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Multi-modal imaging predicts memory performance in normal aging and cognitive decline

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Abstract

This study (n = 161) related morphometric MR imaging, FDG-PET and APOE genotype to memory scores in normal controls (NC), mild cognitive impairment (MCI) and Alzheimer's disease (AD). Stepwise regression analyses focused on morphometric and metabolic characteristics of the episodic memory network: hippocampus, entorhinal, parahippocampal, retrosplenial, posterior cingulate, precuneus, inferior parietal, and lateral orbitofrontal cortices. In NC, hippocampal metabolism predicted learning; entorhinal metabolism predicted recognition; and hippocampal metabolism predicted recall. In MCI, thickness of the entorhinal and precuneus cortices predicted learning, while parahippocampal metabolism predicted recognition. In AD, posterior cingulate cortical thickness predicted learning, while APOE genotype predicted recognition. In the total sample, hippocampal volume and metabolism, cortical thickness of the precuneus, and inferior parietal metabolism predicted learning; hippocampal volume and metabolism, parahippocampal thickness and APOE genotype predicted recognition. Imaging methods appear complementary and differentially sensitive to memory in health and disease. Medial temporal and parietal metabolism and morphometry best explained memory variance. Medial temporal characteristics were related to learning, recall and recognition, while parietal structures only predicted learning.

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Disclosure statement Anders M. Dale is a founder and holds equity in CorTechs Labs, Inc, and also serves on the Scientific Advisory Board. The terms of this arrangement have been reviewed and approved by the University of California, San Diego in accordance with its conflict of interest policies.

Keywords

MCI; AD; PET; MR morphometry; APOE; episodic memory

1. Introduction

The brain's episodic memory network comprises medial temporal lobe (MTL) structures, medial and lateral parietal, as well as prefrontal cortical areas (see Figure 1). This network has been supported by both imaging and clinical studies. Imaging studies have shown these areas to be normally engaged during episodic recall (Buckner, 2004; Buckner and Carroll, 2007; Hassabis and Maguire, 2007; Rugg et al., 2002), and patient studies have pointed to a critical role of MTL structures for the formation (Scoville and Milner, 1957), and likely, maintenance (Moscovitch et al., 2006), of episodic memories. The MTL has rich projections to parietal regions, important for the representation of information being retrieved (Hassabis and Maguire, 2007; Rugg et al., 2002; Wagner et al., 2005). Selected parietal regions have major interconnections with prefrontal areas, which play part in monitoring and control processes supporting memory (Buckner, 2004; Hassabis and Maguire, 2007).

The last two decades of research using structural Magnetic Resonance Imaging (MRI) and metabolic Positron Emission Tomography (PET) with 2[18F]fluoro-2-deoxy-D-glucose (FDG) as the tracer, have shown that probable Alzheimer's disease (AD) and mild cognitive impairment (MCI) are characterized by a specific pattern of cerebral morphometric reductions and hypometabolism (for a review, see (Mosconi et al., 2007)). MCI is often considered a preclinical stage of AD, with an annual conversion rate to AD of 6-25% (Petersen et al., 2001). The alterations in MCI and AD occur within the episodic memory network, including MTL areas, retrosplenial, posterior cingulate, precuneus, lateral parietal and prefrontal cortices (Barnes et al., 2007; Baron et al., 2001; Chetelat et al., 2003; Convit et al., 1995; De Santi et al., 2001; Du et al., 2007; Fischl et al., 2002; Frisoni et al., 2002; Herholz et al., 2002; Ishii et al., 2005), and are presumed to underlie the prominent and progressive memory loss detectable even in early stages of the disease. Below, central research questions are reviewed with reference to select findings.

Different brain characteristics relevant for the understanding of memory and memory problems in MCI and AD may be captured by FDG-PET and MR morphometry. However, few studies combining these imaging methods have been reported (Chetelat et al., 2003; De Santi et al., 2001; DeCarli et al., 1996; Ishii et al., 2005; Jagust et al., 2002). It has been assumed that FDG-PET may detect early neocortical dysfunction before atrophy appears. Consistent with this, DeSanti and colleagues (De Santi et al., 2001) reported that metabolism reductions exceeded volume losses in MCI. Jagust et al., on the other hand, found that cingulate hypometabolism was a significant risk factor in addition to MR measures of hippocampal atrophy, but the latter was a more statistically robust risk factor in a group of cognitively impaired but not demented (CIND) elderly (Jagust et al., 2002; Wu et al., 2002). However, both PET and MR imaging have proven to differentiate between NC, MCI, and AD (Chetelat et al., 2003; Convit et al., 1995; De Santi et al., 2001; Fischl et al., 2002; Ishii et al., 2005; Ishii et al., 1998; Jack et al., 1999; Matsuda, 2001; Mosconi et al., 2007).

In addition to age, the apolipoprotein E (APOE) genotype is the most influential AD risk factor. The APOE ϵ_4 allele is a risk factor for AD (Corder et al., 1995a; Corder et al., 1995b; Corder et al., 1993) compared to the more frequent APOE ϵ_3 , while APOE ϵ_2 carriers develop AD later (Ohm et al., 1999). Different allelic combinations have been related to cognitive function (Jacobson et al., 2002) and both structural and functional

neuroimaging measures (Cherbuin et al., 2007; Espeseth et al., 2006; Han et al., 2007; Lind et al., 2006a; Lind et al., 2006b; Lind et al., 2006c; Persson et al., 2006).

Some cross-sectional studies have reported that healthy elderly and AD patients with APOE ϵ_4 show poorer memory performance whereas others have not (see review by (Nilsson et al., 2002). Nilsson and colleagues (Nilsson et al., 2006) found an interaction of APOE and age, with more pronounced ϵ_4 -related episodic memory deficits for persons 70 years of age and older. They also reported a dose-effect, with worse deficits for carriers of two ϵ_4 -alleles than carriers of one ϵ_4 -allele. Tupler et al. (Tupler et al., 2007) concluded that APOE ϵ_4 predicts longitudinal memory decline in healthy controls and that hippocampal MR volume adds slightly to the predictive value.

