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Depressive Symptoms and Small Hippocampal Volume Accelerate the Progression to Dementia from Mild Cognitive Impairment

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Abstract. Previous studies have highlighted that decreased hippocampal volume, an early neural correlate of dementia, is commonly observed in patients with mild cognitive impairment (MCI). However, it is unclear whether neurodegenerative and resultant clinical trajectories are accelerated in MCI patients with concomitant depressive symptoms, leading to a faster conversion to dementia stages than those who are not depressed. No longitudinal study has investigated whether depressed amnestic MCI (DEP+aMCI) patients show an earlier onset of progression to dementia than non-depressed amnestic MCI (DEP-aMCI) patients and whether progressive hippocampal volume reductions are related in the conversion process. Using data from Alzheimer's Disease Neuroimaging Initiative, we examined 2-year follow-up data from 38 DEP+aMCI patients and 38 matched DEP-aMCI patients and compared their ages of conversion from aMCI to AD and trajectories of progressive hippocampal volume changes. DEP+ and DEP- patients were defined as having baseline Geriatric Depression Scale scores of 5 or above and 0, respectively. DEP+ converters showed earlier ages of conversion to dementia ($p = 0.009$) and greater left hippocampal volume loss than both DEP- converters and DEP+ non-converters over the 2-year period ($p = 0.003$, $p = 0.001$, respectively). These findings could not be explained by changes in total brain volume, differences in their clinical symptoms of dementia, daily functioning, or

[1]Some data used in preparation of this article were obtained from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database (http://adni.loni.usc.edu). As such, the investigators within the ADNI contributed to the design and implementation of ADNI and/or provided data but did not participate in analysis or writing of this report. A complete listing of ADNI investigators can be found at: http://adni.loni.usc.edu/wp-content/uploads/how_to_apply/ADNI_Acknowledgement_List.pdf

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apolipoprotein E4 genotypes. No difference in conversion rate to dementia or progressive hippocampal volume change was found between DEP+ patients and DEP-patients, which suggested depressive symptoms themselves may not lead to progression of dementia from MCI. In conclusion, there is a synergistic effect of depressive symptoms and smaller left hippocampal volume in MCI patients that accelerates conversion to dementia.

Keyword: Dementia, depression, hippocampus, mild cognitive impairment

INTRODUCTION

Patients with mild cognitive impairment (MCI) have a high risk of developing dementia, with conversion rates ranging from 35% over a 3-year period [1] to as high as 80% over a 6-year period [2, 3]. Among several modifiable Alzheimer's disease (AD) risk factors, depression contributes to the second largest proportion of AD cases followed by physical inactivity [4]. Several longitudinal studies suggest that depressive symptoms in patients with MCI are linked to an increased risk of developing dementia [5, 6]. Anatomically, smaller hippocampal volume, an early sign of AD pathology [7], is associated with an increased annual conversion rate from MCI to AD [8–10]. It has been suggested that the association between hippocampal atrophy and dementia may, in part, be mediated by depression [11]. In support of this, a review investigating hippocampal volume measured with magnetic resonance imaging (MRI) and depression revealed that depressed patients had greater bilateral hippocampal volume reductions in comparison to controls [12]. Another longitudinal study with 2 years follow-up demonstrated that depressed patients showed greater left hippocampal reductions than non-depressed individuals [13]. In addition, smaller hippocampal volumes were observed in adults with higher depressive symptom severity [14]. Furthermore, an MRI study of 152 depressed patients showed that depression severity predicted smaller hippocampal volume [15]. Thus, hippocampal atrophy may be a converging point of depression and progression to dementia in patients with MCI.

A longitudinal study found that recurrent depressive episodes in late-life can almost double the incidence of dementia [16]. Furthermore, there are several studies reporting that late-life depression is associated with a two- to five-fold elevated risk of dementia [17–19]. However, the association between depression and conversion to dementia is debatable. In one study, Rozzini et al. found fewer depressed MCI patients ($n = 8$ out of 22 depressed patients) converted to dementia in comparison to non-depressed MCI patients ($n = 17$ out of 24 non-depressed patients) [20]. Similarly, in a longitudinal study of Italian depressed patients with MCI ($n = 139$), depressive symptoms were not associated with an increased rate of conversion from MCI to dementia [21]. These contradictory findings suggest that depression itself may not be a predictor of dementia.

To our knowledge, this is the first study to compare the time of conversion to dementia and pattern of hippocampal volume loss between matched depressed amnestic MCI (DEP+aMCI) and non-depressed amnestic MCI (DEP-aMCI) patients at baseline. Based on the previous findings, we had three *a priori* hypotheses. First, DEP+ patients will have more progressive bilateral hippocampal volume loss and a higher conversion rate to dementia than DEP- patients. Second, DEP+ patients will have a faster progression to dementia than DEP- patients. Third, DEP+ aMCI patients who subsequently convert to dementia will show an accelerated bilateral hippocampal volume loss over time than DEP- aMCI patients who later convert.

