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Change in hippocampal volume on magnetic resonance imaging and cognitive decline among older depressed and non-depressed subjects in the Neurocognitive Outcomes of Depression in the Elderly study

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Abstract

Introduction—Previous studies have linked hippocampal volume change and cognitive decline in older adults with dementia. We examined hippocampal volume change and cognitive change in older non-demented adults with and without major depression.

Methods—The sample consisted of 90 depressed individuals and 72 healthy, non-depressed individuals age 60 and older who completed at least two years of follow-up data. All patients underwent periodic clinical evaluation by a geriatric psychiatrist as well as baseline and two-year magnetic resonance imaging.

Results—Over two years, the depressed group showed a greater reduction in left hippocampal volume (normalized for total cerebral volume) compared with the non-depressed group (mean difference = 0.013 ± 0.0059, t = 2.18, df = 160, $p < 0.0305$). The difference remained significant after controlling for age, sex and baseline normalized left hippocampal volume. We also found that hippocampal change from baseline to two years was associated with subsequent change in MMSE score from two years to two-and-a-half years (left t = 2.81, df = 66, p = 0.0066; right t = 2.40, df = 66, p = 0.0193) among the depressed group.

Conclusions—These findings add to the literature linking hippocampal volume loss and late-life depression. Depressed patients with hippocampal volume loss are at greater risk of cognitive decline.

Keywords

hippocampus; magnetic resonance imaging; depression; elderly; cognition

The relationship between cognitive decline, depression and depression in the elderly is complex (1), yet important both clinically and scientifically given the high comorbidity of depression and cognitive impairment (2). Neuroimaging studies of hippocampal morphology may be particularly informative, as the hippocampus has been shown to be involved in both cognitive and mood disorders. Hippocampal atrophy has been found to predict conversion of mild cognitive impairment to dementia (3,4). Prior studies of hippocampal structure in late life depression using magnetic resonance imaging (MRI) have shown that older depressed patients have lower hippocampal volumes compared with non-depressed subjects (5–8).

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Recurrent depression and longer duration of depressive episodes are associated with volume loss in the hippocampus (9–11). Although memory and other cognitive impairments are common in both acute and remitted late-life depression (12,13), there have been few studies examining hippocampal volume in late life depression and subsequent cognitive decline. In one study of depressed patients, hippocampal volume reduction was significantly associated with continuing memory deficits at six months (14). We previously demonstrated a link between small hippocampal volume and incident dementia in a group of non-demented older depressed patients (15).

Longitudinal studies employing repeated MRI have recently been used in research examining mild cognitive impairment and Alzheimer's disease (AD), with findings including hippocampal volume loss being associated with cognitive decline (16), hippocampal volume changes being detectable even after six months among AD patients (17), and demented patients undergoing treatment with memantine showing less hippocampal loss (18). Few depression studies have used repeated MRI to examine hippocampal volume change. A three-year study of psychiatric inpatients found that depressed patients showed greater decline in grey matter hippocampal density compared with a non-depressed group (19).

We sought to examine changes in hippocampal volume and cognitive decline among older depressed and non-depressed individuals enrolled in the Neurocognitive Outcomes of Depression in the Elderly (NCODE) study. Based on research demonstrating lower hippocampal volumes in depression (5,7–9), our first hypothesis was that older non-demented depressed patients would also show greater loss of hippocampal volume loss than a group of older non-depressed, non-demented individuals. Our second hypothesis was that change in left and right hippocampal volumes would be associated with cognitive changes, particularly among the depressed group, where the combination of deficits in cognition and hippocampal volume may have an adverse additive effect.

Methods

Development of the NCODE cohort

Beginning in November 1994, investigators at Duke University Medical Center began enrolling depressed patients aged 60 and older in the NIMH-sponsored Mental Health Clinical Research Center for the study of Depression in Later Life (MHCRC) and into its longitudinal sister study. The latter study sought to examine neuroimaging factors related to depression outcomes. A neuropsychological evaluation was added in 1997. In conjunction with the newly established Conte Center for the Neuroscience of Depression in the Elderly, the longitudinal study (NCODE) was renewed in 2001 with a focus on both depressive outcomes and neurocognitive outcomes of depression.