A complex relation between APOE genotype and imaging data has emerged. For instance, ϵ_4 has been associated with both increased (Bookheimer et al., 2000) and reduced (Lind et al., 2006b) activity in temporal, parietal and frontal areas in fMRI studies. Likewise, structural MR studies have identified both morphometric reductions (Lind et al., 2006b) and a pattern of regional cortical thinning and thickening related to ϵ_4 (Espeseth et al., 2006). As discussed by Lind and colleagues (Lind et al., 2006c), factors such as task difficulty (in fMRI), and, importantly, health/ cognitive status of the group studied likely influence whether compensatory processes and associated brain activity come into play. It is possible that the same may apply to morphometric changes. The ϵ_4 allele has, however, been associated with lower cerebral metabolism in MCI-patients and healthy young and elderly (Mosconi et al., 2004; Reiman et al., 2001; Reiman et al., 2004; Small et al., 2000). Since no single study has incorporated FDG-PET, MR morphometry, and APOE status in relation to memory in NC, MCI and AD, it is not known how these variables interact or overlap in mediating memory. APOE ϵ_4 is not promoting AD specifically, but is associated with risk for a number of detrimental conditions that may yield burdens on memory processing, including high cholesterol levels and coronary events (Scuteri et al., 2001).

Different relationships between memory and PET metabolism and MR morphometry may be characteristic of normal aging, MCI and AD. For instance, individual differences in volume signify something else in health, i.e. normal variation in synaptic and neuronal count, than in sickness, i.e. variation in neuronal and synaptic dysfunction and death. In normal aging, memory, including list learning measures with clinically applied retention intervals (< 1 h) appear weakly or not related to MTL volumes (Petersen et al., 2000; Van Petten, 2004; Walhovd et al., 2004) and cortical thickness (Walhovd et al., 2006). However, memory has consistently been related to MTL volumes in MCI and AD (Edison et al., 2007; Petersen et al., 2000; Rossi et al., 2007). Different FDG-PET and memory relationships have also been reported in different cohorts. In normal aging, hippocampal PET metabolism has been related to memory (Eustache et al., 1995; Langley and Madden, 2000), while in MCI and AD, broader correlations have been reported, including posterior cingulate (Chetelat et al., 2003), hippocampus, temporal (Edison et al., 2007), temporo-parietal (Bittner et al., 2005; Chetelat et al., 2005) and frontal areas (Chetelat et al., 2005).

The predictive power of different ROIs may also depend on the type of memory measure. There is consensus that explicit memory relies on a specific brain system, with great MTL involvement (see e.g. (Haist et al., 1992)). However, without abandoning this premise, some theoretical views, such as Moscovitch's component process model (Langley and Madden, 2000; Moscovitch, 1992) Moscovitch (Moscovitch, 1992) hold that recognition and recall are mediated by partly different brain areas. Prefrontal regions contribute to strategic, explicit measures of memory by selecting and implementing encoding strategies and

determining the correct context of encoded information, “working with memory” (Langley and Madden, 2000; Moscovitch, 1992). The MTL region, on the other hand, process associative memories that are automatically retrieved with appropriate cues (Langley and Madden, 2000; Moscovitch, 1992). Self-initiated learning and free recall are examples of measures requiring strategic efforts, and should rely on frontal lobe function. Note that in many common neuropsychological tests, including the one used in this study, learning is actually measured by recall (Lezak, 1995), and hence, according to this view, will rely on frontal lobe function. Recognition tasks, on the other hand, rely considerably less on strategic memory. In recognition, the best cues are provided, namely the items themselves, so search demands are low.

The component process model has received considerable support (Langley and Madden, 2000). For instance, aging appears to especially affect strategic, effortful memory and frontal brain regions (Buckner, 2004; Nyberg et al., 2003). According to the component process model, one would expect all memory measures to be related to MTL characteristics, while only free learning and recall should be related to prefrontal characteristics. Based on the above discussion, these relationships would be expected to hold for metabolism for healthy controls, and both metabolism and volume in MCI and AD. However, Haist et al. (Haist et al., 1992) reported that recall and recognition were similarly impaired in amnesic patients with hippocampal and diencephalic damage. Thus, recall and recognition may also be similarly related to ROI characteristics of the episodic memory network in MCI and AD, since both types of memory rely on the MTL, which is a primary site of neural degeneration.

While imaging and lesion data exists to support a special role for prefrontal areas in strategic memory (Cabeza and Nyberg, 2000a; Fletcher and Henson, 2001; Langley and Madden, 2000), relatively little FDG-PET and MR morphometry evidence have provided support for the component-process and similar models. Eustache et al. (Eustache et al., 1995) used PET measures of oxygen consumption, and did find a correlation between right prefrontal cortex and AVLT delayed recall and between left parietotemporal cortex and recognition as well as hippocampal correlations with associate learning from another test (Wechsler Memory Scale - WMS). However, only the correlations for the hippocampal region and associate learning survived correction for age effects, and hence, different roles of prefrontal and MTL areas in free recall and recognition were not supported by these data. Eustache et al.’s (Eustache et al., 1995) sample spanned a broad age range (20-68 years) with a relatively small number of subjects ($n = 25$), so firm conclusions cannot be drawn based on this. However, other PET studies of young adults by Nyberg and colleagues (Nyberg et al., 2002) and Cabeza and colleagues (Cabeza et al., 1997) have not found much evidence for differential frontal activations in recall and recognition. Rather, in the study by Cabeza et al., recognition was associated with higher activation in the right inferior parietal cortex. One study related both FDG-PET and MR volumes to memory scores (Chetelat et al., 2003), and used an experimental paradigm to disentangle encoding and recall in MCI. In their experimental paradigm, Chetelat and colleagues tested encoding by a recognition test, whereas retrieval was tested by free recall. A partial dissociation of metabolic and structural correlates was indicated: hippocampal MR volume was associated with encoding and retrieval, while hippocampal FDG-PET was associated with encoding, and retrieval correlated with posterior cingulate metabolism only. Knowledge is now needed on the relative contribution of morphometric vs. metabolic variables to memory function as typically tested clinically.