MATERIALS AND METHODS

Participants and assessments

The entire database was downloaded from Alzheimer's Disease Neuroimaging Initiative (ADNI)-1, ADNI-2, and ADNI Grand Opportunity (ADNI-GO) databases on March 3rd, 2015 [45]. Briefly, in ADNI-1, 800 participants, including controls, patients with aMCI and patients with mild AD were recruited from 50 different sites in Canada and the United States. Each subject was either an English or Spanish speaker, aged between 55 and 90 years, and had a study partner able to provide an independent evaluation of functioning [46]. The key eligibility criteria for aMCI participants were: a Mini–Mental State Examination (MMSE) score [47] of equal or higher than 24 of 30, a memory complaint, having objective memory loss measured by education adjusted scores on the Wechsler Memory Scale Logical Memory II [48], a clinical dementia rating (CDR) score [49] of 0.5, an absence of significant levels of impairment in other cognitive domains, essentially preserved activities of daily living, and

an absence of dementia. In ADNI-2, 100 early-stage aMCI patients and 150 late-stage aMCI patients were recruited from 55 different sites from Canada and the United States [50]. In ADNI-GO, 200 participants, including patients with mild AD and early aMCI were recruited [51]. Eligibility criteria in ADNI-2 and ADNI-GO were identical to those in ADNI. Scores on the Functional activities questionnaire (FAQ) [52] and Geriatric Depression Scale (GDS) [53] were obtained from ADNI-1, ADNI-2, and ADNI-GO. Data for antidepressant usage was collected from concurrent medication log database from ADNI-1, ADNI-2, and ADNI-GO. The presence of a lifetime history of depression (LMD) was determined using patients' medical history from ADNI-1, ADNI-GO, and ADNI-2 [22]. For our current study, we only included patients with aMCI who had baseline T1-weighted MRI scan with either 1.5 or 3 Tesla unit and at least one MRI scan after 1 year and/or 2 years after the baseline scans.

DEP+ patients were matched to DEP- patients at baseline based on discrete factors such as gender, apolipoprotein E4 (ApoE4) genotype, race, ethnicity, and marital status, as well as continuous factors such as age, education years, and scores on the MMSE.

Depression at baseline status

DEP+ status was determined by depressive symptoms assessed by GDS score of 5 or above at baseline (first visit or screening visit) according to ADNI database. Matched DEP- patients were defined using a GDS score of 0 at baseline in addition to similar demographic and clinical profile such as age, gender, race, ethnicity, ApoE4 genotype, and cognition score. Similarly, the final depression status was determined by using the patients' GDS score at their final clinical assessments with a cut-off GDS score of 5 or above.

Persistently depressed and never depressed

Patients with persistent depressive symptoms were those who had GDS scores of 5 or above both in their baseline and final clinical assessments. Never depressed patients were those who had GDS scores of less than 5 in both their baseline and final clinical assessments.

Conversion to dementia

Converters to dementia were defined with patients' diagnostic status of dementia or MCI to dementia at the final time point in the study. On the other hand, patients were defined as non-converters to dementia when their final diagnostic status remained as aMCI. Patients who did not meet any of aforementioned conversion to dementia criteria were not included in the analysis. Two reverters to controls from DEP+ group and three reverters to controls from DEP- group were excluded because the sample size was too small to be in a separate group for sub-analysis.

Imaging analysis

Hippocampal volume analysis

Using the Multiple Automatically Generated Templates (MAGeT Brain) algorithm [23, 24], fully automated segmentation of the hippocampal subfields was carried out. MAGeT Brain allows a modified multi-atlas segmentation that utilizes high resolution manually segmented MRI-labeled atlases as input files. In our study, the hippocampal subfields atlas was used [25]. Manually delineated hippocampus atlases are propagated through image registration to template images, which are the subset MRI scans from each group that serve as the best representatives of the group. Literature using MAGet Brain suggests that the use of 21 template images in the template library is optimal [23]. Because of the different field strengths of T1 weighted images from the ADNI database, 21 template images were selected from four different groups: DEP+ patients with 3.0 Tesla images, DEP+ patients with 1.5 Tesla images, DEP- patients with 3.0 Tesla images and DEP- patients with 1.5 Tesla images. Each image of the templates was segmented through nonlinear atlas-to-template registration and consequently by label propagation, which produces a unique definition of the subfields for each of the templates. The segmentations through the template images yielded 21 labels for each subject. Consequently, the labels were fused through majority voting as a final segmentation process. For the nonlinear registration, Advanced Normalization Tools (ANTS) was carried out (https://github.com/vfonov/mincANTS). The output files produced volumes from five hippocampal subfields from left and right side. Left and right hippocampus volume was equivalent to the sum of labeled left and right cornus ammonis (CA) 1, CA2/CA3, CA4/dentate gyrus, stratum radiatum/stratum lacunosum/stratum moleculare, and subiculum.