Subjects

Depressed subjects enrolled in the study met criteria for a current episode of unipolar major depression and are age 60 and older. Exclusion criteria included presence of another major psychiatric illness such as schizophrenia, schizoaffective disorder, bipolar disorder, lifetime alcohol or substance dependence, and dementia. Patients with psychotic depression were included, as are those with comorbid anxiety disorders, as long as major depression was deemed by the study psychiatrist to be the primary psychiatric disorder. Aside from dementia, other neurological illnesses that could affect structural brain MRI scans were excluded, such as Parkinson's disease, multiple sclerosis, and seizure disorder. Subjects with contraindications to brain MRI were also excluded. Subjects who subsequently developed

alcoholism were not dropped from the study. After complete description of the study to the subjects, written informed consent was obtained.

The study included a non-depressed group recruited from the Center for Aging Subject Registry at Duke University, which includes over 1,900 community-dwelling elders in the Durham, Chapel Hill, and Raleigh (N.C.) area who have expressed willingness to participate in Duke Center for Aging Research. Eligible individuals had a non-focal neurological examination, no self-report of neurologic or depressive illness, no evidence of a lifetime depression diagnosis based on the NIMH Diagnostic Interview Schedule (DIS, 20) depression module, and no reported history of another major psychiatric illness.

Structured Interview and Depression Assessment

At baseline, a study geriatric psychiatrist interviewed each depressed subject and completed standardized clinical assessments, including the 17-item Hamilton Rating Scale for Depression (21), the Montgomery Asberg Depression Rating Scale (MADRS, 22), and the Clinical Global Impression scale. A trained interviewer administered the Duke Depression Evaluation Schedule (DDES, 23), which assesses depression using the NIMH Diagnostic Interview Schedule (20), as well as cognitive status, physical health, and the four measures that comprise the Duke Social Support Index (DSSI): instrumental social support, social interactions, subjective social support, and non-family social network (24). Clinical assessments were repeated when clinically indicated, but at least every three months. For the present study, the MADRS is the main depression outcome measure. All raters are trained on completion of the MADRS, and high interrater reliability (kappa > 0.9) is established.

Baseline cognitive screen

Subjects were excluded if they have dementia or suspected dementia at baseline based on information available to the assigned NCODE geriatric psychiatrist, who examines the subject, reviews medical records, and confers with referring physicians for all patients. While most (n = 84 of 89, 95.5%) depressed subjects enrolled to date had Mini Mental State Examination (MMSE, 25) scores above 25 at baseline assessment, with 72 (80.9%) scoring 27 or above, 4 severely depressed subjects had scores below 26 (3 with score of 25 and one with score of 22), and one patient did not have an MMSE score at baseline. All non-depressed individuals had MMSE scores 25 or above, with 5 missing baseline MMSE. Among them, 63 of 67 (94.0%) had MMSE scores 27 and above. Regarding the depressed subject with initial MMSE score less than 25, NCODE protocol is to follow such patients through an acute (eight-week) phase of treatment to determine if cognition improves. Subjects whose MMSE scores remain below 25 are not followed longitudinally in the NCODE study. Thus, in the clinical judgment of the study geriatric psychiatrist and by established NCODE protocol, dementia is effectively excluded at or close to baseline in all elderly depressed NCODE subjects.

Clinical Follow-up of depressed subjects

The NCODE study operates in a naturalistic treatment milieu using treatment guidelines established by the Duke Affective Disorders Program (26). Treatment modalities available include antidepressant medications, electro-convulsive therapy, and individual and group cognitive-behavioral psychotherapy. Treatment is monitored to ensure that clinical guidelines are followed appropriately. As indicated above, patients are evaluated when clinically indicated, and at least every three months while they are in the study. The protocol recommends that patients receive continuation treatment for at least one to two years (some indefinitely) once they achieve remission. Each patient is thus assured to receive the most appropriate care we are able to provide.

Referral of subjects with cognitive impairment

When subjects present with cognitive complaints, if family members bring concerns to the study geriatric psychiatrist, or if the psychiatrist has a clinical suspicion of cognitive impairment or dementia, he or she has the option to refer the patient to the Memory Disorders Clinic at Duke University Medical Center. When this happens, the study obtains copies of those medical records.

MRI acquisition protocol

All subjects are screened for the presence of cardiac pacemakers, neurostimulators, metallic implants, metal in the orbit, aneurysm clips or any other condition where MRI is contraindicated. Subjects are imaged with a 1.5 Tesla whole-body MRI system (Signa, GE Medical Systems, Milwaukee, WI) using the standard head (volumetric) radio-frequency coil. Two sets of dual-echo fast spin-echo (FSE) acquisitions were obtained: one in the axial plane for morphometry of cerebrum and a second in a coronal oblique plane for hippocampal measures. Our MRI acquisition protocol has been described previously (5,27).

