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Level of Executive Function Influences Verbal Memory in Amnestic Mild Cognitive Impairment and Predicts Prefrontal and Posterior Cingulate Thickness

Yu-Ling Chang[1], Mark W. Jacobson[1,4], Christine Fennema-Notestine[1,2], Donald J. Hagler Jr[2], Robin G. Jennings[2], Anders M. Dale[2,3], Linda K. McEvoy[2] and Alzheimer's Disease Neuroimaging Initiative

[1]Department of Psychiatry, [2]Department of Radiology, [3]Department of Neurosciences, University of California, San Diego, La Jolla, CA 92037, USA and [4]Veterans Affairs San Diego Healthcare System, San Diego, CA 92161, USA

This study aims to investigate the relationship between executive function and verbal memory and to explore the underlying neuroanatomical correlates in 358 individuals with amnestic mild cognitive impairment (MCI) and 222 healthy controls (HCs). The MCI participants were divided into 2 groups (high vs. low) based on executive function task performance. Results demonstrated that although both MCI groups were impaired on all memory measures relative to HCs, MCI individuals with higher executive function (HEF) demonstrated better verbal memory performance than those with lower executive function (LEF), particularly on measures of learning. The 2 MCI groups did not differ in mesial temporal morphometric measures, but the MCI LEF group showed significant thinning in dorsolateral prefrontal and posterior cingulate cortices bilaterally compared with the MCI HEF and HCs. Further, thickness in numerous regions of frontal cortex, and bilateral posterior cingulate, was significantly associated with memory performance in all MCI participants above and beyond the contribution of the mesial temporal regions known to be associated with episodic memory. Overall, these results demonstrate the importance of evaluating executive function in individuals with MCI to predict involvement of brain areas beyond the mesial temporal lobe.

Keywords: Alzheimer's disease, clinical subtypes, cognition, longitudinal outcome, morphometry

Introduction

Evidence from both neuropsychological and neuroimaging studies has suggested that mild cognitive impairment (MCI) represents a clinical prodrome to degenerative dementias such as Alzheimer's disease (AD; Petersen et al. 2001). Despite a primary emphasis on characterizing memory dysfunction and atrophy in related brain structures, such as hippocampus and entorhinal cortex, it is increasingly recognized that MCI may represent a highly heterogeneous group (Petersen et al. 2001; Nordahl et al. 2005; Busse et al. 2006), based in part on demonstrated variability among MCI individuals in some cognitive domains, such as executive functioning (Nordahl et al. 2005; Belleville et al. 2007). Executive dysfunction alone is not traditionally associated with profound memory loss; however, it is thought to interfere with a number of cognitive skills necessary for successfully engaging in the acquisition and retrieval of information (Stuss and Alexander 2000). These may include, for instance, the organization and elaboration of material at encoding, strategic retrieval of information, and the ability to overcome the effects of interference. Studies based on normal aging (Crawford et al. 2000; Salthouse et al. 2003) and a variety of clinical populations (Tremont et al. 2000; Simard et al. 2003; Busch et al. 2005; Brooks et al. 2006; Temple et al. 2006; Elderkin-Thompson et al. 2007) have found that deficits on measures of executive function have detrimental impact on memory performance. However, little is known about the relationship between executive function and episodic memory in MCI. Brooks et al. (2006) measured executive functions and episodic verbal memory performance in a sample of mixed MCI, probable mild dementia, and individuals with other neurological diagnoses and found that those with executive dysfunction showed lower memory performance than those without. However, due to the nature of the mixed neurological sample, definitive conclusions about the relationship between executive function and memory in MCI could not be drawn.

Lesion and functional imaging studies indicate that episodic memory involves a widespread network of brain structures, including the hippocampal formation, cingulate gyrus, and frontal lobe (Cabeza and Nyberg 2000; Davidson et al. 2006; Dove et al. 2006). Structural imaging studies (Van Petten et al. 2004) have reported a significant relationship between memory performance and gray matter volumes of the middle frontal gyrus and most temporal lobe gyri in healthy aging. There is considerable evidence for volumetric reduction in hippocampus and other medial temporal lobe structures in MCI compared with healthy controls (HCs), and the link between medial temporal atrophy and memory decline is well established (Wolf et al. 2003; Petersen 2004). However, morphometric changes in other regions, particularly frontal lobe and cingulate gyrus, and the impact of these changes on executive and memory function in MCI are less well understood.

The present study aimed to investigate the relationship between executive dysfunction and verbal memory in amnestic MCI and to elucidate the neural correlates of this dysfunction. Although memory impairment is a core feature of amnestic MCI, we hypothesized that amnestic MCI individuals with higher executive function (HEF) would perform better than those with lower executive function (LEF) on verbal memory tasks, particularly during the learning phase when executive support is likely to be critical for the successful organization of material for encoding. We also hypothesized that MCI individuals with LEF would show reduced thickness in frontal and cingulate areas relative to MCI individuals with HEF and that such frontal and cingulate differences would be associated with memory performance above and beyond the contribution of hippocampus and other mesial temporal regions.

Materials and Methods

The raw data used in the current study were obtained from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database (http://www.loni.ucla.edu/ADNI). 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 nonprofit 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, other biological markers, and clinical and neuropsychological assessment can be combined to measure the progression of MCI and early 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 Principle 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 United States and Canada. ADNI has recruited 229 cognitively normal older individuals to be followed for 3 years, 398 people with amnestic MCI to be followed for 3 years, and 192 people with early AD to be followed for 2 years. For up-to-date information, see http://www.adni-info.org. The research protocol was approved by each local institutional review board, and written informed consent was obtained from each participant. The study is conducted in compliance with Health Insurance Portability and Accountability Act regulations.