Voxel-based morphometry

All the T1 scans were analyzed using the voxel-based morphometry (VBM)-8 toolbox (http://www.

neuro.uni-jena.de/vbm/) using Statistical Parametric Mapping 8.0 (SPM8 - http://www.fil.ion.ucl.ac.uk/spm/) running on Matlab 6.5. The detailed instructions of analysis are described here (http://www.fil.ion.ucl.ac.uk/~john/misc/VBMclass10.pdf). VBM with the DARTEL method was performed to obtain total intracranial volume (TIV). TIV was considered to be the sum of grey matter, white matter, and cerebrospinal fluid volume. Total brain volume (TBV) was used as one of the covariates in the later mentioned statistical analysis. TBV was equivalent to the sum of grey matter and white matter.

Statistical analysis

Baseline and final demographic and clinical profiles were compared between groups using independent *t*-tests and χ^2-tests for continuous and discrete variables, respectively.

A mixed-effect model for repeated measurements (MMRM) analysis was employed for the comparisons of hippocampal volume changes over 2 years. The MMRM model included left and right hippocampal volume separately as dependent variables and the different group (DEP+ patients versus DEP- patients, DEP+ converters versus DEP- converters and DEP+ converters versus DEP+ non-converters), year, and hippocampal volume-by-year interaction as fixed effects. The covariates were demographic and clinical factors that differed between groups, baseline hippocampal volume, total brain volume, and field strength of scans. The statistical tests were performed using Statistical Package for the Social Sciences Version 21.0 (IBM, New York, US). Statistical significance indicated $p < 0.05$.

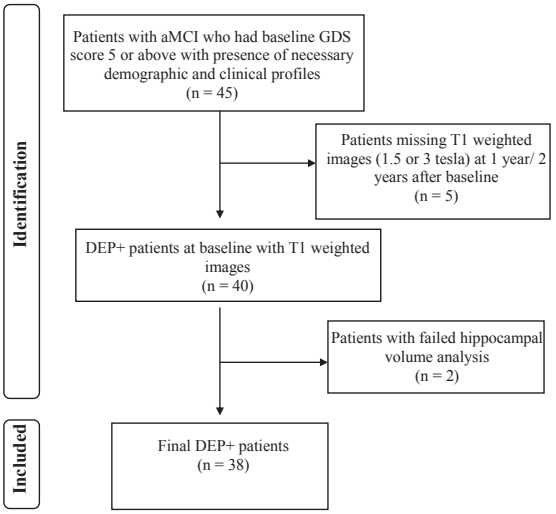
RESULTS

Depressed patients versus non-depressed patients

Baseline demographic and clinical profile

There were 45 patients with aMCI who had a GDS score 5 or above. Five DEP+ patients were excluded, based on the exclusion criteria of missing T1-weighted MRI scan of either 1.5 or 3 Tesla units from one year and/or two years after the baseline scans. Two DEP+ patients were excluded because their hippocampal volume analysis failed due to the presence of artifacts. As a result, 38 depressed patients and 38 matched non-depressed patients were included in this study (Fig. 1).

There were no differences in clinical and demographic characteristics between DEP+ patients and DEP- patients ($n = 38$ each), except for CDR and FAQ scores ($p = 0.01$ and $p = 0.03$, respectively) (Table 1a). No difference was found in the dementia conversion rate between DEP+ patients and DEP- patients (21.05% versus 26.32%, $p = 0.59$).



aMCI, amnestic mild cognitive impairment; GDS, the Geriatric Depression Scale score

Fig. 1. Flow chart showing the selection of depressed at baseline (DEP+) aMCI patients aMCI, amnestic mild cognitive impairment; GDS, the Geriatric Depression Scale score.

Longitudinal hippocampal volume change

There was no difference in left ($p = 0.30$) and right hippocampal volume change ($p = 0.62$) between DEP+ patients and DEP- patients (Table 2a).

Depressed converters versus depressed non-converters

Baseline demographic and clinical profile

DEP+ converters to dementia ($n = 8$) and DEP+ non-converters ($n = 28$) only differed in CDR score, FAQ score, and apoE4 genotype ($p < 0.05, p < 0.01, p < 0.01$, respectively) (Table 1b).

Longitudinal hippocampal volume loss

There was a difference in longitudinal change in left hippocampal volume over 2 years between DEP+ converters to dementia and DEP+ non-converters ($p < 0.01$) (Table 2b). Figure 2 illustrates the change in the hippocampal volumes between the two groups. Additionally, a trend-level change in right hippocampal volume ($p = 0.06$) was found between the groups.