MRI Image Processing protocols

Hippocampus Boundary Determination—The MR images were processed at to the Neuropsychiatric Imaging Research Laboratory (NIRL), located at Duke University Medical Center. Hippocampal volumes were determined using the GRID Program that was developed at NIRL and has been described previously (5,28). GRID allows for semi-automated region tracing and determination of region-of-interest (ROI) volumes and boundaries.

The method for defining the hippocampal perimeter has been previously described (28). On all slices, tracing began along the most inferior border of the main body of the hippocampus, and then moved laterally along the border between the hippocampus and the inferior lateral ventricles. Along the medial and superior borders, tracing included any thin strips of white matter along the lateral or superior surface. Pockets of cerebrospinal fluid were excluded; blood vessels were transected unless they were prominent or did not extend into the hippocampal body. If motion, poor contrast, or other factors rendered any one slice unreadable, a volume for that slice was generated by averaging the volumes from the previous and subsequent slices. If the first or last slices were unreadable, or if two middle slices were unreadable, the subject was excluded from analysis.

Statistical Analysis

We first performed bivariate statistics to test the relationship of predictors and covariates and raw and normalized (i.e., divided by total cerebral volume) change in hippocampal volumes over two years, comparing the depressed and non-depressed groups. T-test, chi-square and Fishers Exact Test were used where appropriate and are presented in Table 1. Participants were required to have baseline and two-year follow-up data to be included in the study. Linear regression models were fit to compare depressed and non-depressed for the change in normalized hippocampal volumes over two years with respect to age (interaction between status and age), while controlling for age, sex and baseline normalized hippocampal volumes. Models were fit for left and right hippocampal separately given our prior finding that showed lateralizing effects in the hippocampus for later cognitive decline (15).

We next developed models to compare change in normalized hippocampal volumes and both concurrent two-year MMSE change and then subsequent change in MMSE scores. Given that patients had semi-annual MMSE assessments while the non-depressed group had annual MMSE assessments, we first fit models for the patient group using the change in

two-year normalized hippocampal volume to predict a six-month change in Mini-Mental State Examination score from two years to two years and six months. Separate models were fit for left and right normalized hippocampal. Age, sex, two-year MMSE score, and change in MADRS score from two years to two years and six months were used as covariates in these models. We then fit similar models for both patients and non-depressed individuals examining the relationship between change in normalized hippocampal volume and subsequent change in MMSE score from year 2 to year 3, with age, sex, two-year MMSE score, and change in MADRS score from two to three years as covariates.

Results

Characteristics of the sample are shown in Table 1. Briefly, compared with the non-depressed group, the depressed group was similar in age, race, and baseline MMSE score. A higher percent of depressives were male, and non-depressed individuals had slightly more education than the depressed group. There were no between-group differences in baseline total cerebral volume or left or right hippocampal volume. In terms of medications, patients were on a variety of antidepressant medications per our treatment algorithm. In addition, five individuals were on cognitive enhancers (either a cholinesterase inhibitor or memantine) at some point during the follow-up period. Medication use did not affect results.

Also shown in Table 1 are calculations of changes in left and right hippocampal volumes and normalized left and right hippocampal volumes, stratified by depression status, which demonstrate that depressed patients had significantly greater reduction in normalized left hippocampal volume. Of note, while the change in left and right hippocampal volumes for the non-depressed group shows an increase, subsequent statistical analyses (not shown) demonstrated that these changes were not significant from zero. Further, when we calculated normalized changes, the differences for the non-depressed group approached zero (0.005 and 0.002 for left and right, respectively). There was no significant relationship between sex and change in hippocampal volume for either the left or right hippocampus.

Regression models for left and right normalized hippocampal volume changes, age, sex and baseline normalized hippocampal volume found a significant association between depressed group status and left normalized hippocampal volume change (Table 2). The finding for right normalized hippocampal volume change and depressed group status was not statistically significant.

