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Voxel and Surface-Based Topography of Memory and Executive Deficits in Mild Cognitive Impairment and Alzheimer's Disease

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Abstract

Mild cognitive impairment (MCI) and Alzheimer's disease (AD) are associated with a progressive loss of cognitive abilities. In the present report, we assessed the relationship of memory and executive function with brain structure in a sample of 810 Alzheimer's Disease Neuroimaging Initiative (ADNI) participants, including 188 AD, 396 MCI, and 226 healthy older adults (HC). Composite scores of memory (ADNI-Mem) and executive function (ADNI-Exec) were generated by applying modern psychometric theory to item-level data from ADNI's neuropsychological battery. We used voxel-based morphometry (VBM) and surface-based association (SurfStat) analyses to evaluate relationships of ADNI-Mem and ADNI-Exec with grey matter (GM) density and cortical thickness across the whole brain in the combined sample and within diagnostic groups. We observed strong associations between ADNI-Mem and medial and lateral temporal lobe atrophy. Lower ADNI-Exec scores were associated with advanced GM and cortical atrophy across broadly distributed regions, most impressively in the bilateral parietal and temporal lobes. We also evaluated ADNI-Exec adjusted for ADNI-Mem, and found associations with GM density and cortical thickness primarily in the bilateral parietal, temporal, and frontal lobes. Within-group analyses suggest these associations are strongest in patients with MCI and AD. The present study provides insight into the spatially unbiased associations between brain atrophy and memory and executive function, and underscores the importance of structural brain changes in early cognitive decline.

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Keywords

Voxel-based morphometry (VBM); Surface-based Analysis; Memory; Executive Function; Alzheimer's disease; Mild Cognitive Impairment

Introduction

Alzheimer's disease (AD) is the most common form of dementia in older adults. AD is a progressive neurodegenerative disorder that is pathologically characterized by the presence of amyloid deposition and neurofibrillary tangles (Armstrong 2009; Hardy and Selkoe 2002; Minati et al. 2009). Thus far, no treatments have been to found to effectively target the underlying neuropathology of AD or substantially modify disease course (Holtzman et al. 2011). Earlier diagnosis of AD has widely been considered to be an important goal for researchers to identify individuals who will ultimately develop AD at a prodromal stage. Mild cognitive impairment (MCI) is considered to be a precursor to the development of AD, as patients with MCI have a highly increased probability of developing AD (Petersen 2000; Petersen et al. 1999). Within five years, approximately half of those with MCI are likely to convert to probable AD (Petersen et al. 1999).

Although some cognitive abilities decline in normal aging, AD is associated with a progressive and significant superimposed loss of cognition. An observed deficit in memory is most commonly the first symptomatic change in patients who ultimately progress to AD, although deficits in other cognitive domains (executive function, visuospatial skills, etc.) are sometimes reported. An AD diagnosis is mainly attained by means of clinical examination and detailed neuropsychological assessment, and the common requisite for a diagnosis of AD is that at least one other cognitive ability in addition to memory is impaired (G. McKhann et al. 1984; G. M. McKhann et al. 2011). Although impairments of episodic memory seem particularly marked in people with MCI and AD, deficits in attentional and executive functions commonly emerge as the pathological processes spread in the brain (Albert et al. 2011; G. M. McKhann et al. 2011).

The observed progression of cognitive deficits, initiated by memory impairments and expanding to encompass deficits in multiple cognitive processes (executive function, visuospatial, sensory/perception, etc.) is thought to be a direct result of the anatomical progression of neurodegeneration associated with AD (Braak and Braak 1996; Braak et al. 1993; Braak et al. 1996). The medial temporal lobe (MTL), including the entorhinal cortex (EC), amygdala, and hippocampus, is one of the first regions of the brain to show AD-related neurodegeneration. The observed memory declines in the early and prodromal stages of AD are likely associated with degeneration of the MTL, most especially in the entorhinal cortex and hippocampus. Several studies have shown important associations between MTL atrophy measured using magnetic resonance imaging (MRI) and memory impairments in people with MCI and AD. Specifically, studies utilizing region of interest (ROI) approaches have shown sizable associations between measures of MTL volume and memory performance in healthy aging, as well as in patients with MCI and AD (Braskie et al. 2009; Convit et al. 2000; Hackert et al. 2002; Juottonen et al. 1998; Laakso et al. 1995; Petersen et al. 2000; Deweer et al. 1995; C. D. Smith et al. 1999). In addition, studies employing whole-brain analysis techniques (e.g., voxel-based morphometry, VBM) have also demonstrated that memory performance is closely associated with MTL measures of grey matter (GM) density and volume, though associations with temporal, parietal and frontal lobe regions are also reported (Barbeau et al. 2008; Berlingeri et al. 2008; Chetelat et al. 2003; Chetelat et al. 2011; Di Paola et al. 2007; Goto et al. 2011; Hamalainen et al. 2007; Leube et al. 2008; Remy et al. 2005; Schmidt-Wilcke et al. 2009). Longitudinal change in memory

performance has also been shown to be associated with hippocampal and MTL atrophy rates in healthy aging, as well as in patients at-risk for AD (Fox et al. 1996; Jagust et al. 2006; Rusinek et al. 2003). Finally, studies of brain function have routinely supported the crucial role of the hippocampus in memory function, both in healthy younger and older adults and in patients with MCI and AD (Cabeza and Nyberg 2000; Grady et al. 2003; Hamalainen et al. 2007; Kato et al. 2001; Remy et al. 2005; S.L. Risacher et al. 2011; Rombouts et al. 2000; Small et al. 1999; Sperling et al. 2010; Sperling et al. 2003; Zakzanis et al. 2003).

In cognitive research, executive function encompasses a number of cognitive processes, including working memory, attention, set-shifting, judgment and problem-solving, verbal reasoning, mental flexibility, and initiation, inhibition, and monitoring of actions. Tests designed to evaluate executive function commonly focus on some, but not all, of these cognitive sub-domains. Executive function is commonly impaired in people with AD and to a lesser extent in people with MCI (Knopman et al. 2001). Previous studies using ROI and whole-brain approaches have reported important associations between executive function deficits and brain atrophy, particularly in regions of the frontal, parietal, and temporal lobes (Cahn-Weiner et al. 1999; Kramer et al. 2007; Oh et al. 2011; Huey et al. 2009; Newman et al. 2007; Pa et al. 2010; Rabin et al. 2009; Thomann et al. 2008). The different executive sub-domains also show overlapping but slightly different anatomical patterns of association. Set-shifting, attention, and working memory deficits appear to be associated especially with frontal and parietal lobe atrophy (Pa et al. 2010; Thomann et al. 2008; Cahn-Weiner et al. 1999; Kramer et al. 2007), while verbal fluency and reasoning deficits appear to be associated especially with frontal and temporal lobe atrophy (Newman et al. 2007; Rabin et al. 2009). Finally, functional studies of executive function have also supported the importance of frontal, parietal, and temporal lobe regions in tasks of working memory and attention, verbal fluency and reasoning, and initiation, inhibition, and monitoring of actions, as well as other executive sub-domains (Ino et al. 2003; Moll et al. 2002; Monchi et al. 2001; Rushworth et al. 2002; A. B. Smith et al. 2004; Taylor et al. 2004; Wager et al. 2004; Zakzanis et al. 2005; Cabeza and Nyberg 2000).

The Alzheimer's Disease Neuroimaging Initiative (ADNI) is a longitudinal multi-center study of the role of biomarkers of AD-related pathology in patients with AD and MCI and healthy age-matched controls (HC). ADNI participants were selected on the basis of specific criteria, described elsewhere (Mueller et al. 2005a; Mueller et al. 2005b; Weiner et al. 2010; Weiner et al. 2011) and at www.adni-info.org, and are followed with clinical, cognitive, functional, behavioral, biological, and imaging assessments every 6–12 months. As seen elsewhere in this issue, psychometrically sophisticated composite scores for assessing memory and executive function were developed using the ADNI psychometric data as part of the 2011 Friday Harbor Advanced Psychometrics workshop. These scores are designed to optimize estimation of memory and executive function in the ADNI sample at baseline, as well as longitudinal changes in memory and executive function.