Table 1
Comparison of demographic and clinical variables between different cohort groups. a) Non-depressed versus depressed; b) Depressed non-converters to dementia versus depressed converters; c) Non-depressed converters to dementia versus depressed converters to dementia. *indicates statistical significance $p < 0.05$ and **indicates statistical significance $p < 0.01$

a)	DEP– ($n = 38$)		DEP+ ($n = 38$)			
	Baseline	Final	Baseline	Final		
Demographic variables	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	Baseline p-value	Final p-value
Age, years	74.5 (7.3)	76.2 (7.3)	73.0 (8.2)	74.5 (8.1)	0.42	0.34
Education years	16.3 (2.7)		16.0 (2.7)		0.64	
MMSE score	27.4 (1.9)	26.2 (3.9)	27.6 (1.9)	26.0 (5.0)	0.63	0.86
CDR score	1.2 (0.7)	2.1 (2.3)	1.7 (0.9)	2.2 (1.7)	**0.01***	0.80
Modified Hachinski	0.5 (0.6)	N/A	0.7 (0.8)	N/A	0.21	N/A
GDS score	0 (0)	1.0 (1.1)	5.1 (0.3)	5.3 (3.4)	–	–
FAQ score	2.4 (3.2)	5.5 (6.7)	4.4 (4.6)	5.5 (7.1)	**0.03***	0.99
TIV	1585.5 (156.7)	1580.6 (161.3)	1545.1 (173.4)	1549.9 (176.7)	0.29	0.43
Demographic variables	Number (frequency [%])	Number (frequency [%])	χ^2 (two-tailed)			
CVD+	21 (55.3)	25 (65.8)	0.48			
Psychiatric+	13 (34.2)	22(57.9)	0.07			
Neurological+	8 (21.1)	15 (39.5)	0.13			
Alcohol abuse+	2 (5.3)	5 (13.2)	0.43			
Drug abuse+	1 (2.6)	0 (0)	1.00			
Smoking+	15 (39.4)	17 (44.7)	0.82			
White	35 (92.1)	35 (92.1)	1.00			
Hispanic/Latino	1 (2.6)	1 (2.6)	0.6			
Married	27 (71.1)	28 (73.7)	0.98			
Females	21(55.3)	22(57.9)	1.00			
0 ApoE4	20 (52.6)	19 (50.0)	0.97			
1 ApoE4	16 (42.1)	17 (44.7)	0.97			
2 ApoE4	2 (5.3)	2 (5.3)	0.97			
Antidepressant	14 (36.8)	20 (52.6)	0.25			
LMD+	1 (2.6)	6 (15.8)	0.11			

Depressed at baseline aMCI patients and non-depressed at baseline aMCI patients were matched in all the demographic variables listed above, but there was significant difference in CDR and FAQ score between two groups (t-test, two-tailed for the continuous demographic variables; χ^2-test, two-tailed for the discrete demographic variables).

b)	DEP + Nconv ($n = 28$)		DEP + Conv ($n = 8$)			
	Baseline	Final	Baseline	Final		
Demographic variables	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	Baseline p-value	Final p-value
Age, years	74.6 (8.4)	76.1 (8.2)	69.9 (6.6)	71.5 (6.8)	0.42	0.13
Education years	17.2 (1.8)		17.4 (1.7)		0.64	
MMSE score	27.3 (1.9)	27.2 (2.6)	27.9 (1.9)	26.0 (1.3)	0.63	0.10
CDR score	1.5 (1.0)	1.7 (1.0)	2.1 (0.6)	4.7 (1.1)	**0.05***	**0.00****
Modified Hachinski	0.7 (0.8)	N/A	0.6 (1.1)	N/A	0.21	N/A
GDS score	5.1 (0.3)	5.6 (3.6)	5.3 (0.5)	5.4 (2.1)	0.43	0.79
FAQ score	2.8 (2.7)	2.8 (4.1)	10.4 (5.6)	15.0 (7.9)	**0.01****	**0.00****
TIV	1518.3 (145.0)	1525.9 (144.1)	1632.4 (255.1)	1659.4 (257.0)	0.29	0.20
Demographic variables	Number (frequency [%])	Number (frequency [%])	χ^2 (two-tailed)			
CVD+	17 (17.9)	5 (62.5)	1.00			
Psychiatric+	16 (57.1)	4(50.0)	1.00			
Neurological+	11 (39.3)	3(37.5)	1.00			
Alcohol abuse+	3 (10.7)	1(12.5)	1.00			
Drug abuse+	0 (0)	0(0)	1.00			

(*Continued*)

Table 1
(*Continued*)