The present study investigated how FDG-PET and MR morphometry of the above described episodic memory network (Buckner, 2004; Cabeza and Nyberg, 2000b; Matsuda, 2001; Wagner et al., 2005) predict memory in healthy aging, MCI, and AD. One of the most frequently used neuropsychological memory tests, the Auditory Verbal Learning Test (AVLT; see e.g. (Lezak, 1995)), was used, and the samples were drawn from the publicly

available Alzheimer's Disease Neuroimaging Initiative (ADNI) study. We also investigated whether APOE genotype, age and gender explained any unique variance in memory performance once the cerebral variables are taken into account. This study is important for two reasons 1) To further understanding of how and which brain characteristics are important for memory function, and 2) To uncover the measures' sensitivity to memory in patients and healthy elderly, possibly indicating independent or overlapping potential for predicting diagnostic change. No study relating both cerebral MRI and PET to memory function in NC, MCI and AD has been conducted, so hypotheses must be tentative. However, based on theoretical frameworks and previous more narrow studies, the following hypotheses were made:

1. Both MRI morphometry and PET contribute to explain variance in memory, with PET showing a slight advantage. APOE genotype may add to the explained variance. In line with previous literature, we expect positive relationships with both MR morphometry and FDG-PET: higher volume/thickness and metabolism is related to better memory (Chetelat et al., 2003), yet PET may have a superior diagnostic sensitivity (De Santi et al., 2001) that may also be reflected in greater sensitivity to memory. The latter part of the hypothesis is based on APOE genotype being a broad risk factor with some relationship with memory as well as imaging findings (e.g. (Espeseth et al., 2006; Han et al., 2007; Nilsson et al., 2002; Scuteri et al., 2001)).
2. MR morphometry is not related to memory in NC, but positively related to memory function in MCI and AD. The strongest morphometry-memory relationships are expected for MTL, intermediate for medial parietal areas, and somewhat weaker for inferior parietal and medial orbitofrontal ROIs. This is in accordance with findings of atrophic changes in MCI and AD starting in MTL areas, then spreading to medial parietal, and later inferior parietal and frontal areas (Edison et al., 2007; Mosconi et al., 2007; Petersen et al., 2000; Rossi et al., 2007; Van Petten, 2004; Walhovd et al., 2006; Walhovd et al., 2004).
3. PET metabolism is related to memory function in all groups, but ROI-wise broader and stronger relationships are expected in MCI and AD than NC. MTL metabolism is expected to relate to memory in all groups. Parietal and prefrontal metabolism will likely also be related to memory in NC, but stronger positive relationships are expected in MCI and AD, especially for posterior cingulate. In normal aging, hippocampal metabolism has been related to memory (Eustache et al., 1995; Langley and Madden, 2000). In MCI and AD, variance in pathology is influential, and more correlations have been reported involving hippocampus/temporal (Edison et al., 2007), temporo-parietal (Bittner et al., 2005; Chetelat et al., 2005), PC (Chetelat et al., 2003), and frontal areas (Chetelat et al., 2005). PC hypometabolism is a hallmark of AD (Mosconi et al., 2007) and has been linked to retrieval problems in MCI (Chetelat et al., 2003).
4. MTL measures are related to both learning/recall and recognition, while prefrontal and PC characteristics will be relatively more related to learning/recall. The hypothesis is based on knowledge that prefrontal regions contribute to implementing encoding and retrieval strategies, while MTL regions mediate automatic retrieval. The PC has previously been related especially to recall, relative to recognition in MCI (Chetelat et al., 2003).

2. Methods

The raw data used in the preparation of this article were obtained from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database (www.loni.ucla.edu/ADNI). The ADNI

was launched in 2003 by the National Institute on Aging (NIA), the National Institute of Biomedical Imaging and Bioengineering (NIBIB), the Food and Drug Administration (FDA), private pharmaceutical companies and non-profit organizations. The primary goal of ADNI has been to test whether serial MRI, PET, other biological markers, and clinical and neuropsychological assessment can be combined to measure the progression of MCI and early AD. The Principal Investigator of this initiative is Michael W. Weiner, VA Medical Center and University of California – San Francisco. There are many co-investigators, and subjects have been recruited from over 50 sites across the U.S. and Canada. The initial goal of ADNI was to recruit 800 adults, ages 55 to 90, including healthy elderly, MCI and AD patients to participate and be followed for 2-3 years. For up-to-date information see www.adni-info.org.

2.1. Sample

ADNI eligibility criteria are described at http://www.adniinfo.org/index.php?option=com_content&task=view&id=9&Itemid=43. Briefly, subjects are 55-90 years of age, had an informant able to provide an independent evaluation of functioning, and spoke either English or Spanish. All subjects were willing and able to undergo all test procedures including neuroimaging and agreed to longitudinal follow up. Specific psychoactive medications are excluded. General inclusion/exclusion criteria are as follows: 1. Normal subjects: Mini-Mental State Examination (MMSE) (Folstein et al., 1975) scores between 24-30 (inclusive), a CDR of 0, non-depressed, non-MCI, and nondemented. 2. MCI subjects: MMSE scores between 24-30 (inclusive; exceptions made on a case by case basis), a memory complaint, objective memory loss measured by education adjusted scores on Wechsler Memory Scale Logical Memory II, a CDR of 0.5, absence of significant levels of impairment in other cognitive domains, essentially preserved activities of daily living, and an absence of dementia. 3. Mild AD: MMSE scores between 20-26 (inclusive; exceptions made on a case by case basis), CDR of 0.5 or 1.0, and meets NINCDS/ADRDA criteria for probable AD. For the present study, we further used memory and conversion information to exclude low functioning controls: a criterion for excluding a subject as a control the combination of 5 or 30 minutes recall at floor (hits minus intrusions = 0) with conversion to MCI at the first follow-up at 6 months. This led to the exclusion of 1 subject.

2.2. Neuropsychology

The AVLT (see e.g. (Lezak, 1995)) administration format used in the ADNI consists of reading a list of 15 words aloud to the participant. There are a total of eight recall trials and a recognition test. The first five trials (1-5) are *learning trials*, involving repeated reading of the test list (List A) followed each time by free recall of this list by the participant. The next trial is an interference trial in which a new list (List B) is read aloud and free recall is requested. Trial 6 follows, requesting recall as many words as possible from the first list (A), without reading this again. This is termed *5 minute recall*. Trial 7 is administered in the same way as trial 6 (i.e. no reading of List A) but following a delay, in the ADNI study 30 minutes. This is termed *30 minute recall*. Then there is a recognition test with 30 words read aloud, and the patient/participant is asked to indicate whether or not each word was on the list. This is termed *Recognition*. *Intrusions* are words that are recalled on each trial that were not on the list read aloud. For the present analyses, we summed the 5 learning trial to one learning score, and subtracted the number of intrusions (for recognition: errors) from the number of correctly recalled items for each memory measure.

