognitively intact older adults, greater A β burden is cross-sectionally and longitudinally associated with greater depressive symptoms.^{2,3} In turn, cortical amyloid and depressive symptoms may interact to influence cognitive decline.^{4,5} Late-life depression (LLD) in the absence of dementia is associated with a higher plasma A β_{40} :A β_{42} ratio,⁶ similar to what is seen in Alzheimer's disease (AD) and also an increased risk for cognitive decline and developing AD.⁷ While several studies demonstrated that depressed elders exhibit a greater cortical A β burden than never-depressed older adults,⁸⁻¹⁰ there are also negative reports.¹¹

Beyond cognitive decline,^{4,5} it is unclear whether cortical amyloid influences clinical outcomes in nondemented LLD. Some work suggests that increasing levels of treatment resistance in LLD may be associated with increased A β deposition, particularly in the temporal lobe.¹² This ambiguity is in contrast to our broader understanding of pathological brain and cognitive aging in LLD, as cerebrovascular disease, executive dysfunction and episodic memory impairment are associated with poor antidepressant responses.¹³ Antidepressant medications have poor efficacy for depression in dementia,¹⁴⁻¹⁶ however it is unclear whether A β or other neuropathological factors contribute to treatment resistance in depressed patients with dementia.

The purpose of this preliminary study was to examine how A β in nondemented LLD is associated with response to antidepressant medications. We hypothesized that greater cortical amyloid burden and amyloid positivity would be associated with less improvement in depression severity and lower frequency of achieving remission with sequential antidepressant treatment.

METHODS

Participants

Participants were recruited at Vanderbilt University Medical Center (VUMC; Nashville, TN) from clinical referrals and community advertisements. They enrolled in a pharmacoinaging trial combining baseline MRI with sequential antidepressant treatment (NCT02332291).

Participants were then eligible to participate in this optional ancillary study that added a baseline florbetapir (18F) PET scan. Enrollment in this ancillary study ranged from June 2018 through March 2020.

Inclusion criteria specified subjects be age 60 years or older and meet *DSM-IV-TR* criteria for major depressive disorder with a Montgomery-Asberg Depression Rating Scale (MADRS)¹⁷ score of ≥ 15 . Participation required a Mini-Mental State Exam (MMSE)¹⁸ score > 24 and no diagnosis of dementia or other neurological disorders. Additional exclusion criteria included: 1) other Axis 1 diagnoses, other than anxiety symptoms occurring during depressive episodes; 2) history of alcohol or drug abuse or dependence in the last 3 years; 3) history of psychosis; 4) presence of acute suicidality; 5) acute grief in last month; 6) MRI contraindications; 7) a failed trial of escitalopram in the current episode; 8) ECT in the last 6 months; and 9) current psychotherapy.

All participants provided written informed consent. The VUMC Institutional Review Board approved the study.

Assessments, Study Visits, and Antidepressant Treatment

Diagnosis and evaluation of exclusionary psychiatric disorders was determined using the Mini-International Neuropsychiatric Interview (version 5.0).¹⁹ After determination of eligibility, individuals taking an antidepressant medication had that tapered and discontinued over several weeks. After a two-week period without antidepressant medications, they completed their baseline assessment, including neuropsychological testing, MRI, and PET scans. Participants then started study medication.

Neuropsychological Testing—Neuropsychological testing procedures have been previously described.²⁰ Briefly, the neuropsychological test battery included a range of tests probing cognitive domains impaired in LLD. Similar to our previous approach,^{21,22} we combined tasks into rationally constructed cognitive domains. We then created z-scores for each measure based on the performance of all participants in the larger parent study and averaged the z-scores for all tests within each domain for each individual. Domains and tests included:

- **Episodic Memory:** Word List Memory Recall (delayed), Paragraph Recall test, Constructional Praxis test, and Benton Visual Retention Test.
- **Executive Function:** Controlled Oral Word Association test, Mattis Dementia Rating Scale Initiation-Perseveration Subscale, Trail-Making Test Part B, the Stroop test color-word interference condition, and the Wisconsin Card Sorting Test
- **Language Processing:** Shipley vocabulary test, Boston Naming Test, and Stroop test word reading condition.
- **Processing Speed:** Symbol-Digit Modality Test, Stroop test color naming condition, Trail-Making Test Part A.
- **Working Memory:** Digits Forwards, Backwards, and Ascending.