Previous studies using the ADNI data have evaluated the relationship between cross-sectional and longitudinal brain atrophy and cognition (Weiner et al. 2011). Reduced baseline global cognition as measured using the Mini-Mental State Examination (MMSE, (Cockrell and Folstein 1988; Folstein et al. 1975) and the Alzheimer's Disease Assessment Scale-Cognitive subscore (ADAS-Cog, (Mohs 1994), and increased clinical dementia severity as measured by the Clinical Dementia Rating Scale Sum of Boxes score (CDR-SB, (J. C. Morris 1993) were associated with greater baseline hippocampal and amygdalar atrophy, greater whole brain and cortical atrophy, reduced caudate volume, expanded ventricular volume, and faster rates of cortical thinning and hippocampal atrophy in the combined sample and in people with AD and MCI (Chou et al. 2009; Hua et al. 2008; King et al. 2010; Madsen et al. 2010; Morra et al. 2009a; Morra et al. 2009b; Park and Seo 2011;

Poulin et al. 2011; Sabuncu et al. 2011; Stonnington et al. 2010; Vemuri et al. 2010a; Vemuri et al. 2009a; Zhang et al. 2011; Wolz et al. 2010). More longitudinal decline in MMSE total score, as well as a greater increase in ADAS-Cogscore and CDR-SB was associated with reduced baseline retrosplenial volume, more whole brain atrophy, and higher ventricular volumes, as well as a faster rate of decline in hippocampal volume and ventricular expansion (Chou et al. 2010; Evans et al. 2010; Jack et al. 2009; Kovacevic et al. 2009; Leow et al. 2009; Lo et al. 2011; Madsen et al. 2010; Morra et al. 2009b; Nestor et al. 2008; Vemuri et al. 2010b; Vemuri et al. 2009b; Walhovd et al. 2010a; Wolz et al. 2010). Impairment on individual measures of memory function (i.e., immediate and delayed sub-scores of the Rey Auditory Verbal Learning Test (RAVLT (Rey 1964)), Wechsler Memory Scale-Revised Logical Memory (LM (Wechsler 1987)), and ADAS-Cog) were shown to be associated with greater baseline hippocampal and MTL atrophy, expanded ventricular volume, lower caudate volumes, and reduced baseline frontal lobe, parietal lobe, cingulate, and lateral temporal lobe cortical thickness, as well as lower inferior parietal lobule GM volume, in the combined sample, people with MCI, people with AD, and amyloid-positive HC (Chang et al. 2010a; Chang et al. 2010b; Chou et al. 2010; Greene and Killiany 2010, 2011; Hua et al. 2008; Apostolova et al. 2010; Kovacevic et al. 2009; Madsen et al. 2010; Mormino et al. 2009; Nettiksimmons et al. 2010; Shen et al. 2011; Stonnington et al. 2010; Vemuri et al. 2011; Walhovd et al. 2010b; Wolk and Dickerson 2011). Interestingly, deficits in different memory processes (i.e., learning, retention, recognition) may show associations with atrophy of different brain structures across and within diagnostic groups, as learning processes were most associated with parietal, frontal and temporal cortical atrophy measures, while retention and recognition processes were most associated with hippocampal and entorhinal/parahippocampal cortical atrophy measures, respectively (Wolk and Dickerson 2011; Chang et al. 2010a; Walhovd et al. 2010b). Genetic background (APOE ε4 genotype) may also modulate the relationship between memory performance and MTL atrophy measures (Wolk and Dickerson 2010). Longitudinal decline in memory performance is also associated with baseline MTL and parietal lobe atrophy measures, baseline ventricular volume, rate of atrophy in the medial and lateral temporal lobes, and rate of ventricular expansions in HC and patients with MCI (Chiang et al. 2011; Chou et al. 2010; Leow et al. 2009; McDonald et al. 2012; Murphy et al. 2010; Walhovd et al. 2010a). Finally, executive function as measured using the Trail-Making Test A and B (TMT-A, TMT-B, (Reitan and Wolfson 1985; Spreen and E. 1998), the Clock Drawing Test (CDT, (Goodglass and Kaplan 1983) and the Wechsler Adult Intelligence Scale-Revised (WAIS-R) Digit Symbol Substitution test (Digit Symbol, (Wechsler 1981) were associated with hippocampal, inferior parietal lobule, and whole brain atrophy in a combined sample and in people with MCI and AD only (Greene and Killiany 2010, 2011; Vemuri et al. 2011). The relationship between TMT performance and brain structure was also shown to be modulated by APOE ε4 genotype (Wolk and Dickerson 2010). Longitudinal change in TMT performance was also associated with frontal lobe atrophy rate and ventricular expansion in people with MCI only (Evans et al. 2010; McDonald et al. 2012).

The present study evaluates the relationship between brain atrophy and cognition, particularly in the domains of memory and executive function. First, the relationship between memory and executive function composite scores and grey matter (GM) and cortical atrophy across the whole brain is assessed in a combined sample of HC, MCI, and AD. Next, we evaluate the relationship between brain atrophy and memory and executive function performance within each diagnostic group (HC, MCI, AD) independently. We evaluate the independent relationship of executive function to brain atrophy after controlling for memory performance in the full sample and within each diagnostic group. We hypothesized that significant associations between memory performance and atrophy in the MTL would be observed across the full sample and within the MCI and AD diagnostic groups more than within controls. We also hypothesized that executive function would be

associated with frontal, parietal, and temporal lobe brain atrophy, both in the combined sample and within diagnostic groups. Finally, we predicted that executive function, after adjusting for memory performance, would be associated with more focal regions within the frontal and parietal lobes.

Although previous studies have evaluated the relationship of cognition to brain structure, this study is important for several reasons: (1) we investigated the relationship between brain structure and psychometrically refined composite scores, which may provide a more precise estimation of memory/executive function ability by combining results from multiple tests, rather than estimates from a single psychometric test; (2) we used measures of both GM density and cortical thickness across the whole brain on a voxel-wise and surface-based level to estimate brain atrophy, providing a more comprehensive analysis of neurodegeneration; (3) we performed the analysis using the largest sample of HC, MCI, and AD participants to date in such a study.

Methods

Alzheimer's Disease Neuroimaging Initiative (ADNI)

All individuals whose data were used in the preparation of this article were participants of the ADNI project (http://adni.loni.ucla.edu/). ADNI was launched in 2003 to evaluate biomarkers of AD-related neuropathology in patients with mild cognitive impairment (MCI) and early AD. This multi-site longitudinal study is supported 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. ADNI participants were recruited from 59 sites across the U.S. and Canada and include approximately 200 HC), 400 people diagnosed with MCI, and 200 people diagnosed with early probable AD aged 55–90 years. Written informed consent was obtained from all participants and the study was conducted with prior Institutional Review Board approval at each participating institution. Inclusion and exclusion criteria, clinical and neuroimaging protocols, and other information about ADNI has been published previously (S. L. Risacher et al. 2009; S. L. Risacher et al. 2010) and can be found at www.adni-info.org. All demographic information, neuropsychological test scores, and diagnostic information were downloaded from the ADNI clinical data repository (http://www.loni.ucla.edu/ADNI/).

Participants

Eight hundred and ten participants (188 AD, 396 MCI and 226 HC at baseline) in the ADNI cohort with initial MRI scans were included in the present analyses (Table 1). Twelve participants were excluded for failed MRI processing and/or missing data.