2.3. MR scanning and morphometry

All scans used for the present paper were from 1.5 T scanners. Raw DICOM MRI scans (including two T1-weighted volumes per case) were downloaded from the public ADNI site

(<http://www.loni.ucla.edu/ADNI/Data/index.shtml>); these data were collected across a variety of scanners with protocols individualized for each scanner, as defined at <http://www.loni.ucla.edu/ADNI/Research/Cores/index.shtml>. After download, data 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. Using volumetric segmentation and cortical surface reconstruction and parcellation methods described below, analyzed image volumes were produced and reviewed for technical adequacy. The ROI measures include the volume of the hippocampus, and thickness of the entorhinal, parahippocampal, retrosplenial, posterior cingulate, precuneus, inferior parietal, and orbitofrontal cortices, averaged across hemispheres. (Initial correlation analyses with left ROIs compared to ROIs averaged across hemispheres showed that Pearson's r for learning and recognition for all ROIs differed by less than .10). There are also other areas of interest available, however, to limit multiple comparisons, a selection was made on the basis of involvement in healthy memory and neurodegeneration common in MCI and AD.

Scans were segmented as described by Fischl et al. (Fischl et al., 2002), yielding volumetric data for a number of subcortical brain structures, including the hippocampal formation, shown in Figure 1A. The present segmentation of the hippocampal formation includes dentate gyrus, CA fields, subiculum/parasubiculum and the fimbria (Makris et al., 1999). The automated, fully 3D whole-brain segmentation procedure (Fischl et al., 2002; Fischl et al., 2004) uses a probabilistic atlas and applies a Bayesian classification rule to assign a neuroanatomical label to each voxel. The atlas consists of a manually-derived training set created by the Center for Morphometric Analysis (<http://www.cma.mgh.harvard.edu/>) from 40 non-ADNI subjects across the age range, including individuals with AD. This procedure automatically assigns a neuroanatomical label to each voxel in an MRI volume based on probabilistic information automatically estimated from a manually labeled training set. The segmentation uses three pieces of information to disambiguate labels: (1) the prior probability of a given tissue class occurring at a specific atlas location, (2) the likelihood of the image given that tissue class, and (3) the probability of the local spatial configuration of labels given the tissue class. This latter term represents a large number of constraints on the space of allowable segmentations, and prohibits label configurations that never occur in the training set (e.g. hippocampus is never anterior to amygdala). The technique has been shown to be comparable in accuracy to manual labeling (Fischl et al., 2002).

The cortical surface was reconstructed to measure thickness at each surface location, or vertex, using a semi-automated approach described elsewhere (Dale et al., 1999; Dale, 1993; Fischl and Dale, 2000; Fischl et al., 1999a; Fischl et al., 1999b; Salat et al., 2004). Thickness measurements were obtained by reconstructing representations of the gray/white matter boundary (Dale et al., 1999; Dale, 1993) and the pial surface and then calculating the distance between those surfaces at each point across the cortical mantle. This method uses both intensity and continuity information from the entire three dimensional MR volume in segmentation and deformation procedures to produce representations of cortical thickness. The surface is created using spatial intensity gradients across tissue classes and is therefore not simply reliant on absolute signal intensity. The surface produced is not restricted to the voxel resolution of the original data and thus are capable of detecting submillimeter differences between groups (Fischl and Dale, 2000). The measurement technique used here has been validated via histological (Rosas et al., 2002) as well as manual measurements (Kuperberg et al., 2003). The cortical surface then is parcellated according to procedures described by Fischl et al. (Fischl et al., 2004), including the presently selected ROIs. Each surface location, or vertex, is assigned a neuroanatomical label based on 1) the probability of each label at each location in a surface-based atlas space, based on a manually parcellated training set; 2) local curvature information; and 3) contextual information, encoding spatial

neighborhood relationships between labels (conditional probability distributions derived from the manual training set). The parcellation scheme (Desikan et al., 2006) labels cortical sulci and gyri, and thickness values are calculated in the ROIs. The cortical parcellations used as ROIs in the present study are shown in Figure 1B.

2.4. FDG-PET

Subjects were scanned after a 4 hour fast (water only) and had blood glucose measured. Plasma glucose had to be ≥ 180 mg/dL for FDG to be injected. An intravenous catheter was placed in one arm for injection of [^{18}F]FDG. Imaging began at 30 min post injection, and the scan was acquired as six 5-min frames.

2.5. Coregistration and MRI-Derived Anatomically Defined ROI Analyses of PET Data

For each subject, FDG-PET frames were averaged and registered to the corresponding distortion-corrected and intensity-normalized MRI volume. ROIs were derived for each subcortical and cortical region defined on the MRI by the cerebral segmentation and cortical parcellation methods described above. PET activity was averaged within each ROI and normalized to activity within the pons (Minoshima et al., 1995). To generate cortical surface maps of continuous metabolic data, normalized PET activity for each subject was sampled onto their reconstructed cortical surface.

2.6. APOE classification

Participants were classified on a cumulative risk scale according to the APOE genotyping results for allele 1 and 2 in the following manner: *Level 4*: Participants with two $\epsilon 2$ alleles or one $\epsilon 2$ allele and one $\epsilon 3$ allele. (There was only one participant with two $\epsilon 2$ alleles, so this could not be coded as a separate group.) *Level 3*: those with two $\epsilon 3$ alleles. *Level 2*: those with one $\epsilon 3$ and one $\epsilon 4$ allele. *Level 1*: those that had two $\epsilon 4$ alleles, conveying maximum risk. Individuals with one $\epsilon 2$ allele and one $\epsilon 4$ allele were excluded from analysis, since the meaning of this combination is hard to conceptualize (i.e. one protective allele and one risk allele). The scale was designed based on findings that $\epsilon 2$ carriers develop AD later, that $\epsilon 3$ carriers have less risk than $\epsilon 4$ carriers, and that there is a dose-dependent effect, so that carrying two APOE $\epsilon 4$ alleles conveys the maximum AD risk (Corder et al., 1995a; Corder et al., 1995b; Ohm et al., 1999). The distribution of participants with different combinations of APOE alleles is shown in Figure 2.