Demographic variables	Number (frequency [%])	Number (frequency [%])	χ^2 (two-tailed)
Smoking+	11 (39.3)	5 (62.5)	0.42
White	25 (89.3)	8 (100.0)	0.82
Hispanic/Latino	1 (3.6)	0 (0)	1.00
Married	20 (71.4)	6 (75.0)	0.23
Females	16(57.1)	4(50.0)	1.00
0 ApoE4	18 (64.3)	0 (0)	**0.00****
1 ApoE4	9 (32.1)	7 (87.5)	**0.00****
2 ApoE4	1 (3.6)	1 (12.5)	**0.00****
Antidepressant	13(46.4)	5(62.5)	0.42
LMD+	4 (14.3)	1 (12.5)	1.00

c)	DEP - Conv ($n = 10$)		DEP + Conv ($n = 8$)			
	Baseline	Final	Baseline	Final		
Demographic variables	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	Baseline p-value	Final p-value
Conversion age		80.0 (4.2)		71.3 (7.0)		**0.01****
Age, years	78.6 (4.3)	80.4 (4.4)	69.9 (6.6)	71.5 (6.8)	**0.01****	**0.01****
Education years	15.7 (2.9)		17.4 (1.7)		0.33	
MMSE score	25.9 (1.5)	22.7 (4.9)	27.9 (1.9)	24.9 (4.1)	**0.03***	0.32
CDR score	1.5 (1.0)	5.0 (2.3)	2.1 (0.6)	4.7 (1.1)	0.13	0.71
Modified Hachinski	0.7 (0.5)	N/A	0.6 (1.1)	N/A	0.86	N/A
GDS score	0 (0)	1.1 (0.9)	5.3 (0.5)	5.4 (2.1)	**0.00****	**0.00****
FAQ score	3.7 (4.6)	12.6 (8.3)	10.4 (5.6)	15.0 (7.9)	**0.02***	0.54
TIV	1592.5 (164.2)	1597.5 (174.4)	1632.4 (255.1)	1659.4 (257.0)	0.71	0.57
Demographic variables	Number (frequency [%])	Number (frequency [%])	χ^2 (two-tailed)			
CVD+	8 (80.0)	5 (62.5)	0.61			
Psychiatric+	3 (30.0)	4 (50.0)	0.63			
Neurological+	2 (20.0)	3 (37.5)	0.61			
Alcohol abuse+	0 (0)	1 (12.5)	0.44			
Drug abuse+	0 (0)	0 (0)	–			
Smoking+	4 (40.0)	5 (62.5)	0.64			
White	9 (90.0)	8 (100.0)	1.00			
Hispanic/Latino	1 (10.0)	0 (0)	1.00			
Married	7 (70.0)	6 (75.0)	0.53			
Females	6 (60.0)	4 (50.0)	1.00			
0 ApoE4	5 (50.0)	0 (0)	0.06			
1 ApoE4	4 (40.0)	7 (87.5)	0.06			
2 ApoE4	1 (10.0)	1 (12.5)	0.06			
Antidepressant	4 (40.0)	4 (50.0)	1.00			
LMD+	0 (0)	1 (12.5)	0.44			

There was significant difference in age, baseline CDR, MMSE, and GDS score between two groups (t-test, two-tailed for the continuous demographic variables; χ^2-test, two-tailed for the discrete demographic variables). Alcohol abuse+, presence of history of alcohol abuse; aMCI, amnestic mild cognitive impairment; Antidepressant, patients who were taking antidepressant within 2 years of follow-up period; ApoE4, apolipoprotein E4; 0 ApoE4, number of 0 ApoE4 allele holders; 1 ApoE4, number of 1 ApoE4 allele holders; 2 ApoE4, number of 2 ApoE4 alleles holders; CDR, the Clinical Dementia Rating; CVD+, presence of history of cardiovascular disease; DEP-, Non-depressed at baseline aMCI patients; DEP-Conv, Non-depressed converters to dementia; DEP+, Depressed at baseline aMCI patients; DEP+Conv, Depressed converters to dementia; DEP+Nconv, Depressed non-converters to dementia; Drug abuse+, presence of history of drug abuse; FAQ, the Functional Activities Questionnaire score; GDS, the Geriatric Depression Scale score; LMD+, presence of lifetime history of depression; MMSE, the Mini-Mental State Examination score; Modified Hachinski, the Modified Hachinski Ischemic scale score; Neurological+, presence of history of neurological disorder; Psychiatric+, presence of history of psychiatric disorder; Smoking+, presence of history of smoking; TIV, total intracranial volume; χ^2-test, Chi-squared test/Fischer's Exact test.