Participants

This study used baseline data collected prior to 14 August 2008. ADNI general eligibility criteria are described at http://www.adni-info.org/index.php?option= com_content&task=view&id=9& Itemid=43. Briefly, participants are 55–90 years old, nondepressed, with a modified Hachinski score of 4 or less, and have a study partner able to provide an independent evaluation of functioning. HCs have a Clinical Dementia Rating (CDR; Hughes et al. 1982) score of 0. MCI participants have a subjective memory complaint, objective memory loss measured by education-adjusted scores on modified Wechsler Memory Scale Logical Memory II (a score $\leqslant$8 for individuals with $\geqslant$16 years of education; a score $\leqslant$4 for individuals with 8–15 years of education; and a score $\leqslant$2 for individuals with 0–7 years of education), a CDR of 0.5, preserved activities of daily living, and an absence of dementia (Petersen et al. 2001). For the current study, we excluded 7 HCs who converted to MCI at any follow-up visit to minimize the possibility of misclassification of HC participants at baseline. Participants with missing or invalid data on any of the executive function and verbal memory measures used here were also excluded (40 MCI individuals). As a result, the present study consisted of 222 HC and 358 amnestic MCI participants. Due to exclusion of MR images that did not pass local quality control (see Materials and Methods), MR morphometric data were available for 208 HC and 318 MCI individuals.

Neuropsychological Measures

The neuropsychological tests used in the analyses were characterized into 4 groups: 1) general cognitive abilities, 2) tests of learning and memory, 3) executive function tests reported to be sensitive to frontal lobe dysfunction, and 4) language and visuoconstruction abilities.

General Cognitive Ability

Mini-Mental state examination (MMSE; Folstein et al. 1975) was used as a global index of general cognitive functioning. The raw score of American National Adult Reading Test (Grober and Sliwinski 1991) and the participant's education level were used together to calculate an estimate of premorbid verbal intellectual ability (VIQ) based on the formula reported by Grober and Sliwinski (1991).

Learning and Memory Measures

The Rey (1941) Auditory Verbal Learning Test (AVLT), a 15-item list-learning task, was presented verbally over 5 trials, and participants were asked to recall as many words as possible after each trial. Following presentation of a 15-word distractor list consisting of novel words, the participant was then asked to recall items from the first list (short delay [SD] recall). Long delay (LD) free recall and a recognition trial were given following a 20-min delay period. AVLT delay recognition discriminability score was calculated by the formula {[1 – (number of false alarms + number of misses)/30] × 100} where 30 is the total number of test stimuli, of which 15 are targets (Underwood 1974; Delis et al. 1987). A modified version of the logical memory (LM) subtest from the Wechsler (1987) Memory Scale-Revised was also given to participants. In this modified version, one short story (Story A) was read aloud to the participant and the participant was asked to recall immediately (LM I) and after a 30-min delay interval (LM II). A retention score was computed by dividing the score achieved during delayed recall by the score achieved during immediate recall.

Executive Function Measures

Trail Making Test part A and B (TMT-A and B; Reitan and Wolfson 1993) and the Digit Span Backward of the Wechsler (1981) Adult Intelligence Scale—Revised (WAIS-R) were used to assess executive function. TMT-A requires participants to draw a line between the numbered circles that arranged randomly on a sheet of paper in ascending order as quickly as possible within 150 s. In TMT-B, half the numbers were replaced with letters, and the task was to connect the circles while alternating between numbers and letters in ascending order within 300 s. The time to complete TMT-A and B was recorded separately. The TMT-B is a commonly used test of prefrontal function (Lezak 1995) and is considered a measure of the ability to flexibly shift the course of an ongoing activity. To minimize influence of motor speed on TMT-B performance, analyses were conducted based on standardized residual values after the effect of TMT-A was regressed out. The Digit Span Backward task of the WAIS-R requires participants to repeat a series of verbally presented digits of increasing length in reverse order. Performance on the task strongly depends upon working memory, cognitive regulation, and manipulation, all of which are components of executive function (Lezak 1995). The total number of correct items was used for analysis in the present study.

Language and Visuoconstruction Measures

Animal fluency (Morris et al. 1989) was used to assess expressive language ability. The participant is asked to name as many animals as possible within a 60-s time interval. Total number of correct responses was used for the analysis in the present study. To assess visuoconstruction ability, we used the visuoconstruction subtest of the Alzheimer's disease assessment scale-cognitive subscale (ADAS-cog; Rosen et al. 1984). In this test, the participant is asked to copy 4 geometric designs of increasing difficulty. The test was scored in terms of number of errors committed (scores ranged 0–5).

MCI Group Assignment

MCI participants were divided into 2 subgroups (LEF and HEF) based on a composite factor derived from scores obtained on the 2 executive function tasks. Specifically, the participant's performance on each of the executive measures was converted to a z-score based on norms obtained from the whole participant pool in the present study. For ease of interpretation, the z-score of the TMT-B was inverted prior to averaging the z-scores of the 2 tests. The resulting composite z-scores thus represented the participant's relative performance on executive function, with positive numbers representing better performance. Based on the Kolmogorov–Smirnov goodness-of-fit test, the resulting distribution of the composite z-scores for all participants on the executive function factor was approximately normal with a mean z-score of 0.06 (standard deviation = 0.7). The MCI participants were divided into HEF and LEF groups based on scores above or below a composite z-score of 0, respectively. This resulted in 163 MCI participants in the HEF group and 195 MCI participants in the LEF group. Group clinical and demographic data are presented in Table 1.