Memory and Executive Function composite scores

The ADNI data contain a detailed neuropsychological assessment including measures of memory and executive function. We used modern psychometric theory methods applied to item-level data from the ADNI neuropsychological battery to develop composite scores separately for memory (ADNI-Mem) and executive functioning (ADNI-EF). For complete details regarding the development of ADNI-Mem and ADNI-EF, please refer to the companion papers in this volume (Crane et al. 2011 submitted; Gibbons et al. 2011 submitted). For executive functioning, we found that a bi-factor model had the best fit to the data. We extracted factor scores for the general factor defined by all of the items from Mplus (http://www.statmodel.com/); this factor score is the ADNI-EF score. For memory, we used a longitudinal single factor model to account for different versions of the ADAS-Cog and of the Rey AVLT. We used parameters from that model to generate scores at each study visit,

also using Mplus (http://www.statmodel.com/). Further details are spelled out in our companion papers (Crane et al. 2011 submitted; Gibbons et al. 2011 submitted). The psychometric tests included in each composite score are as follows: (1) memory composite score includes results from the memory items from the MMSE (Cockrell and Folstein 1988; Folstein et al. 1975) and ADAS-Cog (Mohs 1994), as well as the RAVLT (all immediate and delayed scores; (Rey 1964)) and the LM immediate and delayed scores (Wechsler 1987); (2) executive function composite score includes the Digit Symbol Substitution test (Wechsler 1981), the Wechsler Memory Scale-Revised Digit Span test (Wechsler 1987), TMT-A and TMT-B (Reitan and Wolfson 1985; Spreen and E. 1998), category fluency tests (Animal and Vegetable; (J. Morris et al. 1989)), and the CDT (Goodglass and Kaplan 1983). To evaluate the relationship of brain structure to executive function independent of the effects of memory, we also generated a memory-adjusted executive function composite score by adjusting the executive function composite score for the memory composite score using the following formula:

$$\text{adjusted EF} = \text{EF} - (\beta_{\text{EFvsmem}} * (\text{mem} - \text{mem}_{\text{group}})),$$

where adjusted EF is the executive composite score adjusted for the memory composite score, EF is the original executive function composite score, β_{EFvsmem} is the β-weight for the linear regression of EF on memory, mem is the memory composite scores, and $\text{mem}_{\text{group}}$ is the group mean of the full sample for the memory composite score. An adjusted executive function score was calculated for each individual and the relationship with brain structure was evaluated as described below.

MRI Scans

Baseline 1.5T MRI scans from 820 participants were downloaded from the ADNI scan repository (http://www.loni.ucla.edu/ADNI/) onto local servers at the Indiana University School of Medicine. Scans were collected at either screening or baseline visits. If scans existed from both sessions for a single participant, we used the scan from the screening visit.

Image processing

As detailed in previous studies (S. L. Risacher et al. 2009; S. L. Risacher et al. 2010), we used two widely-employed automated MRI analysis techniques to process the MRI scans: (1) whole-brain, voxel-based morphometry (VBM) (http://www.fil.ion.ucl.ac.uk/spm/; (Ashburner and Friston 2000; Good et al. 2001; Mechelli 2005); and, (2) Freesurfer version 4.0.1 (http://surfer.nmr.mgh.harvard.edu/; (Dale et al. 1999; B. Fischl and Dale 2000; B Fischl et al. 2002; B Fischl et al. 1999).

VBM: We converted T1-weighted brain MRI scans acquired using a sagittal 3D MP-RAGE sequence from DICOM to NIfTI format. We then co-registered scans to a standard T1-weighted template image and segmented them into grey matter (GM), white matter (WM), and cerebrospinal fluid (CSF) compartments with bias correction. Finally, we normalized unmodulated GM density maps to MNI atlas space (1 × 1 × 1 mm voxel size) and smoothed them using a 10 mm full-width at half-maximum (FWHM) Gaussian kernel. We used SPM5 (http://www.fil.ion.ucl.ac.uk/spm/) for all VBM processing.

Automated Parcellation: We used Freesurfer version 4.0.1 to process all available MP-RAGE images from the ADNI cohort using previously described methods (S. L. Risacher et al. 2009; S. L. Risacher et al. 2010). We reconstructed the cortical surface to measure thickness at each vertex. We calculated the cortical thickness by taking the Euclidean distance between the grey/white boundary and the grey/cerebrospinal fluid (CSF) boundary at each vertex on the surface. For surface-based comparison of the cortical thickness, we registered all individual cortical surfaces to a common surface template, which was an

average created from all HC. The cortical thickness was smoothed with a 10 mm FWHM Gaussian kernel to improve the signal-to-noise ratio and statistical power.

Statistical analyses

Voxel-based analysis: We used SPM5 (http://www.fil.ion.ucl.ac.uk/spm/) to perform statistical analyses on a voxel-by-voxel basis using a general linear model (GLM) approach. Memory and executive function composite scores, as well as the executive function composite adjusted for the memory composite, were entered in three separate analyses as independent variables in multiple regression models to identify brain areas where GM was associated with memory/executive composite scores. We initially assessed these relationships in the combined sample of AD, MCI, and HC participants (n=810), followed by analyses within each diagnostic group. We included age at the baseline visit, sex, years of education, and total intracranial volume (ICV) as covariates in all analyses. We used an explicit GM mask to restrict analysis to GM regions. For the analyses in the full cohort, we used a threshold of voxel-level significance $p<0.001$ with a family-wise error (FWE) multiple comparison correction and minimum cluster size (k)=100 contiguous voxels to identify significant clusters. Due to attenuated power, we used a threshold of voxel-level significance $p<0.001$ with a false-discovery rate (FDR) correction for multiple comparison and k=100 contiguous voxels in analyses within each diagnostic group.

Surface-based analysis: We performed multivariate analysis of cortical thickness to examine the relationship between memory and executive function composite scores and cortical thickness measures. We used SurfStat software to perform surface-based analysis using general linear models (GLMs) (http://www.math.mcgill.ca/keith/surfstat/). We constructed GLMs using age at baseline, sex, years of education, intracranial volume (ICV), and composite scores as variables. We examined effects of composite scores on cortical thickness both across diagnostic groups and within each diagnostic group. We performed a correction for multiple comparisons using the random field theory (RFT) correction method at a $p<0.05$ level of significance.

Additional statistical analyses

We compared sample demographic characteristics and performance on the memory and executive composites between diagnostic groups (AD, MCI, HC). We used a one-way analysis of variance to compare continuous variables (age, education, memory and executive function performance), and a chi-square test to evaluate sex. We evaluated the relationship between the memory and executive function composite scores in the combined cohort and within each diagnostic group (AD, MCI, HC) using a linear regression model with and without age, sex, and education as covariates. SPSS (18 or 19) was used for these statistical analyses.

Results

Demographic characteristics and mean composite scores for all groups are presented in Table 1. Mean age was similar across groups, but the groups differed in terms of sex and years of education. As expected, there were important differences in the expected direction across groups on memory and executive function composite scores.

The result of the voxel-wise association between the memory composite score and GM density across all groups is shown in Figure 1A. Lower memory composite scores were associated with reduced GM density in nearly all GM regions with a maximum global association in the left hippocampus and an additional local maximum in the right hippocampus. We did not observe any negative associations with GM regions at the same

statistical threshold. Figure 1B and Figure 1C display the surface-based analysis results of the positive association between the memory composite score and cortical thickness. The thickness of almost the entire cortical surface is associated with memory composite scores in the positive direction. The most significant clusters associated with memory composite scores were found in entorhinal cortex of both hemispheres. We did not observe any negative associations at the same statistical threshold. These SurfStat results are similar in regional distribution to those obtained from VBM analyses of GM density.