Antidepressant Treatment—Antidepressant treatment included two study phases, each lasting 8 weeks. In both phases, depression severity was assessed every two weeks, with participants completing in-clinic visits at baseline, week 4, and week 8, with telephone visits in weeks 2 and 6.

In the double-blinded study phase 1, participants were randomized to either escitalopram or placebo in a 2 to 1 allocation. Randomization was stratified by white matter hyperintensity (WMH) severity, operationalized as “high” or “low” based on the median WMH volume determined from prior studies. Participants, study physicians, and neuroimaging staff were blinded to treatment allocation. Assignment to treatment arm was done through a sequential predetermined assignment created by the study statistician (HK) and managed by the Vanderbilt Investigational Drug Service. Dosing started at 10mg daily (or placebo) and could increase to 20mg as early as week 2. If a participant did not respond or remit during phase 1, they entered phase 2. Phase 2 included open-label treatment with bupropion (24-hour release formulation), beginning at 150mg daily, increasing to 300mg over 1–2 weeks. The dose could be further increased to the maximum of 450mg daily at week 4.

In both phases, the study physician and the study participant jointly decided on titrating above the minimum therapeutic dose (escitalopram 10mg daily and bupropion 300mg daily). For this ancillary study, the majority of participants in each phase completed the full 8 week duration and tolerated the minimum target dose. Only one participant could not tolerate study medication in either phase and ended both phases early.

Magnetic Resonance Imaging

Participants were scanned on a research-dedicated 3.0T Philips Achieva whole-body scanner (Philips Medical Systems, Best, The Netherlands) using body coil radiofrequency transmission and a 32-channel head coil for reception. Structural imaging included a whole-brain T1- weighted MPRAGE image with TR = 8.75ms, TE = 4.6ms, flip angle=9 degrees, and spatial resolution = $0.89 \times 0.89 \times 1.2 \text{ mm}^3$ plus a FLAIR T2-weighted imaging conducted with TR = 10000ms, TE = 125ms, TI = 2700ms, flip angle = 90 degrees, and spatial resolution = $0.7 \times 0.7 \times 2.0\text{mm}^3$.

WMH volumes, findings on T2- weighted or FLAIR images related to cerebral ischemia, were measured using the Lesion Segmentation Toolbox.²³ These analyses, as previously described,^{20,24} were implemented through the VBM8 toolbox in SPM8 using the threshold of 0.3. Per protocol and based on prior preliminary analyses across earlier datasets, WMH severity was determined as being “high” or “low” using a cerebral WMH volume of 3.86ml. This was used to stratify randomization into study phase 1.

Florbetapir (18F) PET Scan Acquisition and Analyses

Florbetapir image data were acquired with a Philips Vereos PET/CT scanner. Florbetapir was administered as a single 370 mBq (10mCi) intravenous bolus with acquisition of image data beginning 40–50 minutes later. Data were acquired in four 5-minute frames with a voxel size of 2mm isotropic and field of view (FOV) of 256mm.

To quantify cortical A β , the four florbetapir image frames were coregistered using mcflirt from FSL²⁵ to create a single mean volume. This mean volume was then registered using mri_coreg to the subject's FreeSurfer space as derived from their MPRAGE image. The transform from this registration was inverted to move the FreeSurfer ROIs to the PET space.

Following ADNI procedures for florbetapir processing, we created a cortical composite gray matter standard uptake value ratio (SUVR) for analyses. We extracted florbetapir binding means from FreeSurfer-defined gray matter within four large regions, including the frontal lobe (excluding the paracentral and precentral gyri), the lateral parietal lobe, the lateral temporal lobe, and the anterior and posterior cingulate gyri.²⁶ Florbetapir binding means from the whole cerebellum were used to calculate the cortical A β SUVR. This cortical A β SUVR was used as a continuous measure in analyses and also used to dichotomize A β -status (amyloid positive or negative), using a cutoff of 1.11.²⁷

Statistical Analyses

Statistical analyses were conducted in R version 4.0.0 (<https://rstudio.com>). Summary statistics were utilized to describe group characteristics. Group differences between A β -status were tested using pooled, two-tailed t-tests or a Welch's t-test if Levene's Test of Homogeneity of Variance indicated unequal variances. Separate general linear models (GLMs) examined effects of A β -status on z-scored cognitive variables adjusting for age, gender, and education. The primary depression outcome variable was change in MADRS over the first antidepressant trial. Secondary outcomes examined change in MADRS over both trials and dichotomous remission status across both trials, defining remission as a final MADRS < 8. Dichotomous A β -status (i.e., amyloid positive/negative) was the primary imaging measure, with cortical A β SUVR being secondary. One subject entered and ended both trials early due to tolerability problems. As the only missing data were five data points across both trials for this individual, we used a single regression imputation to impute these missing data. There were no other missing data.