MR Scanning and Brain Morphometry

Image acquisition and analysis methods were developed within the NIH/NCRR sponsored Morphometry Biomedical Informatics Research Network and the ADNI (Fennema-Notestine et al. 2006, 2009; Han et al. 2006; Jovicich et al. 2006; Jack et al. 2008). Data were collected across

Table 1
Demographic, clinical, and cognitive characteristics of HC participants and individuals with MCI with HEF or LEF

	HC, $n = 222$ (mean, SD)	MCI HEF, $n = 163$ (mean, SD)	MCI LEF, $n = 195$ (mean, SD)	Statistical comparison
Age	76.54 (5.04)	75.49 (7.30)	75.52 (7.35)	$F_{2,577} = 1.73$, $P = 0.18$
Education	16.04 (2.83)	16.16 (2.66)	15.57 (3.03)	$F_{2,577} = 2.19$, $P = 0.11$
Gender (% men)	52%	59%	70%[a]	$\chi^2_{2,\ N\ =\ 580} = 14.20$, $P < 0.005$
VIQ estimate	119.88 (8.62)	118.43 (8.96)	114.89 (9.42)[a]	$F_{2,576} = 16.49$, $P < 0.001$
MMSE	29.12 (0.99)[b]	27.35 (1.75)	26.98 (1.68)	$F_{2,577} = 124.92$, $P < 0.001$
CDR-SB	0.03 (0.12)[b]	1.52 (0.83)	1.61 (0.91)	$F_{2,577} = 342.19$, $P < 0.001$
% APOE ε4 + (+/−)	26% (57/162)[b]	47% (75/84)	58% (111/79)[c]	$\chi^2_{2,\ N\ =\ 568} = 45.35$, $P < 0.001$
Digit span backward	7.28 (2.12)[b]	7.69 (1.78)	5.08 (1.23)[c]	$F_{2,573} = 97.41$, $P < 0.001$
Trail making A (s)	36.09 (13.05)[b]	41.64 (19.76)	43.91 (20.10)	$F_{2,573} = 9.42$, $P < 0.001$
Trail making B (s)	87.37 (41.02)[b]	89.00 (37.47)	150.93 (71.33)[c]	$F_{2,573} = 86.16$, $P < 0.001$
EF score	0.33 (0.63)[b]	0.52 (0.43)	−0.63 (0.51)[c]	$F_{2,573} = 218.94$, $P < 0.001$
Animal fluency	19.97 (5.65)[b]	17.02 (4.37)	15.33 (4.87)	$F_{2,573} = 37.02$, $P < 0.001$
Visuoconstruction (error score)	0.35 (0.50)[b]	0.43 (0.53)	0.60 (0.59)	$F_{2,573} = 6.43$, $P < 0.005$

Note: SD, standard deviation. Statistical comparison refers to the results of overall group comparison, controlling for age, gender, and estimated VIQ.
[a]The MCI LEF group was significantly different ($P < 0.05$) from the HC and the MCI HEF groups.
[b]The HC group was significantly different ($P < 0.05$) from the 2 MCI groups.
[c]Significant difference ($P < 0.05$) between the MCI HEF group versus the LEF group.

a variety of 1.5 T scanners. Protocols are described in detail at http://www.loni.ucla.edu/ADNI/Research/Cores/index.shtml. Two T_1-weighted volumes were acquired for each participant. These raw DICOM MRI scans were downloaded from the public ADNI site (http://www.loni.ucla.edu/ADNI/Data/index.shtml). Locally, images were reviewed for quality, automatically corrected for spatial distortion due to gradient nonlinearity (Jovicich et al. 2006) and B1 field inhomogeneity (Sled et al. 1998), registered, and averaged to improve signal-to-noise. Volumetric segmentation (Fischl et al. 2002, Fischl, Salat, et al. 2004) and cortical surface reconstruction (Dale and Sereno 1993; Dale et al. 1999; Fischl et al. 1999, Fischl et al. 2004) methods based on FreeSurfer software, optimized for use on large, multisite data sets, were used. To measure thickness, the cortical surface was reconstructed (Dale and Sereno 1993; Dale et al. 1999) and parcellated into distinct regions of interest (ROIs; Fischl et al. 2004; Desikan et al. 2006). Details of the application of these methods to the ADNI data have been described in full elsewhere (Fennema-Notestine et al. 2009). To limit the number of multiple comparisons, only regions assumed to be involved in executive and memory function were included in the present analyses, including bilateral hippocampal formation (volumetric measures; not pictured) which included dentate gyrus, CA fields, subiculum/parasubiculum and the fimbria (Makris et al. 1999), and multiple frontal and other temporal lobe areas (thickness measures; Fig. 1). To further decrease numbers of comparisons, the caudal and rostral anterior cingulate ROIs were combined as anterior cingulate cortex (ACC); the isthmus and posterior cingulate ROIs were combined as posterior cingulate cortex (PCC); and the pars opercularis and pars triangularis were combined as the frontal operculum.

Statistical Analyses

Demographic, Clinical, and Neuropsychological Data Analyses
Group comparisons were performed with analyses of variance (ANOVAs) or chi-square tests for demographic (e.g., frequency of apolipoprotein E [APOE] ε4 carriers), clinical (i.e., CDR sum of boxes [SB] scores), and global cognitive (e.g., MMSE scores, estimated VIQ) variables. Group comparisons on neuropsychological variables, including digit span backward scores, TMT-A and B, ADAS-cog visuoconstruction scores, and animal fluency, were performed with separate 1-way analyses of covariance (ANCOVAs), controlling for age, gender, and estimated VIQ. To examine the effect of executive function on memory performance, separate 1-way ANCOVAs were performed on each of the 7 memory-related dependent variables (raw scores) from the 3 groups, controlling for age, gender, estimated VIQ, and CDR-SB scores. The α level for the overall group comparison was set to 0.007 based on Bonferroni corrections. Effect sizes were calculated for comparisons between the 2 MCI groups on memory variables using the *d* of Cohen (1977), computed by dividing the mean difference between groups by the pooled standard deviation. Type I errors for the follow-up multiple comparisons were controlled via Bonferroni adjustment.