A widespread pattern of significant voxels was also detected in the VBM analysis of the relationship between executive function composite scores and GM density (Figure 2A; $p<0.001$ (FWE), k=100 voxels). Executive function was significantly associated with GM density in the bilateral frontal lobes, parietal lobes, cingulate, and temporal lobes, with a global maximum association in the right superior temporal lobe and additional local maxima in the left and right inferior parietal lobes. We did not observe any negative associations with GM. Figure 2 also shows the result of the surface-based analysis of the positive association between executive function and cortical thickness ($p<0.05$ (corrected with RFT)). Cortical thickness across nearly the entire cortical surface shows a significant association with the executive function composite score. The maximum global association between cortical thickness and executive function was observed in the bilateral middle temporal gyri, while additional maxima were observed in the bilateral inferior and medial temporal lobe, as well as the bilateral medial and lateral parietal lobes. The negative association between executive function and cortical thickness did not show any significant clusters.

We found a significant relationship between memory and executive function both in the combined sample and within each diagnostic group (Table 2). The inclusion of age, sex, and education did not significantly alter this relationship. To assess the specific relationship of executive function and brain atrophy independent from memory performance, we estimated the executive function composite score adjusted for memory and evaluated the relationship between the generated score and GM density and cortical thickness. The VBM analysis demonstrated significant associations between the executive function composite adjusted for memory and GM density in more focal regions of the bilateral frontal, parietal, and temporal lobes, as well as the cingulate cortex (Figure 3A; $p<0.001$ (FWE), k=100 voxels), with a global maximum in the left inferior parietal lobe and additional local maxima in the right inferior parietal lobe, bilateral superior parietal lobes, and bilateral lateral temporal lobes. We observed significant associations between the memory-adjusted executive function score and cortical thickness throughout the brain, with maximal associations in the bilateral inferior, medial, and superior parietal lobe, as well as the bilateral inferior temporal lobe (Figure 3B and 3C).

We also evaluated relationships within each group. In people with AD, we observed significant associations between memory and GM density in focal regions of the bilateral medial and lateral temporal lobes, with a global maximum in the left hippocampus (Figure 4A). We observed a similar though expanded pattern of significant voxels among people with MCI. We found associations between memory and bilateral medial and lateral temporal GM density, with a maximal association in the right hippocampus (Figure 4B). We did not find significant associations between memory and GM density among HC. We observed similar results in the surface-based analyses. For people with AD, there were significant associations between memory performance and cortical thickness in focal regions of the bilateral medial and lateral temporal lobe, with the most significant associations in the bilateral entorhinal cortex (Figure 4C). Among people with MCI, there was a significant association between memory and bilateral medial and lateral temporal lobe, frontal lobe, and parietal lobe cortical thickness, with the most significant associations in the bilateral

entorhinal cortex (Figure 4D). No cortical regions were associated with memory performance in HC.

We also evaluated the association between executive function and brain structure within clinical diagnostic groups (Figure 5) using both voxel- and surface-based analyses. Among people with AD, we found significant associations between executive function and both GM density (Figure 5A) and cortical thickness (Figure 5C) in widespread regions of the bilateral lateral and medial temporal lobes, superior, inferior, and medial parietal lobes, and focal frontal lobe regions. We found maximal associations in the bilateral inferior parietal GM density and in the left inferior temporal and bilateral parietal cortical thickness for the voxel-wise and surface-based analyses. Among people with MCI, executive function was associated with GM density across nearly the entire brain (Figure 5B), with the global maximum in the right superior temporal lobe and additional local maxima in the bilateral lateral temporal, parietal, and frontal lobes. We observed significant associations between executive function and cortical thickness among people with MCI across nearly the entire cortical surface (Figure 5D), with maximal associations in the bilateral lateral temporal and parietal lobes. We did not identify any significant associations between executive function and either GM density or cortical thickness in HC.

Discussion

We performed voxel-wise and surface-based association analyses of memory and executive function with grey matter (GM) density and cortical thickness across the whole brain. This whole brain methodology on a voxel-wise and surface-based level facilitates exploration of brain areas not easily assessed with region of interest (ROI) approaches. We found strong positive associations between memory and GM density and cortical thickness in the bilateral medial and lateral temporal lobes, with the most significant associations in the hippocampus and entorhinal cortex. Poorer executive function was also associated with lower GM density and cortical thickness across nearly the entire brain, with the most impressive associations in the bilateral parietal and temporal lobes. To estimate the relationship between executive function and brain structure independent of memory, we also evaluated the relationship between the executive function score adjusted for memory and GM density and cortical thickness, and found focal patterns of associations in the bilateral parietal, temporal, and frontal lobes. Finally, we assessed the associations between cognition and brain structure within each diagnostic group independently. We found significant association of lower memory scores and hippocampus atrophy in people with AD and with MCI, but not in HC. In addition, we found significant associations among people with AD and with MCI between executive function and GM and cortical atrophy in the bilateral temporal, parietal, and frontal lobes. Similar to the memory analysis, we did not observe any significant associations between executive function and brain structure in HC.

Our findings of associations between memory and temporal lobe GM density and cortical thickness are similar to results from a number of previous reports assessing brain structure and function that implicate temporal lobe structures (particularly the hippocampus and other MTL structures) as crucial for memory (Braskie et al. 2009; Cabeza and Nyberg 2000; Remy et al. 2005; S.L. Risacher et al. 2011; Small et al. 1999; Zakzanis et al. 2003; Deweer et al. 1995; Hackert et al. 2002; Laakso et al. 1995; Petersen et al. 2000; C. D. Smith et al. 1999; Barbeau et al. 2008; Chetelat et al. 2003; Goto et al. 2011; Leube et al. 2008; Schmidt-Wilcke et al. 2009; Di Paola et al. 2007). The presence of associations with a number of other cortical regions also suggests other brain regions that may be important in memory performance (Cabeza 2008; Cabeza et al. 2008; Cabeza and Nyberg 2000; Shimamura 1995; Zakzanis et al. 2003; Grady et al. 2003; Convit et al. 2000; Laakso et al. 1995; Barbeau et al. 2008; Di Paola et al. 2007; Leube et al. 2008; Remy et al. 2005).

However, the observed associations between memory performance and brain structure in regions of the frontal and parietal lobes may be partially related to the presence of differences in brain atrophy and memory across the diagnostic groups. When we evaluated these associations separately in the individual diagnostic groups (MCI and AD), the associations between memory and brain structure were more focal in the medial and lateral temporal lobes. The differences in association between the MCI only and AD only analyses were surprising, with MCI participants showing a more significant pattern. However, this difference may be due to increased sample size (396 MCI vs. 188 AD). Finally, the lack of associations in the HC participants is surprising, as some previous reports have reported associations between MTL atrophy and memory performance (Braskie et al. 2009; Convit et al. 2000; Jagust et al. 2006). However, the more stringent statistical thresholds employed in brain wide voxel- and surface-based analyses may have precluded the observation of any associations within the HC. In addition, the ADNI HC group appears to be particularly resistant to decline (Weiner et al. 2011; Chiang et al. 2011).