Depression outcomes from the initial treatment phase and across both phases were examined using multiple regression GLMs. Separate GLMs examined change in MADRS (baseline to 8-week) as a function of A β -status or cortical SUVR, controlling for baseline MADRS score, age, gender, and treatment arm (placebo or escitalopram). Subsequent logistic regression models examined remission status as a function of the same independent variables and covariates. Results were corrected using 10,000 permutations of the permutation of regressor residuals test implemented in the R package 'glmperm' (version 1.0–5, <http://cran.r-project.org/web/packages/glmperm/index.html>). The permutation of regressor residuals test replaced the variable of interest by the residuals of the variable of interest regressed on all other independent variables to yield an exact *p*-value appropriate for inferring results from small sample sizes.²⁸ Exploratory GLMs examined associations between cognitive domain z-scores and MADRS change after adjusting for age and education. We planned to add cognitive domains that were significantly associated with MADRS change as confounds to models assessing the relationship between amyloid measures and MADRS change.

RESULTS

We screened and discussed the study with 34 potential participants identified through the parent study (see Figure 1, CONSORT diagram). Six decided not to participate due to concerns over the infusion and radiation exposure. One agreed to participate and provided informed consent but could not complete PET imaging due to a scanner malfunction. The final sample consisted of 27 older adults (Table 1; age range 60–76y) with a moderate level of depression severity based on mean baseline MADRS score (range 15–34). Participants did not exhibit cognitive impairment on MMSE screening (mean = 29.4, $SD=0.8$, range 28–30) (Table 1).

Five participants were amyloid positive. Neither baseline MADRS ($t=0.775$, 15.39 *df*, $p=0.450$), MMSE ($t=0.588$, 4.71 *df*, $p=0.584$), WMH volume ($t=1.18$, 25 *df*, $p=0.247$) nor assignment to initial treatment arm ($t=0.246$, 25 *df*, $p=0.808$) significantly differed by A β -status (Table 1). After adjusting for age and education, amyloid status was not associated with performance in any cognitive domain (data not shown; p 's=0.201–0.894).

In the blinded first trial involving randomization to escitalopram or placebo (mean doses: drug: 17.8mg, $SD=4.4$ mg; placebo: 17.8mg, $SD=4.3$ mg), 19 subjects remitted while 8 did not. Four A β -positive participants were non-remitters (80%), in contrast to 4 of 22 (18%) of A β -negative participants being non-remitters ($p=0.017$; Fisher's Exact test). Our primary outcome was change in depression severity across the blinded first trial involving randomization to escitalopram or placebo. After adjusting for treatment arm, baseline MADRS score, age, and gender, A β status was significantly associated with change in depression severity ($t=3.07$, 21 *df*, $p=0.003$). We observed a mean 69.9% (range: 7%–100%) reduction in MADRS score for A β -negative subjects and a mean 29.1% (range: 4%–65%) reduction for A β -positive subjects. In this model, treatment arm assignment approached but did not achieve statistical significance ($t=2.07$, 22 *df*, $p=0.051$). In models with similar covariates, A β status was also significantly associated with the secondary outcome of remission status ($z=2.40$, $p=0.002$). Similar effects were observed when A β status was replaced by cortical A β SUV_r measures in models examining MADRS change ($t=2.62$, 21 *df*, $p=0.010$) and remission rate ($z=3.50$, $p=0.002$).

These findings persisted on expanding analyses to examine change across both blinded and open-label study phases (Figure 2). The 8 non-remitting subjects from the first trial entered this open-label study phase (mean dose = 318.8mg, $SD=96.1$ mg), with only one remitting. Across both study phases, 4 of 5 A β -positive participants were non-remitters (80%), while 3 of 22 (14%) of A β -negative participants were non-remitters. In models adjusting for age, gender, baseline MADRS score, and treatment arm in the first trial, A β -status was associated with change in MADRS ($t=2.10$, 21 *df*, $p=0.044$; Figure 2a) and remission status ($z=2.40$, $p=0.001$). Similar effects were observed with cortical A β SUV_r on MADRS change ($t=2.10$, 21 *df*, $p=0.048$; Figure 2b) and remission rate ($z=3.90$, $p=0.001$).