Morphometric Data Analyses
To assess group difference in morphometric variables, multivariate analyses of variance (MANOVAs), followed by univariate ANOVAs with Bonferroni adjustments for Type I error, were performed (the α level was set to 0.0025). Effects of age and gender were regressed from all thickness and volumetric measures and standardized residual values

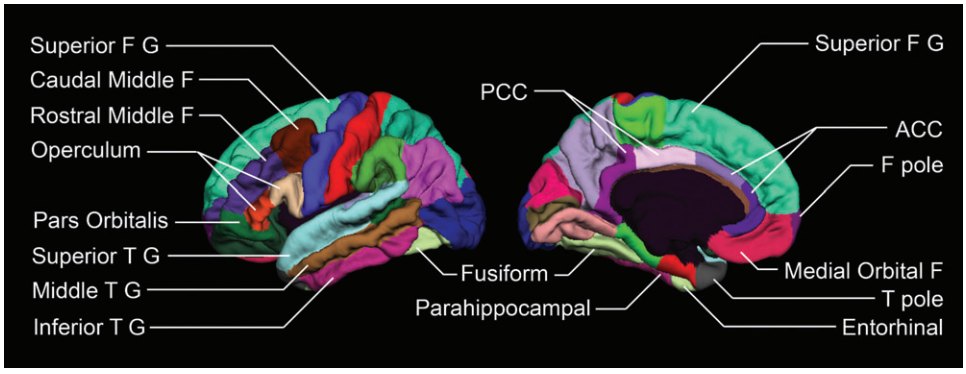

Figure 1. Pial representations of the ROIs derived from an automated labeling system (Desikan et al. 2006). Only labeled ROIs were included for analyses in the present study. For convenience, only left hemisphere ROIs are shown here but bilateral ROIs were analyzed. F = frontal; T = temporal; G = gyrus; ACC = anterior cingulate cortex; and PCC = posterior cingulate cortex.

Table 2
Memory performance of the 3 groups

	HC (mean, SD)	MCI HEF (mean, SD)	MCI LEF (mean, SD)	Statistical comparison	Cohen's *d*
Modified LM I	13.85 (3.48)[a]	8.02 (3.02)	6.57 (3.12)[b]	$F_{2,568} = 93.26$, $P < 0.001$	0.28
Modified LM II	13.03 (3.58)[a]	4.35 (2.77)	3.55 (2.53)	$F_{2,568} = 234.77$, $P < 0.001$	0.15
LM retention	0.96 (0.25)[a]	0.52 (0.32)	0.57 (0.49)	$F_{2,568} = 44.11$, $P < 0.001$	−0.06
AVLT total	43.36 (9.11)[a]	33.80 (9.68)	28.79 (7.80)[b]	$F_{2,568} = 41.83$, $P < 0.001$	0.43
AVLT SD recall	8.16 (3.40)[a]	4.37 (3.62)	3.49 (2.56)	$F_{2,568} = 28.50$, $P < 0.001$	0.19
AVLT LD recall	7.43 (3.70)[a]	3.55 (3.63)	2.36 (2.95)[b]	$F_{2,568} = 30.18$, $P < 0.001$	0.27
AVLT disc (%)	90.29 (9.74)[a]	77.65 (14.85)	74.10 (14.85)	$F_{2,568} = 19.40$, $P < 0.001$	0.22

Note: SD, standard deviation. Statistical comparison refers to the results of overall group comparison, controlling for age, gender, estimated VIQ, and CDR-SB. AVLT SD = AVLT short delay; AVLT LD = AVLT long delay; AVLT disc = AVLT discriminability on the recognition task.
[a]The HC group was significantly different ($P < 0.001$) from the 2 MCI groups; and Cohen's *d* was based on the MCI HEF and MCI LEF comparisons.
[b]Significant difference between the MCI HEF group versus the LEF group ($P < 0.05$).

were used for analyses; bilateral hippocampal volumes also were corrected for differences in head size by regressing the estimated total cranial vault (eTIV) volume (derived from an atlas scaling factor as described in Buckner et al. 2004). Group comparisons on total brain volume (excluding brainstem and cerebellum), total cerebral gray matter volume (excluding brainstem and cerebellum), total cerebral white matter (excluding cerebellar white matter but including white matter hypointensity volume), and eTIV volume were also performed, controlling for age and gender.

Relationship between Cognition (memory and executive function) and Morphometry
In separate analyses, Pearson product-moment correlations were conducted with all participants (HC and MCI), and with only MCI participants to examine associations between executive function and morphometric variables of interest. The α level was set to 0.0025 based on Bonferroni corrections. Partial correlations were performed to examine the unique relationship between verbal memory performance and morphometric variables (standardized residuals) in bilateral ACC, PCC, and frontal lobe regions (i.e., bilateral superior frontal gyrus, caudal and rostral middle frontal areas, frontal perculum, pars orbitalis, frontal pole, and medial orbital frontal lobe areas) after controlling for the effect of bilateral hippocampal volumes or entorhinal thickness. The α level was set to 0.0025 based on Bonferroni corrections. Of note, separate partial correlations, controlling for either bilateral hippocampus or entorhinal morphometric variables, were performed to avoid issues of multicollinearities due to the significant correlation between bilateral hippocampus and entorhinal cortices ($r = 0.63$, $P < 0.001$). Because results controlling for either hippocampus or entorhinal cortices did not differ, only results controlling for bilateral hippocampal volumes were reported here. All analyses were conducted in SPSS (Version 17.0).