Executive function was significantly associated with brain structure especially in regions of the bilateral temporal and parietal lobes and to a lesser extent in the bilateral frontal lobes. The relative significance of clusters in the temporal and parietal lobes compared to the hypothesized clusters in the frontal lobe was notable, as a number of previous reports have shown the importance of the frontal lobe in executive function (Newman et al. 2007; Rabin et al. 2009; Ino et al. 2003; Moll et al. 2002; Monchi et al. 2001; Rushworth et al. 2002; A. B. Smith et al. 2004; Taylor et al. 2004; Wager et al. 2004; Zakzanis et al. 2005; Oh et al. 2011; Huey et al. 2009). However, many of the tasks included in the executive function score target multiple executive and non-executive cognitive processes, including set-shifting (TMT), visuospatial function and motor control (TMT, CDT), working memory and attention (TMT, Digit Symbol, Digit Span), verbal and semantic function (category fluency), and semantic and episodic memory (CDT, Digit Span, category fluency). Previous studies utilizing both structural and functional MRI to evaluate brain structures associated with set-shifting, visuospatial function and motor control, working memory, and attention have repeatedly demonstrated the importance of bilateral parietal and temporal lobe regions, in addition to frontal lobe regions (Zakzanis et al. 2005; Ino et al. 2003; Moll et al. 2002; A. B. Smith et al. 2004; Taylor et al. 2004; Wager et al. 2004; Cahn-Weiner et al. 1999; Pa et al. 2010; Thomann et al. 2008). In addition, lateral temporal and frontal lobes have been shown to be associated with semantic fluency and verbal ability (Amici et al. 2007; Apostolova et al. 2008; Brambati et al. 2006; Costafreda et al. 2006; Grossman et al. 2004; Hart et al. 2007; Hirono et al. 2001; Pantel et al. 2004; Saykin et al. 1999; Venneri et al. 2008; Kramer et al. 2007; Huey et al. 2009; Newman et al. 2007). Therefore, the observed associations between executive function and GM and cortical atrophy in temporal and parietal lobes are likely due to the importance of these regions in the executive sub-domains and non-executive cognitive tasks evaluated by the specific psychometric tests included in the ADNI battery. In fact, previous studies, including one using the ADNI sample, demonstrated that people with MCI with a primary deficit in executive function rather than memory show more atrophy in parietal and frontal regions than people with MCI with a primary memory deficit (Dickerson and Wolk 2011; Pa et al. 2009). Overall, these findings suggest that the executive tasks included in the ADNI battery may test a number of executive and non-executive cognitive sub-domains which are mediated by parietal and temporal lobe in addition to frontal lobe. Another important consideration is the early relative prominence of temporoparietal neurodegeneration in AD.

The current study has a number of strengths. First, this is the first study to our knowledge to assess the relationship between psychometrically sophisticated composite scores of memory and executive function and structural brain atrophy using multiple whole-brain methodologies (VBM and Freesurfer/SurfStat). The association of commonly used

individual cognitive measures with structural MRI changes has been previously examined in detail both in the ADNI sample and independent cohorts. However, previous studies primarily focused on single tests as representative of the entire memory and executive function domains. In this study, we used composite scores obtained by combining multiple tests to better estimate the underlying cognitive functioning levels. In addition, the majority of previous reports utilized ROI methodologies to evaluate relationships between memory and executive function and brain structure. The use of multiple whole-brain analysis methodologies in the present study may provide a more comprehensive assessment of brain areas associated with differences in memory and executive function, as they are not dependent upon a priori hypotheses. Finally, the sample of AD, MCI, and HC participants utilized in the present study (n=810) is the largest cohort to date in a study assessing the relationship of cognition and brain structure both across the combined cohort and within each diagnosis group.

There are some limitations to the current study. Only baseline MRI scans and cross-sectional composite scores were analyzed in the present study. Future investigation of the association of longitudinal decline in memory and executive function with cross-sectional and longitudinal measures of brain atrophy is warranted. In addition, the relationship between other sub-domains of executive function (i.e., judgment and problem-solving) and brain structure could not be assessed due to the limits of the ADNI psychometric test battery. Future studies with more targeted executive function assessments would be beneficial to evaluate the relationship between different executive sub-domains and brain structure. A number of AD and MCI participants were taking AD-indicated medications at the time of assessment which may have altered their cognitive performance (Epstein et al. 2010). Finally, we analyzed relationships between brain structure and composite measures of memory and of executive functioning. Composite measures are attractive for such analyses for a variety of reasons (Crane et al. 2008) particularly given their potential utility for longitudinal modeling and/or as an outcome measures in pharmaceutical or intervention trials. However, these analyses using composite scores by their nature ignore any differential relationships with brain structure across different memory (or executive functioning) sub-domains or component processes. It may be interesting to identify the brain structures associated with these sub-domains. Additional studies applying advanced psychometric methods to the study of cognitive sub-domains of memory and executive function will be important for research on early and later stages of AD and may benefit from inclusion of test measures more specifically designed to reliably segment cognitive component processes than standard clinical tests.

In summary, the present study provides insight into the association of memory and executive functioning with brain atrophy across the whole brain on a voxel-wise and surface-based level. Overall, the results highlight the important role of changes in brain structure in cognitive decline associated with AD.

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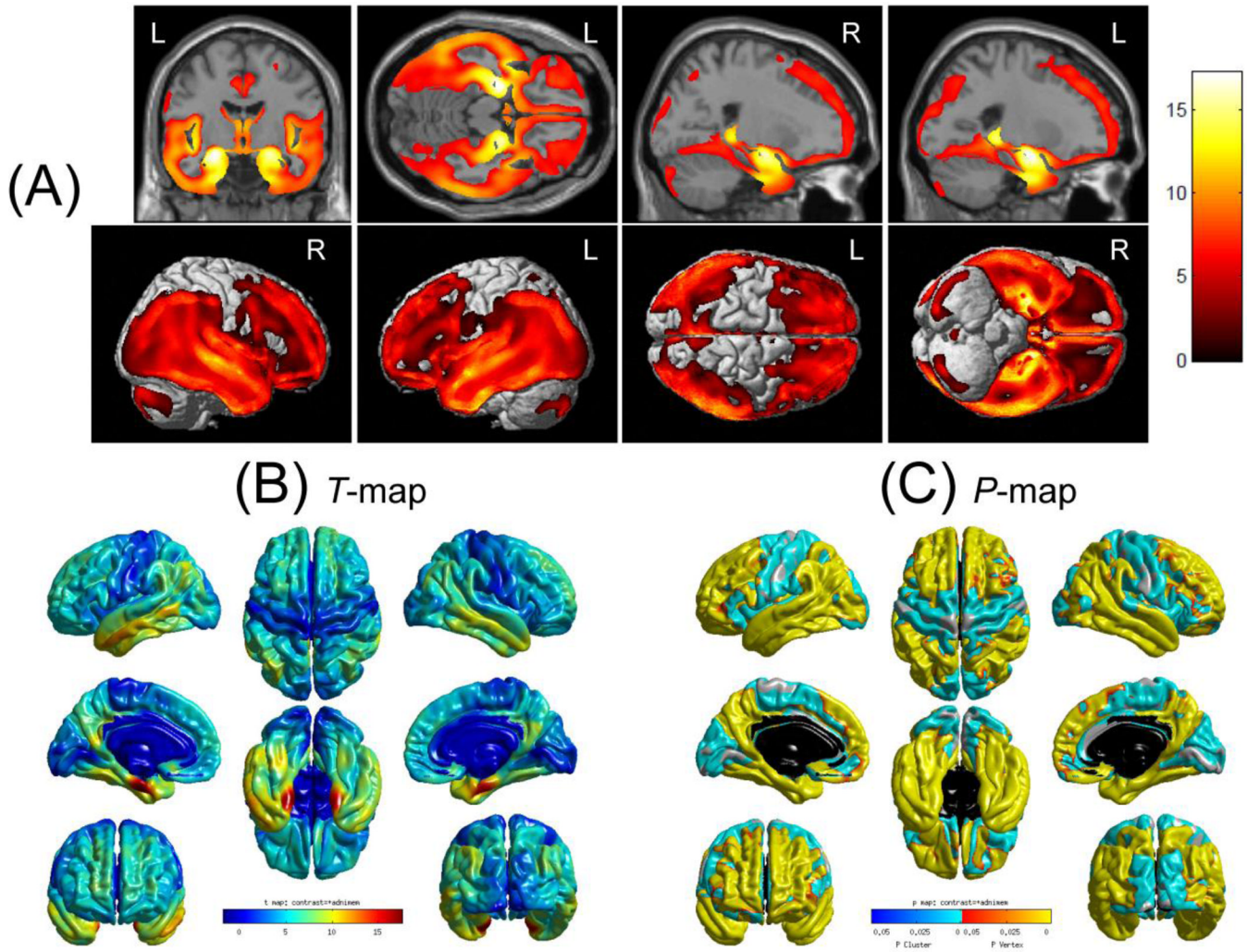