Table 2
Baseline and year 2 hippocampal volume measures in a) depressed at baseline versus non-depressed at baseline; b) depressed at baseline non-converters to dementia versus depressed at baseline converters; c) non-depressed at baseline converters to dementia versus depressed at baseline converters. **indicates statistical significance $p < 0.01$

a) Variables	DEP-aMCI ($n = 38$)	DEP+aMCI ($n = 38$)	p-value
Left hippocampus ($mm^{3)}$			
Baseline	2271.47	2243.68	
Year 1	2263.51	2207.43	0.30
Year 2	2243.04	2207.47	
Right hippocampus ($mm^{3)}$			
Baseline	2293.86	2220.07	
Year 1	2273.18	2180.42	0.62
Year 2	2265.26	2181.54	
b) Variables	DEP+aMCI non-converters ($n = 28$)	DEP+aMCI converters ($n = 8$)	p-value
Left hippocampus ($mm^{3)}$			
Baseline	2257.32	2240.60	
Year 1	2232.38	2181.93	**0.00****
Year 2	2266.14	2106.57	
Right hippocampus ($mm^{3)}$			
Baseline	2247.99	2167.73	
Year 1	2215.81	2151.44	0.06
Year 2	2230.16	2077.53	
c) Variables	DEP-aMCI converters ($n = 10$)	DEP+aMCI converters ($n = 8$)	p-value
Left hippocampus ($mm^{3)}$			
Baseline	2089.59	2240.60	
Year 1	2076.69	2182.00	**0.00****
Year 2	2069.41	2107.31	
Right hippocampus ($mm^{3)}$			
Baseline	2089.75	2167.73	
Year 1	2059.19	2151.44	0.11
Year 2	2057.85	2077.94	

There is significant difference in left hippocampal volume change and trend-level difference in right hippocampal volume change between depressed at baseline converters to dementia and depressed at baseline non-converters, after controlling for the field strength of images, baseline hippocampal volume, total brain volume, baseline CDR score, FAQ score and apoE4 protein genotypes. There is significant difference in left hippocampal volume change between depressed converters to dementia and non-depressed converters to dementia, after controlling for the field strength of images, baseline hippocampal volume, total brain volume, baseline age, baseline MMSE score and baseline FAQ score. There is no difference in hippocampal volume change between depressed at baseline patients and non-depressed patients at baseline, after controlling for the field strength of images, baseline hippocampal volume, total brain volume, baseline CDR and FAQ score. aMCI, amnestic mild cognitive impairment; ApoE4, apolipoprotein E4; CDR, the Clinical Dementia Rating; FAQ, the Functional Activities Questionnaire score; LMD+, presence of lifetime history of depression; MMSE, the Mini-Mental State Examination score.

Depressed converters versus non-depressed converters

Baseline demographic and clinical profile

DEP+ converters ($n = 8$) and DEP- converters ($n = 10$) only differed in age, baseline MMSE score, FAQ score, and GDS score ($p < 0.01$, $p = 0.03$, $p = 0.02$ and $p < 0.01$, respectively) (Table 1c). The age of conversion to dementia was lower in DEP+ converters (mean = 71.28) in comparison to DEP- converters (mean = 80.02) ($p < 0.01$).

Longitudinal hippocampal volume loss

There was a significant difference in longitudinal change in left hippocampal volume over 2 years between DEP+ converters and DEP- converters ($p < 0.01$) (Table 2c). However, there was no difference in right hippocampal volume change between

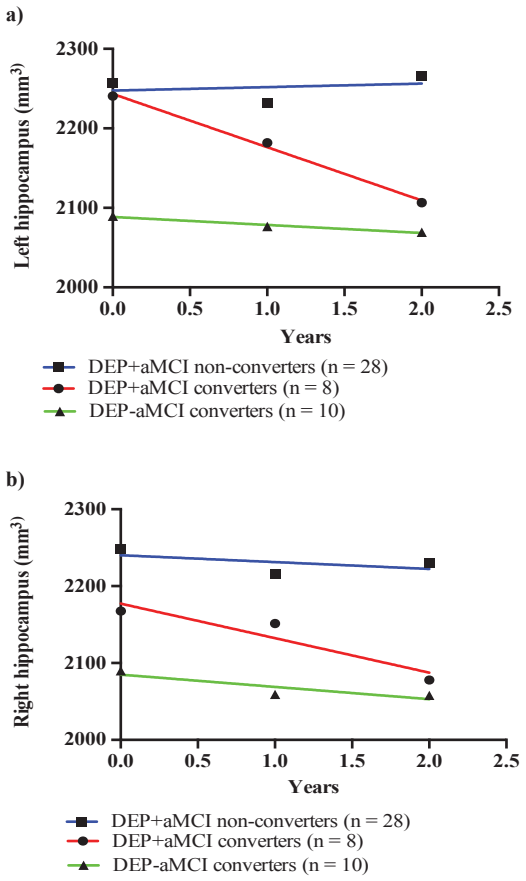


Fig. 2. Graphs showing the changes in the a) left hippocampal volume and b) right hippocampal volume over 2 years period among depressed at baseline converters to dementia, depressed at baseline non-converters and non-depressed at baseline converters. a) and b) are showing left hippocampal volumes and right hippocampal volumes at baseline and year 2, respectively. These figures are showing the estimated marginal means of volumes at each time point.

the groups ($p = 0.11$). Figure 2 displays the change in hippocampal volumes between the two groups.