Results

Demographic, Clinical, and Cognitive Data

The demographic, clinical, and cognitive characteristics for the 2 MCI subgroups and the HC group are presented in Table 1. The groups did not differ in age or education but showed a significant difference in gender. The MCI LEF group contained more men than either the HC ($P < 0.001$) or MCI HEF ($P < 0.05$) groups. As expected, both MCI groups showed lower scores on the MMSE than the HC group ($P < 0.001$ for both); however, the 2 MCI groups were equivalent on this measure. A significant group difference in estimated VIQ was found: the MCI LEF group scored significantly lower than the HC ($P < 0.001$) and the MCI HEF ($P < 0.005$) groups. Chi-square analyses revealed a significant difference in frequency of APOE ε4 carriers among the 3 groups (MCI LEF > MCI HEF > HC, all *P* values < 0.05). As expected, both MCI groups showed higher CDR-SB scores than the HC group ($P < 0.001$ for both); however, the 2 MCI groups did not differ on this measure.

On the animal fluency measure, the HC group showed significantly better performance compared with the 2 MCI groups ($P < 0.001$ for both), whereas the 2 MCI groups showed equivalent scores on this measure. On the visuoconstruction subscale of the ADAS-cog, a similar pattern was observed with the HC group outperforming the 2 MCI groups ($P < 0.005$ for both), with no significant difference between the 2 MCI groups.

Differential Effect of Executive Function on Verbal Memory Performance

As expected, the results based on ANCOVAs controlling for age, gender, estimated VIQ, and CDR-SB showed that the HC group outperformed the 2 MCI groups on all memory variables assessed here. Compared with the MCI LEF group, the MCI HEF group demonstrated better performance on the LM I ($P < 0.005$), AVLT total score across 5 learning trials ($P < 0.001$), and AVLT LD recall ($P < 0.05$) but not on LM II, LM memory retention, AVLT SD recall, or AVLT recognition discriminability, after controlling for age, gender, estimated VIQ, and CDR-SB. Overall, the effect size between the 2 MCI groups ranged from small to medium (Cohen's $d = 0.27$–0.43) with stronger effects on learning than on retention scores (Table 2).

Regional Differences in Morphometry by Group

The overall MANOVA for group effects on all morphometric measures (i.e., volumetric measures of bilateral hippocampus and thickness measures in bilateral ACC, PCC, frontal, and other temporal lobe regions) was significant (Wilks' Lambda = 0.63, $F_{72,976} = 3.26$, $P < 0.001$, partial $\eta^2 = 0.19$). Follow-up univariate analyses revealed that compared with the HC group, the 2 MCI groups demonstrated smaller hippocampal volumes bilaterally and thinner gray matter thickness in several frontal (i.e., caudal and rostral middle frontal, medial orbitofrontal, and superior frontal areas) and temporal lobe (i.e., entorhinal cortex, parahippocampal, superior, middle, and inferior temporal, temporal pole, and fusiform areas) regions bilaterally as well as the left pars orbitalis area (Fig. 2 top rows). Moreover, compared with the HC group, the MCI LEF but not the HEF group showed cortical thinning in additional areas, including

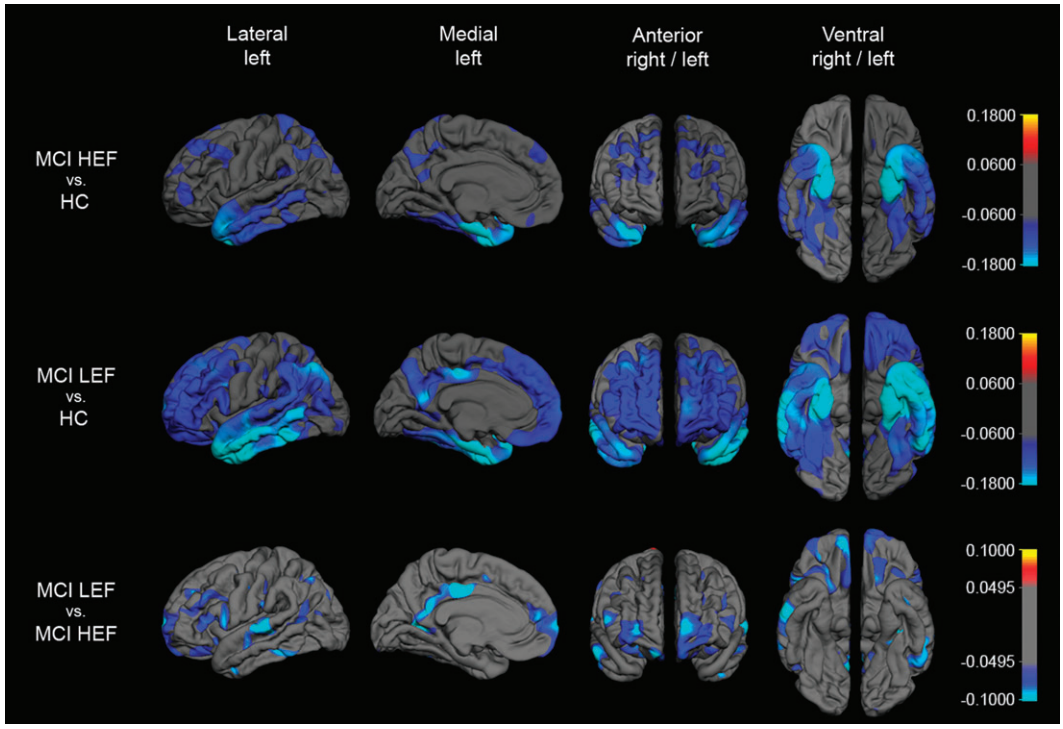

Figure 2. Average mean differences in thickness (mm, $P < 0.0025$) for the 2 MCI groups relative to HC (top 2 rows) and the MCI LEF group relative to the MCI HEF group (bottom row) are shown on the reconstructed cortical surface, after controlling for the effects of age and gender. Blue and cyan indicate thinning, whereas red and yellow indicate thickening. Relative to HC, both MCI groups showed significantly thinner gray matter in several frontal and temporal lobe regions bilaterally; however, the MCI LEF group showed a more widespread pattern of cortical thinning than the MCI HEF group, involving posterior cingulate areas as well as frontal and temporal areas.