Exploratory analyses examined whether the relationship between A β -status and MADRS change persisted after adjusting for cognitive performance. As an initial step, we examined whether cognitive domain performance predicting change in MADRS score. After adjusting

for age, baseline MADRS score, and education, MADRS change was not significantly associated with any baseline cognitive domain measure (data not shown). As cognitive performance was not associated with MADRS change, we did not conduct further analyses.

DISCUSSION

Although a preliminary study, our primary finding in this small sample of cognitively intact, depressed older adults, is that greater A β burden is associated with poorer acute antidepressant response. As A β status was not associated with baseline cognitive performance in this sample, the effect of A β on the antidepressant response may potentially be independent of the effects of cognitive impairment on the antidepressant response.

This finding is concordant with work in AD demonstrating that antidepressants have poor efficacy for treating depression in dementia^{14–16} but extends those findings to cognitively unimpaired individuals with elevated cortical A β . Our current work suggests that the antidepressant treatment resistance observed in dementia may be related to AD neuropathology. Moreover, this adverse effect on treatment outcome may extend to individuals with greater A β burden who are earlier in the disease process and cognitively intact on clinical screening. Although the current study does not provide guidance about what antidepressant treatment approaches may benefit this group, there may be roles for neuromodulation, neurobiologically based psychotherapy, or cognitive remediation.²⁹ There may additionally be future roles for anti-amyloid therapy in A β positive individuals with LLD,¹ either to include them in AD prevention trials or to examine whether anti-amyloid therapy in these individuals may benefit depression.

It is important to consider the mechanism by which A β may contribute to poor antidepressant responses. The earliest accumulation of A β plaques occurs within default-mode network (DMN) regions,³⁰ including the posterior cingulate cortex (PCC), precuneus, and prefrontal cortex (PFC).³¹ A β deposition in turn is associated with alterations in resting-state functional connectivity (rsFC) of the DMN, reported as both network disruptions (characterized by decreased rsFC) and network reorganizations (characterized by increased rsFC).^{32–34} Altered rsFC of the DMN is also reported in LLD^{35–37} and successful antidepressant treatment is associated with changes in DMN rsFC.³⁸ Assuming these dynamic changes in rsFC of the DMN contribute to the clinical antidepressant response, the presence of greater A β burden may decrease the ability of antidepressants to facilitate these critical functional network changes, resulting in treatment resistance. Alternatively, there may be underlying causes that independently contribute to A β accumulation, vulnerability to depression and antidepressant treatment resistance. For example, inflammation and cerebrovascular pathology are both associated with depression, poorer antidepressant response, and dementia.^{13,39}

Although our findings are preliminary, they have potential clinical implications in understanding variability in antidepressant response in clinical populations. However, for several reasons this study alone should not be used as the sole rationale to use PET imaging or other techniques to assess A β burden in older adults with treatment resistant depression. First, we do not have a good treatment alternative, so a positive amyloid scan would not

inform treatment choice. Second, the study's relatively small sample size makes the results preliminary and raises issues about the generalizability of our findings.

Although our findings are robust and consistent across analyses, the study has limitations. Primarily, this study examined a small sample with a limited proportion of A β -positive participants. While performance deficits across a range of cognitive domains predict depression outcomes,¹³ the small sample size limited our ability to discern whether the effects of A β status on treatment response persist when adjusting for cognitive impairment, or to probe for potential interactive effects between A β , vascular disease and cognitive performance on depression outcomes. Future work could examine a sample better balanced between A β -positive and -negative subjects. Additionally, other markers of pathological brain aging such as tau deposition should be considered.

Despite these issues, this preliminary report provides a valuable insight that in some individuals with LLD, AD pathology may contribute to antidepressant treatment resistance. Further work is needed to confirm this finding, determine how AD pathology contributes to longer-term outcomes such as depression recurrence,⁴⁰ and to establish alternative, effective treatments for A β -positive LLD.

Acknowledgments

DISCLOSURES AND CONFLICTS OF INTEREST

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Highlights

What is the primary question addressed by this study?

Does cortical amyloid burden affect the response to antidepressant medications in patients with late-life depression who are cognitively intact on screening?

What is the main finding of this study?

In this preliminary study, high amyloid burden is associated with poor response and failure to achieve remission with sequential antidepressant treatment.