2.7. Statistics

In all analyses, standardized residual values after the effects of age and gender had been regressed out were used for morphometric variables. Standardized residuals after the effects of age, gender, and corresponding morphometric variables had been regressed out were used for PET variables. I.e. for entorhinal metabolism, the effect of entorhinal thickness was regressed out, and so forth. This was done to make sure partial voluming effects did not bias PET results – i.e. thinner cortex in MCI/AD may lead to a larger part of the PET voxels falling outside the cortex, and hence yield artificially low metabolism. One-way ANOVAs were performed for group effects in demographic and ROI variables. Correlations of ROI MR morphometry and FDG-PET, as well as APOE, with AVLT learning, 5 minute recall, 30 minute recall and 30 minute recognition, controlling for the effect of gender and age, were calculated for the three subsamples (NC, MCI, AD) separately as well as for the total sample. For 5 min recall, the majority of the AD sample ($n = 24$, 67%) scored zero or below when subtracting number of intrusions. For 30 min recall, nearly the entire AD group ($n = 32$, 89%) and the majority of the MCI sample ($n = 47$, 60%) scored zero or below. Therefore, further analyses, described below, were restricted to learning and recognition scores for the AD group. Additional recall analyses were performed

for those NC and MCI subjects that had positive subtraction scores on 5 (NC = 45, MCI = 52) and 30 (NC = 41, MCI = 31) min recall. All correlation analyses were Bonferroni corrected for 17 comparisons (8 ROIs x 2 imaging methods and APOE). Next, stepwise regression analyses were performed with total learning (trial 1-5), 5 minute recall, 30 minute recall (all hits minus intrusions), and recognition (hits minus errors) respectively as the dependent variables. This was done to examine the extent to which these variables provided unique contributions in the prediction of memory function, and to test which were the strongest predictors in each case.

3. Results

Demographic characteristics of the three groups are presented in Table 1. As expected based on diagnosis, one-way ANOVA showed significant ($p < .05$, Bonferroni corrected) differences in MMSE ($F[2,158] = 109.121$, $p = .000$, NC > MCI > AD) and CDR ($F[2,158] = 552.790$, $p = .000$, NC < MCI < AD) across groups. There were no significant differences in age ($F[2,158] = .896$, $p = .410$) or education ($F[2,158] = 1.885$, $p = .155$) across groups, but a significant gender difference was found between NC and MCI ($F[2,158] = 4.433$, $p = .013$, more males in the MCI group). Memory scores of the 3 subgroups are presented in Table 2. A one-way ANOVA including all cases, showed significant ($p < .05$, Bonferroni corrected) differences in all memory measures across all groups (learning: $F[2,158] = 60.490$, $p = .000$, 5 minute recall $F[2,158] = 53.993$, $p = .000$, 30 minute recall: $F[2,158] = 45.997$, $p = .000$, recognition: $F[2,158] = 51.416$, $p = .000$). NC > MCI > AD, with the exception of 30 minute recall, where the difference between MCI and AD was marginal ($p = .059$). Results for the MR morphometry and FDG-PET variables in each group are presented in Figures 3 and 4. In general, NC had larger hippocampal volume, thicker cortical regions and higher ROI metabolism than the MCI group, which had larger morphometric measures and higher metabolism than the AD group. A one-way ANOVA showed a significant effect of group on morphometry and metabolism in all ROIs (see Online Table 1 for statistics). There were also significant differences ($p < .05$, Bonferroni corrected) in most ROIs for pairwise contrasts (NC > MCI > AD), with the following exceptions: There was no significant difference between NC and MCI in thickness of the retrosplenial, precuneus, inferior parietal cortex, and lateralorbitofrontal cortex. Posterior cingulate thickness, precuneus and lateral orbitofrontal cortical thickness did not significantly differ between MCI and AD. The difference between NC and AD in posterior cingulate thickness was marginally significant. Metabolic activity was significantly different across all groups (NC > MCI > AD) for all ROIs, with the exception of hippocampal metabolism, which did not differ between NC and MCI.

Correlations for MR morphometry, FDG-PET and APOE and AVLT learning and 30 minute recognition are presented in Table 3. No correlations in NC, MCI or AD reached significance when bonferroni-corrected for 17 comparisons. In the total sample, all morphometric variables correlated significantly with learning, with the exceptions of cortical thickness of the PC and lateral orbitofrontal cortex, and all but cortical thickness of the PC, precuneus and lateral orbitofrontal ROIs correlated significantly with recognition. All PET ROI variables correlated significantly with learning and recognition in the total sample. APOE correlated significantly with both learning and recognition in the total sample. Corresponding analyses for 5 and 30 min recall were performed for the subsamples showing above floor recall, and the results of these are shown in Online Table 2. In NC and MCI, there were no significant correlations after bonferroni-correction. In the total sample, entorhinal and parahippocampal cortical thickness, and all metabolism measures correlated with 5 minute recall. Only inferior parietal metabolism correlated significantly with 30 minute recall, for which less than half the total sample (47%) had above-floor scores and were included.

Results of the stepwise regression analyses with the learning score as the dependent variable and FDG-PET and MR variables and APOE entered as predictors are presented in Table 4 for the diagnostic groups separately and in Table 5 for the total sample. In NC, hippocampal metabolic activity explaining 12% of the variance. In the MCI group, entorhinal cortical thickness was included in model I, and cortical thickness of the precuneus was included in model II, yielding an increase in explained variance from 11 to 40 %. In the AD group, cortical thickness of the posterior cingulate was the only variable included, explaining 13% of the variance. For the total sample, hippocampal volume was included in model I, and hippocampal metabolism was added in model II. In model III, cortical thickness of the precuneus was added, and finally inferior parietal metabolism in model IV, yielding 32 % explained variance.

The equivalent analyses for recognition are presented in Table 6 for the diagnostic groups separately and in Table 7 for the total sample. Within groups, only metabolic ROI variables were included as predictors of recognition. In NC, entorhinal metabolism explained 15% variance. In MCI, parahippocampal metabolism was the only predictor, and the only predictor in AD was APOE genotype. For the total sample, hippocampal volume was included in the first model, hippocampal metabolism was added in the second, parahippocampal cortical thickness in the third, and finally, APOE was added in the fourth model. In sum, among the ROIs, only MTL variables served as unique predictors of recognition. Scatter plots showing the linear relationships of learning and recognition and the metabolic and volumetric ROIs for the three diagnostic groups are depicted in Figure 5. Scatter plots showing the linear relationships of learning and recognition and the metabolic and volumetric ROIs for the total sample are depicted in Figure 6.

The stepwise regression analyses for 5 and 30 minutes recall were restricted to those NC and MCI subjects that had positive subtraction scores on 5 (NC = 45, MCI = 52) and 30 (NC = 41, MCI = 31) minute recall. For 5 minute recall, hippocampal metabolism served as the only significant predictor in NC ($F[1,43] = 6.353$, $R^2 = .13$, $\beta = .36$). There were no significant predictors of 5 min recall in MCI, and no significant predictors of 30 min recall in either NC or MCI.