left ACC, bilateral PCC, frontal operculum, lateral orbitofrontal, frontal pole, and right pars orbitalis (Fig. 2 middle row).

The 2 MCI groups showed comparable hippocampal volumes and thickness in entorhinal, parahippocampal regions as well as in temporal pole, superior temporal lobe, fusiform, caudal middle frontal, medial orbitofrontal, superior frontal, pars orbitalis regions, and ACC bilaterally. However, relative to the MCI HEF group, the LEF group demonstrated significant cortical thinning in frontal lobe (i.e., bilateral rostral middle frontal, lateral orbitofrontal, operculum, and left frontal pole), bilateral PCC, middle temporal lobe, and left inferior temporal lobe regions (Fig. 2, bottom row).

The groups did not significantly differ ($P > 0.05$) in estimated total intracranial vault volume or cerebral white matter volumes. The HC group showed significantly greater ($P < 0.001$) cerebral gray matter volume compared with the 2 MCI groups, whereas the 2 MCI groups did not differ on this measure. Similarly, the HC group showed significantly larger ($P < 0.001$) whole-brain volume compared with the 2 MCI groups, whereas the 2 MCI groups showed equivalent brain volumes. The raw values of all morphometric measures including global brain measures are presented in the Supplementary Table 1.

Relationship of Morphometry and Cognition

Pearson correlations based on all participants (HC and MCI) were performed to examine the relationship between executive function indicated by the composite score and morphometry in the frontal lobe areas and the cingulate cortex. The results showed that executive function was significantly associated ($P < 0.0025$) with cortical thickness of bilateral PCC (left $r = 0.22$; right $r = 0.19$), caudal middle frontal lobe (left $r = 0.17$; right $r = 0.15$), rostral middle frontal lobe (left $r = 0.18$; right $r = 0.21$), superior frontal (left $r = 0.16$; right $r = 0.17$), operculum (left $r = 0.14$; right $r = 0.16$), left lateral orbitofrontal ($r = 0.15$), left frontal pole ($r = 0.17$), and right pars orbitalis ($r = 0.14$) areas. Because the bilateral middle temporal and left inferior temporal regions significantly differed between the 2 MCI groups, we also examined the correlations between executive function composite score and thickness in these regions in post hoc analyses. The results demonstrated that executive function was significantly associated ($P < 0.0025$) with bilateral middle temporal lobe (left $r = 0.22$; right $r = 0.19$) and left inferior temporal lobe ($r = 0.20$) regions.

Restricting the analysis to MCI participants resulted in a similar pattern of findings except that the correlations between executive function and right caudal middle frontal lobe and right superior frontal regions were no longer significant, whereas a significant correlation emerged between executive function and the right lateral orbitofrontal region ($r = 0.16$).

To examine the relationship between memory and morphometric measures, we performed partial correlations controlling for the effect of average left and right hippocampal volume (standardized residuals) on all participants. Results are presented in Table 3. Briefly, after controlling for the effect of bilateral hippocampal volume, PCC but not ACC thickness was significantly correlated with LM I and AVLT total learning scores (r's = 0.13 ~ 0.15). In addition, cortical thickness of several frontal regions, including bilateral caudal and rostral middle frontal, superior frontal, and pars orbitalis, was

Table 3

Partial correlation coefficients between learning and memory function and cortical thickness of frontal lobe regions and cingulate gyrus using the full cohort after controlling for the effect of bilateral hippocampal volumes

	LM I	LM II	LM retention	AVLT total	AVLT SD	AVLT LD	AVLT disc
Left ACC	0.052	0.074	0.035	0.041	0.029	0.020	0.055
Left PCC	0.145**	0.120	−0.003	0.138**	0.113	0.071	0.052
Right ACC	0.008	0.056	0.084	0.082	0.062	0.064	0.075
Right PCC	0.119	0.114	0.016	0.129*	0.080	0.054	0.057
Left frontal pole	0.044	0.051	0.009	0.094	0.100	0.019	0.040
Left caudal middle frontal	0.137**	0.091	−0.055	0.103	0.091	0.048	0.002
Left rostral middle frontal	0.083	0.067	−0.016	0.126*	0.128*	0.064	0.060
Left lateral orbitofrontal	0.077	0.088	0.078	0.078	0.058	0.013	0.081
Left medial orbitofrontal	0.031	0.086	0.064	0.072	0.121	0.076	0.080
Left superior frontal	0.133**	0.118	0.009	0.116	0.130**	0.070	0.046
Left pars orbitalis	0.049	0.070	0.036	0.107	0.124*	0.057	0.100
Left operculum	0.063	0.057	−0.001	0.098	0.096	0.038	0.014
Right frontal pole	0.042	0.060	0.056	0.107	0.122	0.076	0.045
Right caudal middle frontal	0.129*	0.116	−0.020	0.072	0.067	0.010	0.006
Right rostral middle frontal	0.107	0.129*	0.067	0.132**	0.109	0.051	0.069
Right lateral orbitofrontal	−0.001	0.035	0.047	0.029	0.049	−0.005	0.052
Right medial orbitofrontal	0.051	0.087	0.068	0.101	0.098	0.053	0.083
Right superior frontal	0.142**	0.138**	0.032	0.127*	0.129*	0.060	0.044
Right pars orbitalis	0.065	0.104	0.059	0.117	0.125*	0.066	0.089
Right operculum	0.044	0.061	0.030	0.085	0.088	0.026	0.018