What is the meaning of the finding?

Cortical amyloid may contribute to antidepressant treatment resistance in late-life depression. Further work is needed to confirm these findings and determine the optimal treatment approach for amyloid positive individuals.

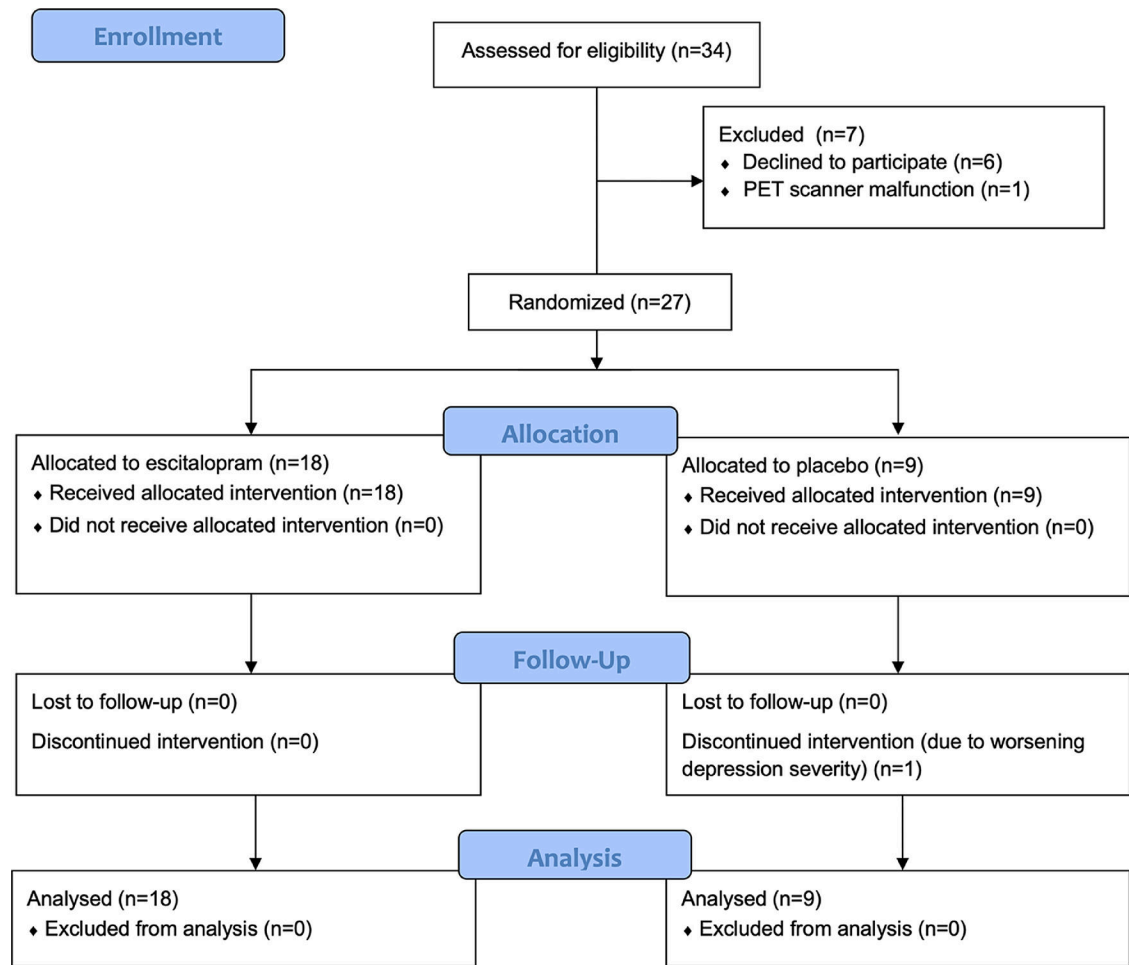


Figure 1.
Study CONSORT Diagram

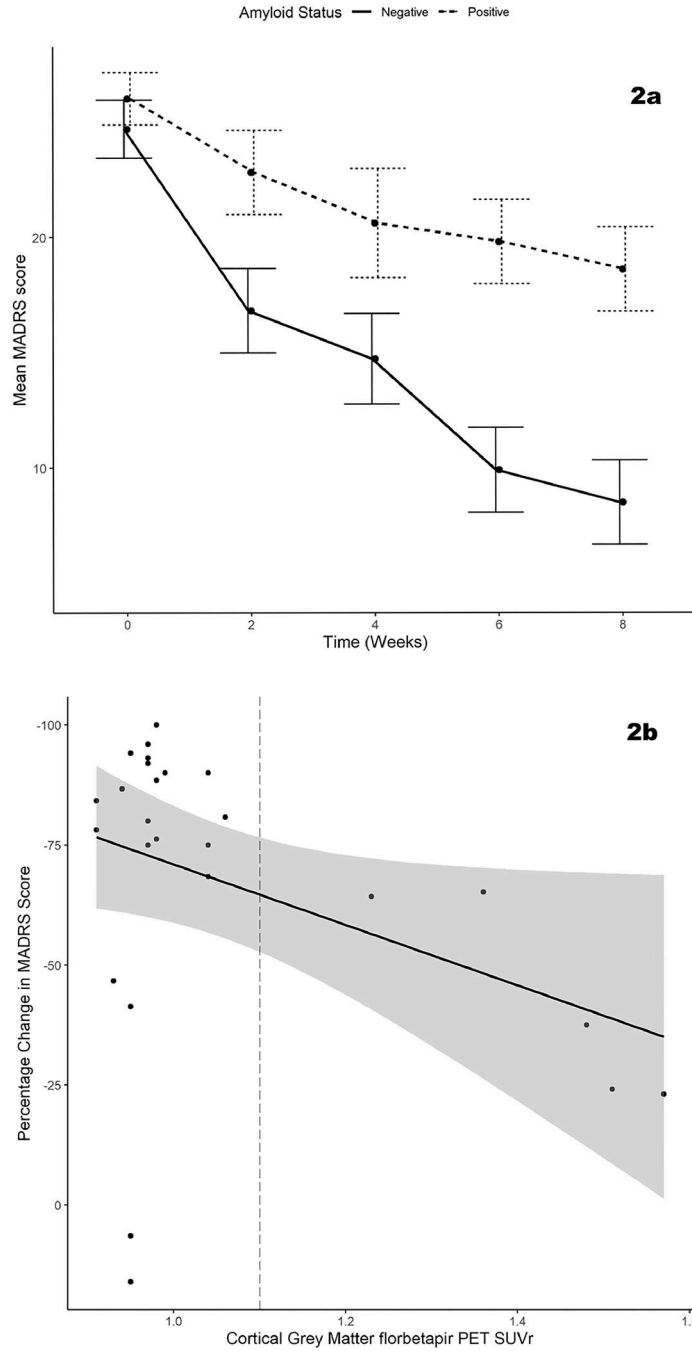


Figure 2. Amyloid effects on depression severity change with treatment

Figure 2a displays change in MADRS score across by A β -status in Trial 1 (escitalopram vs placebo, weeks 0–8). Error bars display the standard error at each timepoint. Figure 2b displays the relationship between cortical A β SUVR and percent change in depressive symptoms from baseline across both trials to study completion, showing the regression line and 95% confidence interval.

Table 1:

Demographic characteristics of the sample