Persistently depressed versus non-depressed

Demographic and clinical profile

Persistently depressed MCI patients ($n = 23$) non-depressed MCI patients ($n = 37$) only differed in GDS score, CDR score, FAQ score, and history of neurological disorder ($p < 0.01$, $p = 0.03$, $p < 0.05$ and $p = 0.02$, respectively) (Supplementary Table 1a).

Longitudinal hippocampal volume loss

No difference was found in left ($p = 0.12$) and right hippocampal volume ($p = 0.77$) change over 2-year period, after controlling for field strength of scans, baseline hippocampal volume, and clinical variables that differed between groups (Supplementary Table 1b).

DISCUSSION

This is the first study to examine the age of conversion to dementia between DEP+aMCI and DEP-aMCI patients and whether progressive hippocampal volume reductions are related in the conversion process. As predicted, we observed that DEP+ patients showed earlier onset of progression to dementia than DEP- patients. Also similar to our hypothesis, DEP+ patients who converted to dementia revealed greater volume loss in the left hippocampus over two years in comparison to DEP+ non-converters and DEP- converters. Our results are consistent with a recent finding showing that MCI patients with depressive symptoms converted more rapidly to AD than MCI patients without depression [26]. Notably, controlling for TBV revealed that changes in hippocampal volume over time were not affected by changes in the total brain volume. Therefore, these changes seem to be region-specific, rather than related to global cortical atrophy.

However, contrary to our first hypothesis, we did not observe that DEP+ patients had an accelerated rate of hippocampal volume change over 2 years in comparison to DEP- patients. This finding is keeping in line with previous studies, including a meta-analysis, which have reported no difference in hippocampal volume change between depressed and non-depressed patients [27–29], although several studies have noted an association between depression and smaller hippocampal volume [30, 31]. There are several explanations for the similarity in conversion rate to dementia and progressive hippocampal volume changes between the DEP+ and DEP- group. First, heterogeneity exists within the illness itself, including the onset and duration of depressive symptoms. For example, we found that only one out of 38 DEP- patients and 23 out of 38 DEP+ patients still had GDS scores of 5 or above at their final clinical assessments, demonstrating fluctuations in illness presentation. To address this, we compared the difference in hippocampal volume changes between persistently depressed and never depressed patients in order to increase the specificity of depression criteria. However, no differences were found between the groups. There was also no difference in conversion rate to dementia between persistently depressed and never depressed patients ($p = 0.56$, data not shown). Thus, findings from our longitudinal study reinforce the

hypothesis that depressive symptoms do not independently contribute to progressive hippocampal volume reductions and do not increase the risk of developing dementia.

Importantly, there are studies reporting that MCI patients who carry ApoE4 alleles are more likely to convert to dementia than non-carriers [32]. Our demographic and clinical profiles showed that all DEP+ converters had either one or two ApoE4 alleles, whereas more than 50% of non-converters did not carry any ApoE4 allele, supporting the role ApoE4 carrier status in developing dementia. Furthermore, DEP+ converters showed higher severity of dementia symptoms at baseline and final assessment and greater functioning impairment in comparison to DEP+ non-converters (Table 1b). This finding is consistent with the results from a longitudinal study that emphasized conversion to dementia was driven strongly by a sharp decline in functional ability [33]. However, the differences in ApoE4 genotypes, symptoms of dementia and functional deficits between DEP+ converters and DEP+ non-converters did not account for the accelerated hippocampal volume loss in converters.

The MMRM result between DEP+ converters and DEP+ non-converters, controlling for CDR score, FAQ score, ApoE4 genotype, baseline hippocampal volume, total brain volume, and field strength of scans, highlights that differences in symptoms of dementia, functional deficits, and ApoE4 genotypes do not account for the accelerated hippocampal volume loss in converters. Furthermore, depressed patients showed more severe symptoms of dementia at baseline in comparison to matched non-depressed patients. Mounting evidence supports that elderly individuals with depressive symptoms are more likely to develop dementia than those without depressive symptoms, thus more likely to have higher symptoms of dementia [4, 34, 35].

Additionally, it is unlikely that smaller left hippocampal volume in DEP+ converters was solely due to difference in depressive symptoms between DEP+ converters and non-converters. There was no difference in their baseline GDS scores and their final GDS scores between the groups (Table 1b). Based on all these aforementioned findings, we state that rather than depressive symptoms alone, the synergic influence of depressive symptoms and left hippocampal volume reduction may contribute to the accelerated progressions to dementia.