4. Discussion

Hypothesis 1

Both MRI morphometry and PET contribute to explain variance in memory, with PET showing a slight advantage. APOE genotype may add to the explained variance. The main message from the present results is that both FDG-PET and MR morphometry of selected cerebral ROIs uniquely predict memory function. There was some redundancy of these methods, but the inclusion of both explained more variance. In the total sample, a blend of morphometry and metabolism variables best predicted memory function. FDG-PET was superior to MR morphometry in explaining memory variance in NC, where no morphometric variable was predictive, while hippocampal and entorhinal metabolism were. However, in MCI and AD, morphometric variables were at least as predictive of memory as metabolic variables. This is contrary to the hypothesis based on a few previous studies on these methods' differential sensitivity to memory function and diagnostic group. In their smaller study (11 NC, 15 MCI, 12 AD), DeSanti et al. (De Santi et al., 2001) concluded that FDG-PET had superior diagnostic sensitivity over MRI, with partially overlapping ROIs as in the present study. DeSanti et al. (2001) did correct their metabolism measures for atrophy, by dividing their PET images with binary images coding for brain (= 1) and CSF (=0). This correction appears fair, but does not necessarily eliminate the effect of volume (for a discussion of ratio corrections, see van Petten et al., 2004). In the present study, all effects of volume or thickness were regressed out of the PET volumes, yielding a measure of

metabolism independent of morphometric characteristics, and it is likely that this correction is stricter. Ishii et al (Ishii et al., 2005), on the other hand, reported complementary diagnostic sensitivity of PET and MR in mild AD (30 NC, 30 AD), with volumetric reductions in the MTL and metabolic reductions in the PC and parietal areas. The metabolic/structural discrepancy in MTL has been referred to by Ishii et al. and others as a plastic response in mild AD, where early regional synaptic malfunction in affected areas cannot be detected due to compensatory activity in unaffected neurons (Geddes et al., 1985; Matsuda et al., 2002)

APOE was only significantly related to recognition in AD, and not to any memory measure in NC or MCI. This lack of a relationship in normal controls may not be surprising, since previous cross-sectional studies have yielded mixed findings (Nilsson et al., 2002). However, a recent large-scale study did report effects in old age (70 yrs and above), and the present sample is primarily in the older age range. As discussed by Nilsson and colleagues (Nilsson et al., 2006), a number of other factors likely also mediate APOE-cognition relationships, including sample size. The present sample of controls was relatively small and included only nine ϵ_4 carriers, only one of whom had two ϵ_4 -alleles. This may be too small a sample for any relationships to be uncovered, especially since dose-effects have previously been observed (Nilsson et al., 2006). APOE may still predict individual memory differences longitudinally (Tupler et al., 2007). Sample sizes may also have been non-optimal for relationships to be detected in MCI and AD. The stepwise regression still showed that APOE was a unique predictor of recognition in the total sample, besides hippocampal morphometry and metabolism and parahippocampal cortical thickness. This indicates that APOE genotype contributes to explain variance in memory performance across the entire sample, and in AD, that is not captured by the metabolic and morphometric variables. The present study cannot determine whether this predictive influence of APOE status is related directly to the ϵ_4 allele or whether it is an indirect marker for another disease-related factor. In the total sample, the frequency of the ϵ_4 allele is higher in MCI and more so in AD relative to NC, therefore, APOE status may be a marker of diagnostic classification.

Hypothesis 2

MR morphometry is not related to memory in NC, but positively related to memory function in MCI and AD. The strongest morphometry-memory relationships are expected for MTL, intermediate for medial parietal areas, and somewhat weaker for inferior parietal and medial orbitofrontal ROIs. The present data confirmed that MR morphometry variables were not related to memory performance in NC. No morphometry variable served as a significant predictor of memory in NC in the stepwise regression analysis, and correlations were low. There have been discrepant findings regarding the relationship of hippocampal size and normal memory function, but the present results are in agreement with van Petten's (Van Petten, 2004) meta-analysis conclusion that bigger is not necessarily better for this type of memory. The cortical findings are in line with a recent study by Walhovd et al. (Walhovd et al., 2006), reporting that cortical thickness had little influence on memory for shorter intervals (30 minutes, as opposed to months). For the MCI and AD groups, morphometric variables were related to learning. Cortical thickness of MTL (entorhinal, parahippocampal) areas in MCI, and medial parietal areas, the precuneus in MCI, and the posterior cingulate in AD, were the only unique morphometric predictors when entering all morphometry and PET ROIs in the stepwise regression models. However, for learning, correlations were not in general much stronger for MTL than medial parietal areas. In fact, parietal morphometric characteristics were more predictive of memory in AD. None of the morphometry-memory correlations within groups were significant after multiple comparison correction. Still, looking at the sample as a whole, a special role of the hippocampus is apparent, in that these correlations stand out as showing the strongest morphometry relationships with memory.

Hypothesis 3

PET metabolism is related to memory function in all groups, but ROI-wise broader and stronger relationships are expected in MCI and AD than NC. MTL metabolism is expected to relate to memory in all groups. Parietal and prefrontal metabolism will likely also be related to memory in NC, but stronger positive relationships are expected in MCI and AD, especially for posterior cingulate (PC). The regression analyses showed that hippocampal and entorhinal FDG PET was related to memory function in NC. This is in line with previous findings which have primarily pointed to a relationship between hippocampal metabolism and explicit memory in normal aging (Eustache et al., 1995; Langley and Madden, 2000). Parahippocampal metabolism predicted recognition in MCI. However, in contrast to the hypothesis, FDG PET did not generally show stronger or broader memory relationships in MCI and AD than morphometry did. Only morphometry predicted learning in MCI and no metabolic variable predicted either learning or recognition in AD independently of morphometric characteristics. PC and frontal metabolism were not significantly related to memory in any single group, only in the total sample, in contrast to previous findings for MCI by Chetelat et al. (Chetelat et al., 2003). The reason for this discrepancy is unclear. Chetelat et al. (Chetelat et al., 2003) also corrected for partial volume effects in an apparently similar way as DeSanti et al. (De Santi et al., 2001) mentioned above. Again, the present correction may be stricter in that it demands metabolic effects independently of any morphometric effects for PET to be a unique predictor. However, Chetelat et al. (2003) also used an experimental memory paradigm, and we are not aware of any previous studies that have investigated standardized clinical list learning in relation to FDG-PET. Hence, discrepancies may be due to methodological differences. In contrast to our hypothesis, the PC did not stand out as the most predictive metabolic ROI in the present study. This may be somewhat surprising, since the PC repeatedly has been targeted as an integral part of the episodic memory network, with rich projections from the MTL, and is among the most frequent and earliest areas to show metabolic decline in Alzheimer's disease (e.g. Ishii et al., 2005). The apparent discrepancy may be due, in part, to different anatomical delineations of this region. The present PC ROI definitely overlaps although perhaps more anterior than the area identified by e.g. Ishii et al. (Ishii et al., 2005) using voxel-based morphometry (VBM). However, cortical thickness of the PC was a unique predictor of learning in AD, so it may be that strong morphometric effects left little for metabolism alone in this area to explain.