Fig. 1. Relationship between Memory and Brain Structure

A significant positive association was observed between the memory composite score and GM density throughout the brain (A; $p<0.001$ (FWE), k=100 voxels) in the combined sample (n=810; 188 AD, 396 MCI, 226 HC), with the most significant differences observed in the bilateral medial temporal lobes. The surface-based analysis also showed significant associations between memory and cortical thickness shown as a T-value map (B) and corrected *P*-value map (C; thresholded at $p<0.05$ (corrected with RFT)). In B, positive t values (red, yellow) indicate thicker cortical thickness. In C, two *p* values (*p* values for each vertex and *p* values for each cluster) are shown simultaneously. The *p*-value for clusters indicates significant corrected *p* values with the lightest blue color and the *p*-value for vertices indicates significant corrected *p* values with the lightest yellow color. Note that the *p*-value for vertices overlaps the *p*-value for clusters. (Note: VBM results in (A) are displayed on the following cross-sections to emphasize the maximum clusters (left to right; MNI coordinates): (−23, −8, −16, coronal), (−23, −8, −16, axial), (−23, −8, −16, sagittal), (23, −7, −15, sagittal))

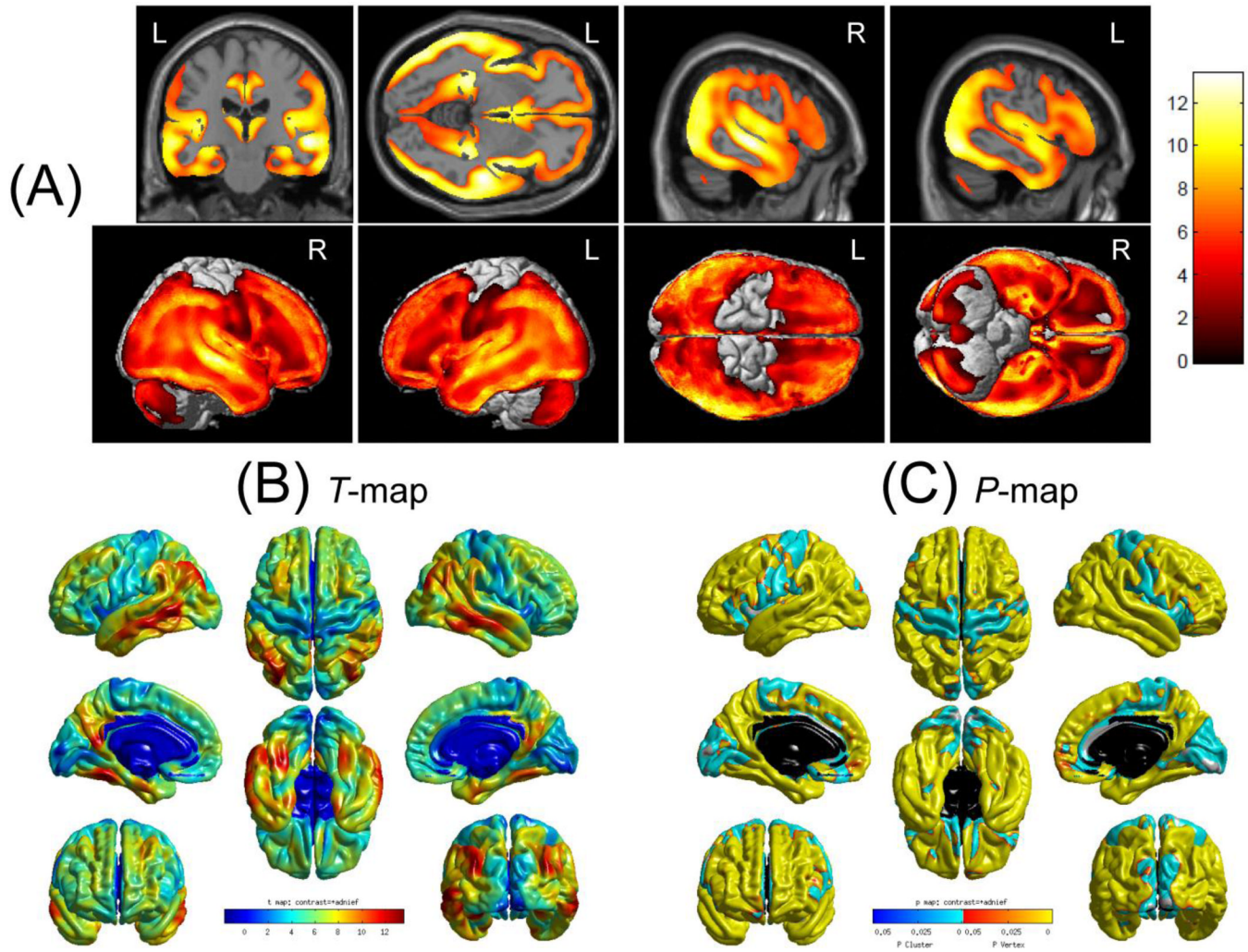

Fig. 2. Relationship between Executive Function and Brain Structure

Executive function was significantly positively associated with GM density across nearly the entire brain (A; p<0.001 (FWE), k=100 voxels) in the combined sample (n=810; 188 AD, 396 MCI, 226 HC), with local maxima in the bilateral temporal and parietal lobes. A significant positive association was also observed between executive function and cortical thickness across nearly the entire cortex, displayed as a T-value map (B) and corrected *P*-value map (C; thresholded at p<0.05 (corrected with RFT)). In B, positive t values (red, yellow) indicate thicker cortical thickness. In C, two p values (p values for each vertex and p values for each cluster) are shown simultaneously. The p-value for clusters indicates significant corrected p values with the lightest blue color and the p-value for vertices indicates significant corrected p values with the lightest yellow color. Note that the p-value for vertices overlaps the p-value for clusters. (Note: VBM results in (A) are displayed on the following cross-sections to emphasize the maximum clusters (left to right; MNI coordinates): (53, −22, −5, coronal), (53, −22, −5, axial), (53, −22, −5, sagittal), (−49, −70, −8, sagittal))