	Overall Sample (N=27)	A β negative (N=22)	A β positive (N=5)
Age (y)	67.9 (3.9)	67.3 (4.1)	70.8 (1.5)
Sex (% female)	55.6% (N=15)	50.0% (N=11)	80.0% (N=4)
Education (y)	15.5 (2.3)	15.4 (2.0)	16.2 (3.5)
WMH volume (ml)	0.9 (1.2)	1.0 (1.3)	0.5 (0.8)
MMSE	29.4 (0.8)	29.5 (0.7)	29.2 (1.1)
MADRS, Baseline	24.9 (5.4)	24.7 (5.9)	26.0 (2.5)
MADRS, Phase 1 End	10.0 (9.7)	8.0 (9.3)	18.6 (7.0)
Phase 1 Remitted	70.4% (N=19)	81.8% (N=18)	20% (N=1)
Phase 1 Dose (mg)	17.8 (4.24)	17.7 (4.3)	18.0 (4.5)
	(N=8)	(N=4)	(N=4)
MADRS, Phase 2 End	19.0 (10.3)	20.8 (14.5)	16.8 (5.4)
Phase 2 Dose (mg)	318.7 (96.13)	262.5 (75.0)	375.0 (86.6)

Continuous measures presented as mean (standard deviation) and categorical variables presented as % (number). Phase 1 dose calculated on number of pills as participants received either escitalopram or matching placebo. Phase 2 involved open-label bupropion administration.

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