Hypothesis 4

MTL measures are related to both learning/recall and recognition, while prefrontal and PC characteristics will be relatively more related to learning/recall. This hypothesis received partial support from the present data. Among the ROIs, only MTL variables served as unique predictors of recognition, within and across diagnostic groups. For learning, a somewhat different pattern was observed. This may partly be due to learning being an aggregate across five trials and thus having better reliability. However, one relatively consistent difference compared to recognition, was that parietal structures served as unique predictors within MCI and AD and across all groups. Thickness of the entorhinal and precuneus cortex predicted learning in MCI, and cortical thickness of the posterior cingulate predicted learning in AD. Also across samples, hippocampal volume and metabolism, precuneus thickness, and inferior parietal metabolism, served as unique predictors. Neither metabolism, nor thickness of the lateral orbitofrontal cortex was significantly related to either learning or recognition in any of the diagnostic groups. Significant correlations with lateral orbitofrontal metabolism were observed in the total sample both for learning and recognition. Hence, a relatively more prefrontal predictor of recall relative to recognition is not supported by the present data. It might be that other prefrontal ROIs would have shown a more differential relationship with these two classes of measures.

Chetelat et al. (Chetelat et al., 2003) indicated another partial dissociation between metabolic and structural correlates: Hippocampal volume was associated with both recognition and recall, while hippocampal metabolism was associated with recognition only, and recall correlated with posterior cingulate metabolism only. We did not find that posterior cingulate metabolism correlated with recall in MCI in the present study. However, MTL characteristics served as unique predictors of recognition, whereas a blend of MTL and medial parietal characteristics served as predictors of learning. The parietal predictors were not restricted to PC alone, but also included precuneus and, in the total sample, inferior parietal cortex. However, particularly with respect to the total sample, the learning and recognition correlations were rather similar. Within methods, the strongest correlations were observed for PET, rather than MR for NC, irrespective of memory measure.

5. Limitations

Eight ROIs were selected to represent the episodic memory network in the present analyses. It is possible that choice of alternative or additional ROIs could be fruitful. A further limitation is the uneven gender balance across groups in the primary cohort, with males being somewhat overrepresented in all groups, especially among MCI patients. The full ADNI cohort shows a similar bias towards greater representation of males, particularly in the MCI group. We used all available, ADNI-approved PET images at the time this project was initiated.

Conclusion

FDG-PET metabolism and MRI morphometry of episodic memory network ROIs predicted memory function in a large sample of controls, MCI and AD patients. Regardless of imaging method, medial temporal, and to some extent, parietal brain characteristics served as the strongest predictors of memory performance. It appears that parietal characteristics showed a differential sensitivity for learning and recall compared to recognition, for which only MTL characteristics were unique predictors. Combined with imaging data, APOE genotype did not serve as a unique predictor of memory performance within NC or MCI, but was among the predictors of recognition in AD and across groups. FDG-PET was clearly more sensitive than MR morphometry in predicting memory in healthy controls, while both metabolic and volumetric variables uniquely accounted for memory variance in MCI and in the total group. Only PC morphometry and APOE genotype uniquely explained memory variance in AD. The present results indicate that FDG-PET and MR morphometry are not redundant methods, but are differentially sensitive to memory performance in healthy elderly and in different stages of cognitive decline.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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A

Hippocampus segmentation

B

Figure 1.

A) The hippocampus segmentation shown in gold on a coronal slice (top part) and as 3D renderings (top: head, bottom: tail).

B) Along with the hippocampal formation, the cortical areas shown here are part of the episodic memory network. Shown here are pial cortical representations of selected parcellations in the left hemisphere. From left to right: medial, ventral and lateral views

Figure 2.

The distribution of allelic combinations of APOE in the three groups. The proportionalized allele frequency within each group was as follows: NC: 2.1% 4/4, 17.0% 3/4, 59.6% 3/3, 21.3% 2/2-3, MCI: 14.1% 4/4, 38.5% 3/4, 41.0% 3/3, 6.4% 2/2-3, AD: 30.6% 4/4, 47.2% 3/4, 22.2 % 3/3, 0% 2/2-3.

Figure 3.

Bar chart showing MR values for hippocampal volume and thickness of each cortical ROI for the different groups. All values are standardized residuals after the effects of age and gender have been regressed out. A one-way ANOVA showed significant main effects of group for morphometry in all ROIs, as indicated by an asterisk (*). Hippo: Hippocampus, Entorh: Entorhinal cortex; Parahi: Parahippocampal gyrus; Retrospl: Retrosplenial cortex; PC: Posterior cingulate; Precun: Precuneus; Inf. P: Inferior parietal gyrus; L. Orbf: Lateral Orbitofrontal gyrus;.

Figure 4.

Bar chart showing FDG_PET values for hippocampal volume and thickness of each cortical ROI for the different groups. All values are standardized residuals after the effects of age, gender, and volume (for hippocampus) or thickness (for cortical ROIs) have been regressed out.. As indicated by asterisks (*), a one-way ANOVA showed significant main effects of group for all ROIs. Hippo: Hippocampus, Entorh: Entorhinal cortex; Parahi: Parahippocampal gyrus; Retrospl: Retrosplenial cortex; PC: Posterior cingulate; Precun: Precuneus; Inf. P: Inferior parietal gyrus; L. Orbf: Lateral Orbitofrontal gyrus;.

Figure 5. Scatterplots showing the linear relationships of the metabolic and morphometric ROIs uniquely predicting learning and recognition in each group.

Figure 6. Scatter plots showing the linear relationships of the metabolic and morphometric ROIs uniquely predicting learning and recognition and in the total sample.

Table 1

Demographic characteristics of the three subsamples.