Note: AVLT SD = AVLT short delay recall; AVLT LD = AVLT long delay recall; and AVLT disc = AVLT discriminability on the recognition task.
*$P < 0.0025$; **$P < 0.001$.

significantly correlated with verbal memory performance (r's = 0.12 ~ 0.14), after controlling for the effect of bilateral hippocampal volumes. No regions were significantly related to LM retention, AVLT LD recall, or recognition discriminability.

Restricting the analysis to MCI participants resulted in fewer significant correlations compared with the results obtained based on the full cohort (Supplementary Table 2). Specifically, the LM I and LM II were no longer significantly correlated with any of the ROIs analyzed. A similar pattern of results, however, was observed for the AVLT total score and AVLT SD recall (r's = 0.16 ~ 0.20). For example, even after restricting subjects to those with MCI only, significant positive relationships were observed between AVLT Total score and thickness in the bilateral PCC but not ACC and in bilateral rostral middle frontal areas.

One-Year Clinical Follow-up

Clinical outcome data of the 1-year follow-up were available for 327 MCI participants (147 MCI HEF individuals and 180 MCI LEF individuals). As post hoc analyses, we examined the proportion of MCI individuals who have progressed into AD over 1-year follow-up. The result showed that significantly more MCI LEF individuals (47 of 180 participants; 26.1%) converted to a clinical diagnosis of probable AD after 1 year than MCI HEF individuals (17 of 147 participants; 11.6%; $\chi^2_{1,\ N\ =\ 327} = 10.88$, $P < 0.005$).

Discussion

In this study, we examined the influence of executive function on memory performance in amnestic MCI based on the assumption that amnestic MCI is a heterogeneous population and that multiple factors may contribute to the observed memory impairment in these individuals. To that end, we examined the relationship between morphometric measures and cognition (i.e., memory and executive function). Results showed that executive function modulates some aspects of memory ability and that MCI individuals with poorer executive function demonstrate greater thinning in frontal and cingulate cortices relative to those with HEF. Further, thinning in these areas was related to memory performance beyond effects attributable to hippocampal atrophy.

We hypothesized that amnestic MCI individuals with HEF would show better performance on memory relative to amnestic MCI individuals with LEF, particularly during the learning phase when executive support is likely to be critical for the successful organization of the material to be encoded. As predicted, and consistent with previous studies in normal aging (Crawford et al. 2000; Salthouse et al. 2003), the MCI HEF group outperformed the MCI LEF group on the LM immediate recall, AVLT total learning, and LD recall. However, on other memory variables such as LM retention or SD recall of AVLT, the 2 MCI groups demonstrated comparable performance. The finding that greater differences occurred between the 2 MCI groups on learning components than on memory retention is consistent with literature regarding the differential roles of frontal and medial temporal lobes in memory, with the frontal lobe more associated with the acquisition of information, and the medial temporal lobe more associated with memory consolidation (Ferbinteanu et al. 2006). Our findings also support the evidence that AVLT performance relies on executive function to a greater degree than does the LM. It has been suggested that differential performance between list learning and story recall measures reflects differences in the respective task demands on the encoding process (Tremont et al. 2000). As opposed to the unstructured word list, the LM test is presented in a structured story format that provides contextual cues, thus potentially reducing the need to actively organize the information for learning and recall.

Regarding the relationship between morphometric variables and executive function in MCI, we hypothesized that MCI individuals with LEF would show reduced thickness in frontal and cingulate areas relative to MCI individuals with HEF. Results showed that the MCI group as a whole demonstrated significant gray matter thinning in bilateral medial and lateral temporal lobe as well as frontal lobe regions compared with the HC group, consistent with previous studies (Wolf et al. 2003; Fennema-Notestine et al. 2009). In support of our hypothesis, the results indicated that relative to the HC group, the MCI LEF group showed greater and more widespread atrophy than the HEF group. Although the 2 MCI groups showed comparable morphometry in bilateral mesial temporal lobe regions, the LEF group demonstrated greater cortical thinning in left orbitofrontal region, left frontal pole, right rostral middle frontal lobe, bilateral middle temporal lobe, and left inferior temporal lobe regions relative to the MCI HEF. Cortical thinning observed in the MCI LEF group in the frontal regions is consistent with previous studies that have highlighted the role of prefrontal regions in executive functioning (for a review, see Stuss and Alexander 2000). However, the results regarding the difference between the 2 MCI groups in middle and inferior temporal lobe regions and their significant correlations with executive function were unexpected because middle and inferior temporal cortices have not traditionally been associated with

executive function. These significant relationships, however, may reflect language or visual abilities required in the executive function tasks used in the current study.