We also observed a difference in changes in hippocampal volume between DEP+ converters and DEP+ non-converters, and between DEP+ converters and DEP- converters, within the left hippocampus. These findings are supported by the evidence showing that volumetric reduction in patients with MCI and dementia is more prominent in the left hippocampus than the right hippocampus [36, 37]. However, there are mixed results supporting the association between depression and the side of hippocampus with volume reduction (i.e., bilateral bilateral [38, 39], left [40, 41], and right [42]. One meta-analysis revealed that depression was associated with bilateral hippocampal volume, but was more pronounced in the right than the left [43]. This meta-analysis also emphasized the heterogeneities within analyzed studies, such as demographic and clinical differences among patients, may account for these different results.

Notably, there are several limitations in this study. First, the sample size is small, especially considering those who converted to dementia. We employed criteria of GDS scores of 5 or above to clearly define the presence of depression. Increasing the sample size by lowering the GDS score cut-off for the depression criteria would reduce the specificity for truly depressed patients. Despite the small sample size, the DEP+ and DEP- group were matched on demographic and clinical characteristics that may influence the hippocampal volume, including age, ApoE4 protein genotype, cognition, and antidepressant medications. Second, the follow-up duration was 2 years, which may be too short to see large changes in the hippocampal volume. A longer-term follow-up study is required to confirm our finding of progressive left hippocampal volume reduction in association with accelerated conversion to dementia. Third, our findings do not imply the causality between the depressive symptoms and hippocampal volume reductions from this study. Future studies should investigate the causal relationship between depressive symptoms and hippocampal volume. Fourth, patients' conversion status was determined using their final diagnostic status, either 1 year or 2 years after baseline. The conversion rate may be more precisely measured if all patients were assessed 2 years after baseline. Fifth, GDS score is a self-report assessment of depressive symptoms; therefore, reporting may be influenced by patients' cognitive abilities and awareness of their own clinical symptoms. This was partially addressed by matching the DEP+ and DEP- groups according to their cognition score. Sixth, in this manuscript we focused on the hippocampus as a priori region. Although progressive hippocampal volume loss was not explained by changes in total brain volume, future studies should focus on atrophy within

other cortical regions, including cingulate and frontal, which are highly implicated with depression. Seventh, we did not assess the progressive hippocampal volume changes in patients who reverted back to MCI due to their small sample size ($n = 5$). Future studies should investigate whether there is a different pattern of hippocampal volume changes in converters to controls. According to the diagnostic criteria of mild behavioral impairment, other affective deregulations, such as anxiety and delusion, are very common in patients with predementia syndromes [44]. Future studies are needed to examine the synergic influence between cortical atrophy and other neuropsychiatric symptoms on the progression to dementia.

In conclusion, this is the first longitudinal analysis to demonstrate that DEP+ patients convert to dementia at earlier ages in comparison to DEP- patients, and that DEP+ converters to dementia show progressive left hippocampal volume reduction over a 2-year period. There was no difference in the hippocampal volume change between DEP+ patients and DEP- patients, suggesting that depression itself may not be sufficient to accelerate conversion to dementia. Together, these findings suggest that there is a synergistic effect of depression and smaller left hippocampal volume in MCI patients that promotes earlier conversion to dementia. Future longer-term prospective studies with larger sample sizes should be conducted to replicate our results.

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The ADNI was launched in 2003 by the National Institute on Aging (NIA), the National Institute of Biomedical Imaging and Bioengineering (NIBIB), the Food and Drug Administration (FDA), private pharmaceutical companies and non-profit organizations, as a $60 million, 5-year public private partnership. The primary goal of ADNI has been to test whether serial magnetic resonance imaging (MRI), positron emission tomography (PET), other biological markers, and clinical and neuropsychological assessment can be combined to measure the progression of mild cognitive impairment (MCI) and early Alzheimer's disease (AD).

Determination of sensitive and specific markers of very early AD progression is intended to aid researchers and clinicians to develop new treatments and monitor their effectiveness, as well as lessen the time and cost of clinical trials.

The Principal Investigator of this initiative is Michael W. Weiner, MD, VA Medical Center and University of California – San Francisco. ADNI is the result of efforts of many coinvestigators from a broad range of academic institutions and private corporations, and subjects have been recruited from over 50 sites across the U.S. and Canada. The initial goal of ADNI was to recruit 800 subjects but ADNI has been followed by ADNI-GO and ADNI-2. To date these three protocols have recruited over 1500 adults, ages 55 to 90, to participate in the research, consisting of cognitively normal older individuals, people with early or late MCI, and people with early AD. The follow up duration of each group is specified in the protocols for ADNI-1, ADNI-2 and ADNI-GO. Subjects originally recruited for ADNI-1 and ADNI-GO had the option to be followed in ADNI-2. For up-to-date information, see http://www.adni-info.org.

Authors' disclosures available online (http://j-alz.com/manuscript-disclosures/15-0679r1).

SUPPLEMENTARY MATERIAL

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