We examined change in normalized hippocampal volume and change in cognition as measured by the MMSE. We examined concurrent change in hippocampal measures and change in MMSE over an initial two-year period and conducted a prospective analysis measuring the association of change in hippocampal measures from baseline to two years and subsequent change in MMSE score from Year 2 to Year 2.5. We examined these changes among the entire sample and separately for the depressed and non-depressed groups. Note that the sample sizes are slightly smaller for these analyses owing to missing MMSE scores at different time points for some individuals. As shown in Table 3, we found a significant association between baseline to Year 2 change in normalized hippocampal volume and subsequent change in MMSE score from Year 2 to Year 2.5 for both left and right hippocampal volumes, controlling for the effects of age, sex, and Year 2 MMSE score. That is, reduction in hippocampal volume over two years was associated with an incident decline in MMSE performance from Year 2 to Year 2.5. In data not shown, there were no significant associations for non-depressed individuals, depressed patients, or the combined sample on change in baseline to Year 2 hippocampal volume and subsequent change in MMSE score from Year 2 to Year 3.

In post-hoc analyses, we examined the effect of age of onset (with late onset of depression set at age 60 and above) on hippocampal atrophy (defined as decrease in hippocampal volume from baseline to Year 2). For the right hippocampus, 82.14% of those with late-onset depression (LOD) versus 67.74% of those with early-onset depression (EOD) had hippocampal atrophy ($\chi^2 = 1.9940$, df = 1, p = 0.1579). For the left hippocampus, 67.86% of those with LOD versus 48.39% EOD had hippocampal atrophy ($\chi^2 = 2.9481$, df = 1, p = 0.0860).

In addition, to further explore our finding that two-year change in hippocampal volume was associated with subsequent change in MMSE from Year 2 to Year 2.5 but not with change in MMSE from Year 2 to Year 3, we undertook a series of analyses examining comparing results including and excluding three individuals with missing MMSE data at Year 3. We found that the main variable accounting for the difference was MMSE at Year 3 for both samples. That is, there was no evidence that our finding was influenced by drop-out.

Conclusions

In this study, we report two main findings. First, depressed older adults experience a greater decrease in left normalized hippocampal volume than non-depressed elders. This result remained significant after controlling for the effects of age, sex and baseline left normalized hippocampal volume. For the right hippocampus, the result fell short of significance. Our second finding is that among older depressed patients, reduction in normalized hippocampal volumes from baseline to Year 2 were significantly associated with subsequent decline in MMSE score from Year 2 to Year 2.5.

Our results are consistent with a sizable literature linking neuroimaging hippocampal findings and major depression (29), and a growing literature on late-life depression and the hippocampus (15,30–33). In addition, one prior study of adults with major depression (mean age 46.1) and non-depressed individuals (mean age 43.6) noted a significant difference in three-year change in hippocampal volume, with the depressed group showing greater volume loss (19). Our findings extend prior research on middle aged adults to an older population. They also extend our own research which found that among older depressives, having a small left hippocampal volume at baseline was significantly associated with development of incident dementia (15). We do note a recent study showing that increased depressive symptoms were associated with smaller temporal lobe volumes among older adults, but that depressive symptoms were not associated with hippocampus volumes, and there were no significant effects of depressive symptoms on rates of longitudinal volume decline in temporal regions (34).

A clear understanding of the role of the hippocampus in depression, particularly in late-life depression, remains to be articulated. Some have argued, with supporting evidence, for a stress model of depression (9,19), linking the depression literature to an established body of research associating stress with glucorticoid-induced hippocampal neurotoxicity (35,36). In this model, it has been suggested that glucocorticoid- and stress-related cognitive impairments involving declarative memory may be related to the changes they effect in the hippocampus, whereas the stress-induced catecholamine effects on emotionally laden memories may involve structures such as the amygdala (36).

Previously, we proposed an alternate view to the stress model of depression, namely that hippocampal volume reduction in late life depression may be explained in part by the clinical observation that for many depressed patients, particularly those with late-onset depression, their condition may represent a neurodegenerative disorder manifesting as a neuropsychiatric syndrome that initially presents with depression (15). Unlike the

depression-as-stress model, which would predict hippocampal volume reduction in early-onset depression, the depression-as-late-life-neuropsychiatric-disorder model would suggest that hippocampal volume loss would be more associated with later age of depressive onset. A prior study in geriatric depression found that hippocampal volume reduction was not associated with increased cortisol levels but was significantly correlated with continuing memory deficits at 6 months (37). The authors concluded that, while older depressed subjects may have persisting cognitive impairments associated with hippocampal volume reduction, their findings do not support cortisol-mediated hippocampal neurotoxicity as the major etiological mechanism. Rather, other neurodegenerative or vascular mechanisms might explain their neuroimaging and cognitive results.