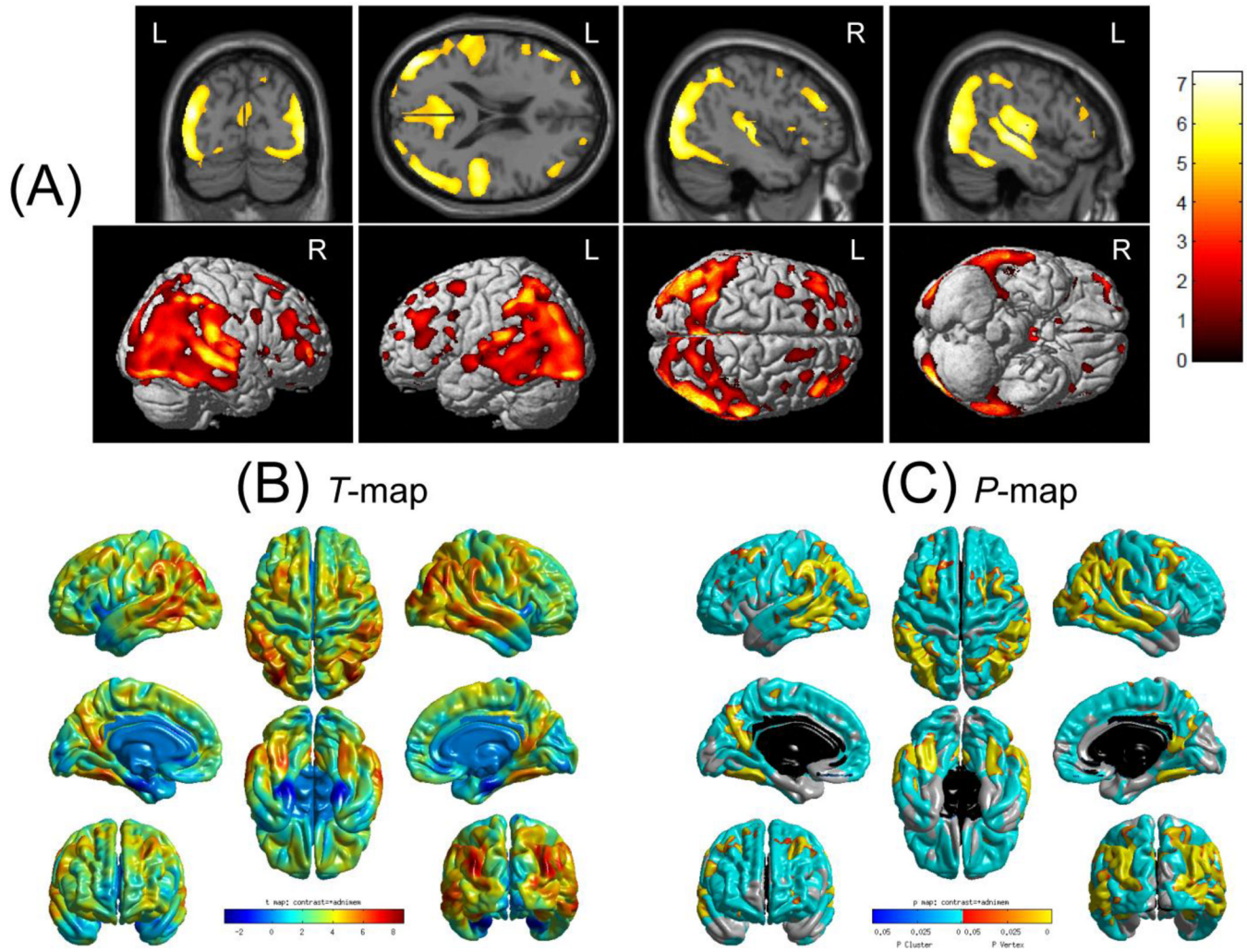

Fig. 3. Relationship between Executive Function Adjusted for Memory and Brain Structure

The results of the VBM analysis demonstrated a significant positive association between memory-adjusted executive function and GM density in the parietal, temporal, and frontal lobes (A; $p<0.001$ (FWE), k=100 voxels) in the combined sample (n=810; 188 AD, 396 MCI, 226 HC), with maximal clusters observed in the bilateral inferior parietal lobes. A significant association between executive function adjusted for memory and cortical thickness was also observed across nearly the entire brain, with maximal associations in the bilateral temporal and parietal cortices. These results are displayed as a T-value map (B) and corrected *P*-value map (C; thresholded at $p<0.05$ (corrected with RFT)). In B, positive t values (red, yellow) indicate thicker cortical thickness. In C, two *p* values (*p* values for each vertex and *p* values for each cluster) are shown simultaneously. The *p*-value for clusters indicates significant corrected *p* values with the lightest blue color and the *p*-value for vertices indicates significant corrected *p* values with the lightest yellow color. Note that the *p*-value for vertices overlaps the *p*-value for clusters. (Note: VBM results in (A) are displayed on the following cross-sections to emphasize the maximum clusters (left to right; MNI coordinates): (−43, −78, 19, coronal), (−43, −78, 19, axial), (−43, −78, 19, sagittal), (51, −76, −3, sagittal))

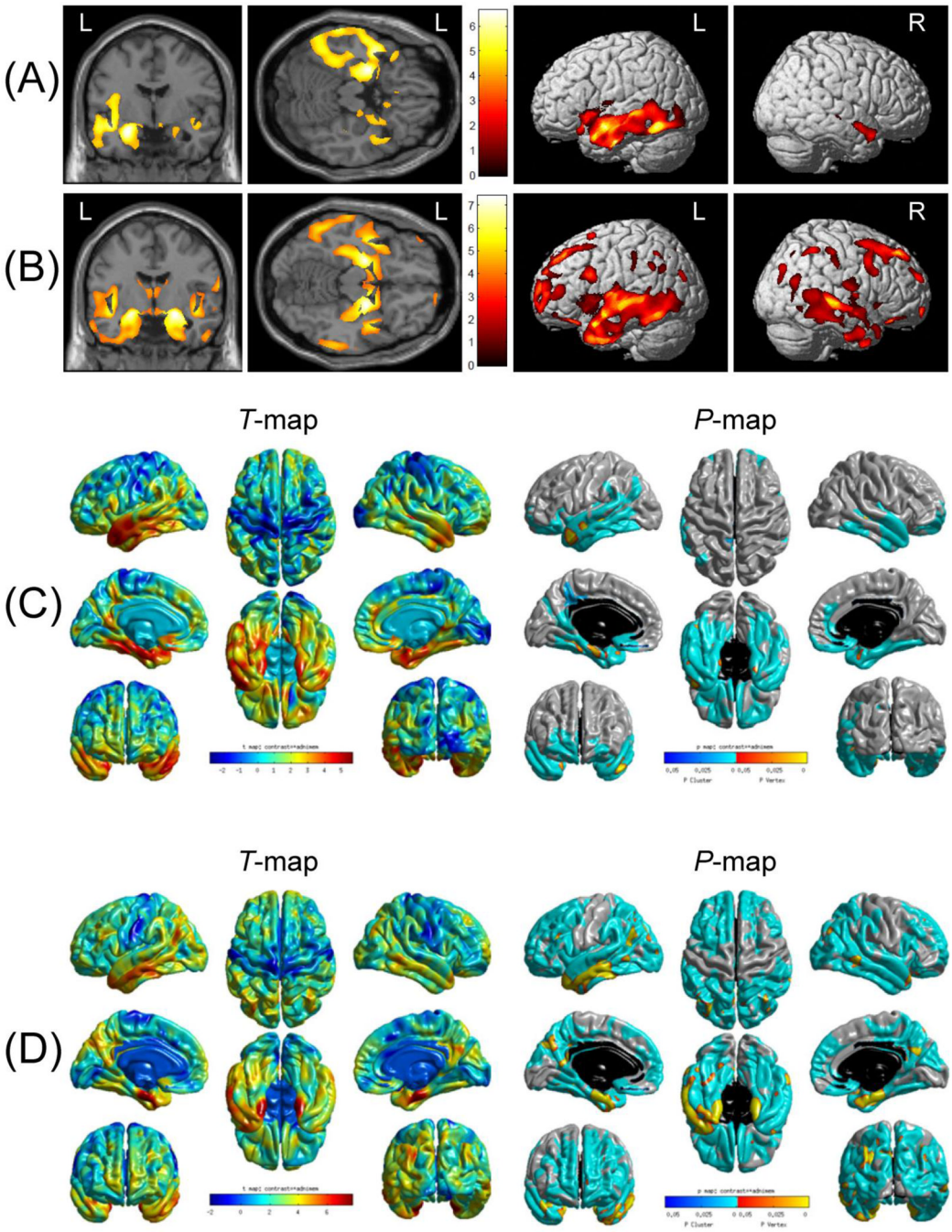

Fig. 4. Relationship between Memory and Brain Structure within Diagnostic Groups

Significant positive associations between memory and medial and lateral temporal GM density were observed in the AD only group (A; n=188) and the MCI only group (B; n=396). All VBM analyses are displayed at a voxel-wise threshold of $p<0.001$ (FDR) and a minimum cluster size of 100 voxels. Similar results were observed in the surface-based analyses, with significant associations between memory and cortical thickness in the AD only group (C; T-value map on the left and corrected *P*-value map (thresholded at $p<0.05$ (corrected with RFT) on the right) and in the MCI only group (D; T-value map on the left and corrected *P*-value map (thresholded at $p<0.05$ (corrected with RFT) on the right). In B, positive t values (red, yellow) indicate thicker cortical thickness. In C, two *p* values (*p*

values for each vertex and *p* values for each cluster) are shown simultaneously. The *p*-value for clusters indicates significant corrected *p* values with the lightest blue color and the *p*-value for vertices indicates significant corrected *p* values with the lightest yellow color. Note that the *p*-value for vertices overlaps the *p*-value for clusters. No significant associations were observed using either the voxel- or surface-based analysis in the HC only group. (Note: VBM results are displayed on the following cross-sections to emphasize the maximum clusters (left to right; MNI coordinates): for (A), (−26, −3, −20, coronal), (−26, −3, −20, axial); for (B), (22, −6, −14, coronal), (22, −6, −14, axial))