Significantly decreased thickness was also found in bilateral PCC but not ACC in the MCI LEF group compared with the MCI HEF group, which was somewhat unexpected given that ACC is considered to be involved in executive function and is part of the frontal circuitry (Kobayashi and Amaral 2003, 2007). Cortical thinning in PCC in the MCI LEF group compared with the MCI HEF group was not unexpected given that the PCC is considered part of the limbic system and has reciprocal connections with the medial temporal lobe, including entorhinal cortex and hippocampal formation as well as frontal areas, particularly BA 46, 9, 10, and 11 (Kobayashi and Amaral 2003, 2007). Hypometabolism and volumetric reduction in PCC has been identified as a feature of early AD (Chua et al. 2008; Choo et al. 2008; Pengas et al. 2008), and several recent studies have reported PCC hypometabolism or/and volume reduction in individuals with MCI (Choo et al 2008; Chua et al 2008; Fennema-Notestine et al. 2009; Pengas et al. 2008). Our findings support the notion that PCC abnormality can be detected in a preclinical stage of AD and suggest that atrophy in the PCC is associated with executive dysfunction. Overall, the results of cortical thinning in the frontal lobe and PCC region observed in the MCI LEF group compared with the MCI HEF group are consistent with prior studies (Bell-McGinty et al. 2005; Whitwell et al. 2007; Fennema-Notestine et al. 2009) that examined volumetric differences between different MCI subtypes (i.e., MCI-amnestic vs. MCI-multiple cognitive domain subtype) using criteria proposed by Petersen et al. (2001).

In support of our final hypothesis, the results showed that thickness in numerous regions of frontal cortex and bilateral PCC were significantly associated with memory performance above and beyond the contribution of mesial temporal regions known to be associated with episodic memory. These relations remained significant when the analysis was restricted to the MCI groups, suggesting that they did not arise principally from the large difference between controls and MCI participants. These results correspond with the finding that MCI individuals with LEF showed lower memory performance and greater cortical thinning in frontal and PCC regions relative to those with HEF; despite equivalent hippocampal volumes and thickness of mesial temporal lobe regions (Supplementary Table 1).

There are a number of interindividual differences that may account for the current executive function/memory findings including premorbid cognitive function, genetic factors, and diagnostic heterogeneity. It is unlikely that the relationship observed here between executive function and memory is an artifact of differences in general cognitive functioning because the HEF and LEF groups evidenced comparable CDR-SB scores as well as similar performance on many other neuropsychological measures, including MMSE, memory retention, TMT-A, animal fluency, and the visuoconstruction subscale of the ADAS-cog. Furthermore, the group effects on learning and recall measures remained significant after controlling for estimated VIQ and CDR-SB. Genetic factors, however, may have contributed to the observed effects. APOE ε4 has been documented as a genetic risk factor for late-onset AD (Bennett et al. 2003) with some studies suggesting that the APOE ε4 genotype is associated with subtle impairments in executive functions such as working memory, inhibition, and attentional switching in healthy adults and prodromal dementia (Greenwood et al. 2000; Small et al. 2004; Jacobson et al. 2005; Wetter et al. 2005; McQueen et al. 2007). Consistent with this, we found that both MCI groups had a higher frequency of APOE ε4 carriers than the HC group and that the LEF group had a higher frequency of APOE ε4 carriers than the HEF group. Diagnostic heterogeneity may also have contributed to the relationship between executive function and memory. MCI groups with more widespread gray matter loss at baseline have been shown to progress more rapidly to AD relative to those with focal gray matter loss (Whitwell et al. 2008; McEvoy et al. 2009). Evidence from neuropsychological data shows a parallel indication: Executive dysfunction in addition to memory decline improves prediction of conversion to AD in individuals with MCI (Albert et al. 2001; Chen et al. 2001; Backman et al. 2005; Rapp and Reischies 2005; Belleville et al. 2007; Blacker et al. 2007). Consistent with this, we found that the 1-year conversion rate to a clinical diagnosis of probable AD was higher in the MCI LEF group than the MCI HEF group. Thus, the 2 MCI groups in the present study may represent a continuum of the MCI-AD course with the MCI LEF group having progressed farther toward AD than the MCI HEF group, or they may represent different underlying etiologies. For example, the MCI LEF group may show more vascular or mixed pathologies than the MCI HEF group. Future analysis of longitudinal change in brain structure and neuropsychological task performance over ADNI's 3-year follow-up period, once sufficient data have been collected and processed, may help elucidate this issue.

Potential limitations of the present study include the restricted number of executive measures and nonverbal memory tasks available for analyses. Executive function is a broad cognitive domain that includes many subcomponents such as working memory, planning, inhibition, problem solving, and mental set shifting capacities (Stuss and Alexander 2000). With the limited number of executive function tests available in the ADNI, it is not possible to determine the extent to which each of these components relates to memory performance. Additionally, the present study is unable to provide information about the relation between nonverbal memory and executive function measures. Finally, the relationships observed between cognition and morphometric measures in frontal and temporal lobe areas were low (r's = 0.12–0.22), suggesting that much of the variance in cognitive scores is not explained by brain morphometry. It is likely that the above-mentioned factors related to interindividual differences, such as premorbid cognitive function, genetic factors, and diagnostic heterogeneity, may contribute more to the variance in executive functioning.

Despite these limitations, the present study suggests that executive function influences verbal memory ability in amnestic MCI, particularly with regard to learning components of memory. This influence is not related to variation in hippocampal volume but reflects cortical thinning in bilateral prefrontal lobe areas and the PCC. These results demonstrate the importance of evaluating executive function in individuals with amnestic MCI to predict involvement of brain areas beyond the mesial temporal lobe. Future follow-up analyses will provide information on the ability of these measures to predict decline in MCI.

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Supplementary Material

Supplementary tables 1 and 2 can be found at: http://www.cercor.oxfordjournals.org/.

Notes

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Address correspondence to Dr Yu-Ling Chang, PhD, Department of Psychiatry, University of California, San Diego, 8950 Villa La Jolla Drive Suite C101, La Jolla, CA 92037, USA. Email: yuling@ucsd.edu.

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