Of course, it is quite plausible that some depressed elders (particularly those with early-onset depression) have smaller hippocampal volumes because of glucocorticoid neurotoxicity experienced over repeated episodes, while others (particularly those with late-onset depression), have hippocampal volume loss related to a neurodegenerative disorder. Our finding of a subsequent drop in MMSE score associated with a two-year reduction in hippocampal volume is consistent with the notion that late-life depression may, in some patients, represent a neuropsychiatric disorder with mood and cognitive components. Previously, we found that small left hippocampal volume was significantly associated with later dementia among older depressed patients (15). It will be important in future studies to determine if change in hippocampal volume is associated with incident dementia, particularly Alzheimer's disease.

Alcohol use is also an important consideration when examining depression and cognition in the elderly. Our study focusing on depression in the elderly had an exclusion of current or past alcohol use disorders. However, this exclusion does not preclude new onset of alcoholism. In fact, in data not shown, we found one individual in the depressed sample who developed signs of alcohol abuse during the follow-up period.

One unexpected finding was the significant association in depressives between two-year change in hippocampal volume and subsequent change in MMSE from Year 2 to Year 2.5, which occurred in the absence of a significant association for subsequent change from Year 2 to Year 3. Minor differences in the two samples, including drop-outs did not explain these findings. The 2.5 year time point was the most proximal subsequent MMSE assessment after the two year MRI scan, and we believe that the cognitive effect of two-year change in hippocampal volume might be expected to be greatest during this short time period. As the cognitive assessment moves to the 3-year time point, other additional factors may become more salient in determining MMSE performance, such as changes in depression status, acute stressors, cerebrovascular changes, or progression of underlying neurodegenerative disease. Our post-hoc analyses found that drop-out was an unlikely contributor to the finding.

Similarly unexpected was a lack of significant association between concurrent baseline to 2-year changes in hippocampal volume and MMSE score. One might have expected a significant relationship given the significance of two-year change in hippocampal volume and subsequent MMSE change. Our lack of a finding for concurrent hippocampal volume/MMSE change, at least for analyses including the depressed sample, might be explained by our method of assessing baseline MMSE during an acute depressive episode.

Our study revealed several findings of clinical importance. One is that the two-year MMSE was a strong predictor of subsequent cognitive decline in all of our models. Clinicians caring for older depressed adults who have even a mild degree of cognitive impairment should carefully monitor cognition during follow-up treatment for the depressive disorder. While it would be premature to recommend serial MRI scans in the management of late-life

depression, these results support neuroimaging among older depressed patients with cognitive impairment. In such cases, hippocampal atrophy would be a worrisome clinical prognosticator of further cognitive decline.

As for future research directions, older depressed patients are generally at risk for cognitive decline, and our study helps refine the risk group. Individuals with significant hippocampal volume loss are at greater cognitive risk and could be an excellent group to pursue with interventions to prevent cognitive decline. Studies to determine what constitutes “significant hippocampal volume loss” are needed, but it is clear that older depressed patients with hippocampal volume changes could be considered a prime target for established or novel cognitive interventions.

Our study is not without limitations. While it is among the largest longitudinal MRI studies in late life depression, each group still had fewer than one hundred subjects. Thus, sample size might account for our lack of a significant finding for a group difference for right normalized hippocampal volume change. Another limitation attends to our use of the MMSE to measure cognition. Other measures such as the Modified Mini-Mental State (3MS) examination (38) or a more complete cognitive battery might have been more sensitive to cognitive change. Also, while our results are statistically significant, the associated model R-squares and partial R-squares suggest a small-to-medium effect.

In sum, these findings support continued research into the relationship between the hippocampus and depression, particularly depression in late life. Compared with non-depressed older counterparts, older depressed patients are at higher risk for hippocampal volume loss, and as a consequence, for cognitive decline. Future studies should focus on the underlying pathophysiology linking the hippocampus to depression and cognition in the elderly with particular focus on the interplay between course of depression and course of cognitive performance on hippocampal volume change. Finally, older depressed subjects with hippocampal volume losses may be an important group to target with pharmacological and non-pharmacological cognitive interventions.