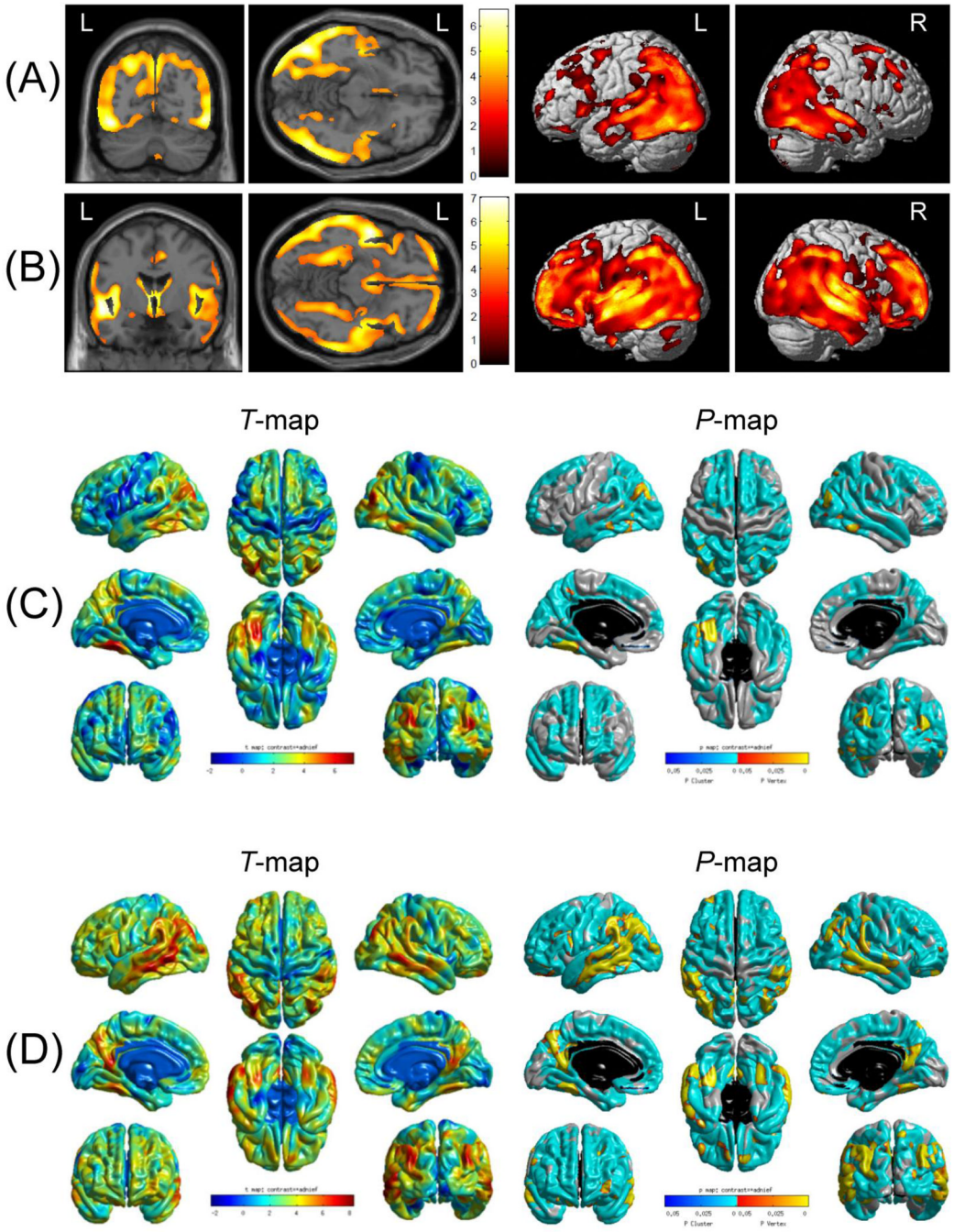

Fig. 5. Relationship between Executive Function and Brain Structure within Diagnostic Groups

The VBM analyses showed significant associations between executive function and GM density in the bilateral frontal, temporal, and parietal lobes in both the AD only group (A; n=188) and MCI only group (B; n=396). All VBM analyses are displayed at a voxel-wise threshold of $p<0.001$ (FDR) and a minimum cluster size of 100 voxels. A similar pattern of association was observed in the surface-based analyses, with significant associations between executive function and temporal and parietal lobe cortical thickness in the AD only group (C; T-value map on the left and corrected *P*-value map (thresholded at $p<0.05$ (corrected with RFT) on the right) and cortical thickness across nearly the entire cortical surface in the MCI only group (D; T-value map on the left and corrected *P*-value map

(thresholded at $p<0.05$ (corrected with RFT) on the right). In B, positive t values (red, yellow) indicate thicker cortical thickness. In C, two p values (p values for each vertex and p values for each cluster) are shown simultaneously. The p-value for clusters indicates significant corrected p values with the lightest blue color and the p-value for vertices indicates significant corrected p values with the lightest yellow color. Note that the p-value for vertices overlaps the p-value for clusters. No significant associations between executive function and brain structure were observed using either the voxel- or surface-based analysis in the HC only group. (Note: VBM results are displayed on the following cross-sections to emphasize the maximum clusters (left to right; MNI coordinates): for (A), (−44, −67, −11, coronal), (−44, −67, −11, axial); for (B), (−52, −3, −11, coronal), (−52, −3, −11, axial))

Table 1

Sample characteristics

	AD (n=188)	MCI (n=396)	HC (n=226)	*p*-value[a]
Age at baseline	75.5±7.4	74.8±7.4	75.9±5.0	0.145
Gender (Male/Female)	98/90	255/141	118/108	0.002
Years of education	14.7±3.1	15.7±3.0	16.1±2.8	< 0.001
Memory composite score	−0.84±0.54	−0.09±0.58	0.97±0.53	< 0.001
Executive function composite score	−0.91±0.82	−0.04±0.78	0.71±0.69	< 0.001

Values are Mean±Standard Deviation; AD = Alzheimer's disease, MCI = mild cognitive impairment; HC = healthy older adult;

[a]For categorical variables, *p*-value was computed using Pearson chi-square; for continuous variables, *p*-value was computed using one-way analysis of variance.

Table 2

Associations between memory and executive function (EF) composite scores

	Memory vs. EF (R-value)	*p*-value	Memory vs. EF (Partial correlation coefficient)	*p*-value[a]
Full sample (n=810)	0.676	<0.001	0.657	<0.001
AD only (n=188)	0.430	<0.001	0.432	<0.001
MCI only (n=396)	0.454	<0.001	0.424	<0.001
HC only (n=226)	0.373	<0.001	0.288	<0.001

[a]Includes age at baseline, gender, and years of education as covariates