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Table 1

Sample characteristics and between-group hippocampal volume changes

	Depressed (N = 90)	Non-depressed (N = 72)	Test statistic, df, p value
Age, years, mean (SD)	69.88 (6.799)	69.44 (6.201)	−0.42, 160, 0.6757
Sex, male, N (%)	38.89 (35)	19.44 (14)	7.1681, 1, 0.0074
Race, White, N (%)	86.67 (78)	88.89 (64)	Fisher's exact
Black, N (%)	6.67 (6)	8.33(6)	Pr <= P: 0.5134
Education, years, mean (SD)	14.34 (2.757)	15.5 (1.627)	3.32, 148, 0.0011
Baseline MADRS, mean (SD)	25.94 (6.895)	---	---
Baseline MMSE, mean (SD)	28.65 (1.567)	28.85 (1.184)	0.90, 154, 0.3676
Baseline total cerebral Volume, ml, mean (SD)	1160.8 (132.34)	1133.8 (112.54)	−1.38, 160, 0.1698
Baseline left hippocampal volume, ml, mean (SD)	2.984 (0.417)	2.950 (0.421)	−0.51, 160, 0.6127
Baseline right hippocampal volume, ml, mean (SD)	3.108 (0.424)	3.089 (0.410)	−0.30, 160, 0.7679
Change in left hippocampal Volume, ml, mean (SD)	0.077 (0.433)	−0.063 (0.424)	−2.06, 160, 0.0406
Change in right hippocampal Volume, ml, mean (SD)	0.077 (0.491)	−0.039 (0.388)	−1.68, 160, 0.0952
Change in normalized left hippocampal volume, mean (SD)	0.0084 (0.037)	−0.005 (0.038)	−2.18, 160, 0.0305
Change in normalized right hippocampal volume, mean (SD)	0.0086 (0.041)	−0.002 (0.034)	−1.82, 160, 0.0707

MMSE = Mini-Mental State Examination score

Change in MRI variables indicates Baseline – Year 2 values; thus, positive values indicate volume loss.

Table 2

Models examining group differences in left and right normalized hippocampal volume changes controlling for age, sex and baseline normalized hippocampal volume

Model of change in left normalized hippocampal volume[a]	**Estimate of regression coefficient (SE)**	**T statistic, P value**
Age	0.0006 (0.0004)	1.35, 0.1797
Sex	0.0092 (0.0062)	1.49, 0.1390
Baseline left normalized hippocampal volume	0.4350 (0.0718)	6.06, <0.0001
Group (Non-depressed vs depressed)[b]	0.0118 (0.0055)	2.14, 0.0339
Model of change in right normalized hippocampal volume[c]	Estimate of regression coefficient (SE)	T statistic, P value
Age	0.0008 (0.0004)	1.92, 0.0567
Sex	0.0095 (0.0062)	1.54, 0.1255
Baseline right normalized hippocampal volume	0.5010 (0.0782)	6.41, <0.0001
Group (Non-depressed vs depressed)[d]	0.0105 (0.0055)	1.91, 0.0578

[a] Model R-squared = 0.2155

[b] partial R-squared = 0.0284

[c] Model R-squared = 0.2288

[d] partial R-squared = 0.0227

df = 157 for each T test

Table 3

Models examining the effect of baseline to Year 2 change in left and right normalized hippocampal volume change on change in Mini-Mental State Examination (MMSE) scores from Year 2 to Year 2.5 in depressed patients, controlling for age, sex, and Year 2 MMSE score

Model of change in MMSE score[a]	**Estimate of regression coefficient (SE)**	**T statistic, P value**
Age	−0.0371 (0.0314)	−1.18, 0.2423
Sex	−0.7907 (0.3900)	−2.03, 0.0467
Year 2 MMSE score	0.2830 (0.0914)	3.10, 0.0029
Change in Year 2 to 2.5 MADRS score	−0.0700 (0.02332)	−3.00, 0.0038
Change in left normalized hippocampal volume[b]	14.7609 (5.2596)	2.81, 0.0066
Model of change in MMSE score[c]	Estimate of regression coefficient (SE)	T statistic, P value
Age	−0.0396 (0.0322)	−1.23, 0.2240
Sex	−0.8722 (0.3956)	−2.20, 0.0309
Year 2 MMSE score	0.2712 (0.0925)	2.93, 0.0046
Change in Year 2 to 2.5 MADRS score	−0.0665 (0.0236)	−2.81, 0.0065
Change in right normalized hippocampal volume[d]	11.3650 (4.7380)	2.40, 0.0193

[a] Model R-squared = 0.2988

[b] partial R-squared = 0.0801

[c] Model R-squared = 0.2781

[d] partial R-squared = 0.1066

df = 66 for each T test