	NC			MCI			AD		
	N = 47, 21 F / 26 M			N = 78, 16 F / 62 M			N = 36, 13 F / 23 M		
	M	SD	Range	M	SD	Range	M	SD	Range
Age	75.8	(5.5)	62.1-85.9	74.4	(7.3)	55.2-88.4	75.8	(6.5)	59.0-87.8
Education	15.3	(3.6)	7-20	15.7	(2.9)	8-20	14.5	(2.9)	4-18
MMSE	29.0	(1.0)	26-30	27.0	(1.7)	24-30	23.7	(2.1)	20-26
CDR	0.0	(0.0)	0-0	0.5	(0.0)	0.5-0.5	0.8	(0.2)	0.5-1.0

Table 2

Memory scores, given as hits minus intrusions/errors, for males and females in the three subsamples.

	NC (n = 47)						MCI (n = 78)						AD (n = 36)					
	Males			Females			Males			Females			Males			Females		
	M	SD	Range	M	SD	Range	M	SD	Range	M	SD	Range	M	SD	Range	M	SD	Range
Learning	37.0	9.1	20-60	44.0	8.8	34-69	27.0	7.5	9-44	28	8.5	12-48	20.4	5.5	9-32	23.4	9.2	7-42
Recall 5	6.3	3.5	-2-14	8.3	4.1	-1-15	2.7	3.1	-3-9	1.8	3.7	-3-12	0.2	1.5	-2-4	0.2	2.8	-4-6
Recall 30	4.9	4.2	-1-14	7.0	4.1	-7-15	1.0	3.2	-6-11	0.9	3.6	-7-13	-0.5	1.3	-4-1	-0.8	2.1	-7-1
Recog.	10.7	3.3	4-15	13.2	1.9	8-15	7.3	4.7	-8-15	5.2	4.8	20-85	2.9	3.3	-5-8	3.2	2.8	-2-8

Table 3

Correlations for learning and recognition score and ROI variables and APOE, controlled for age and gender.
Bold signify p .05, bonferroni-corrected for 17 comparisons.

	NC		MCI		AD		Total	
	Learn	Recog	Learn	Recog	Learn	Recog	Learn	Recog
MR								
Hippocampus	-.23	-.12	.31	.21	.08	.27	.45	.47
Entorhinal	.13	-.10	.33	.20	.04	.32	.43	.42
Parahippocampal	-.07	-.04	.21	.12	.06	.28	.31	.33
Retrosplenial	-.01	-.03	.27	.17	.24	.12	.33	.30
Posterior Cing.	-.09	.03	.18	.07	.36	-.08	.23	.15
Precuneus	.09	-.13	.31	.11	.06	-.07	.28	.17
Inferior Parietal	-.09	-.03	.32	.11	.05	-.06	.30	.24
Lateral Orb.front.	-.10	.00	.23	.17	.20	-.25	.21	.16
PET								
Hippocampus	.35	.27	.14	.18	-.04	.14	.26	.28
Entorhinal	.21	.39	.11	.03	-.01	.12	.35	.35
Parahippocampal	.21	.16	.16	.23	-.28	.00	.32	.38
Retrosplenial	.30	.09	.17	.09	-.25	.07	.38	.35
Posterior Cing.	.19	.04	.08	.08	-.31	.02	.30	.31
Precuneus	.25	.14	.10	.09	-.22	.02	.33	.33
Inferior Parietal	.28	.17	.12	.19	-.09	-.03	.33	.34
Lateral Orb.front.	.31	.23	.17	.13	-.34	-.16	.31	.29
APOE genotype	-.05	.02	.01	.09	-.12	.30	.28	.37

Table 4

Stepwise regression analyses performed for the three subsamples with learning score (hits minus intrusions) as the dependent variable. FDG-PET and MR morphometry ROI variables controlled for age and gender ($M = 0$, $F = 1$) were included as predictor variables along with APOE genotype.

		β	p	R^2	F	Model p
NC	Model I					
	PET Hippocampus	.35	.015	.12	6.396	.015
MCI	Model I					
	MR Entorhinal Cortex	.33	.003	.11	9.282	.003
	Model II					
	MR Entorhinal Cortex	.26	.019			
	MR Precuneus Cortex	.24	.033	.40	7.221	.001
AD	Model I					
	MR Posterior Cingulate	.36	.032	.13	4.979	.032

Table 5

Stepwise regression analyses for the total sample with learning score (hits minus intrusions) as the dependent variable. FDG-PET and MR morphometry ROI variables controlled for age and gender (M = 0, F = 1) were included as predictor variables along with APOE genotype.

		β	p	R ²	F	Model p
Total sample	Model I					
	MR Hippocampus	.45	.000	.000	40.091	.000
	Model II					
	MR Hippocampus	.45	.000			
	PET Hippocampus	.26	.000	.27	29.312	.000
	Model III					
	MR Hippocampus	.40	.000			
	PET Hippocampus	.26	.000			
	MR Precuneus Cortex	.17	.017	.30	22.073	.000
	Model IV					
	MR Hippocampus	.35	.000			
	PET Hippocampus	.15	.046			
	MR Precuneus Cortex	.22	.002			
	PET Inf. Parietal Cortex	.23	.005	.32	19.383	.000

Table 6

Stepwise regression analyses performed for the three subsamples with recognition score (hits minus intrusions) as the dependent variable. FDG-PET and MR morphometry ROI variables controlled for age and gender (M = 0, F = 1) were included as predictor variables along with APOE genotype.

		β	p	R ²	F	Model p
NC	Model I					
	PET Entorhinal Cortex	.39	.006	.15	8.201	.006
MCI	Model I					
	PET Parahippocampal cortex	.23	.047	.05	4.064	.047
AD	Model I					
	APOE	.34	.042	.12	4.464	.042

Table 7

Stepwise regression analysis for the total sample with recognition (hits minus errors) as the dependent variable. FDG-PET and MR morphometry ROI variables controlled for age and gender were included as predictor variables along with APOE genotype.

		β	p	R ²	F	Model p
Total sample	Model I					
	MR Hippocampus	.47	.000	.22	44.850	.000
	Model II					
	MR Hippocampus	.47	.000			
	PET Hippocampus	.28	.000	.30	33.890	.000
	Model III					
	MR Hippocampus	.40	.000			
	PET Hippocampus	.29	.000			
	MR Parahippocampal Cortex	.17	.018	.33	25.160	.000
	Model IV					
	MR Hippocampus	.34	.000			
	PET Hippocampus	.25	.000			
	MR Parahippocampal Cortex	.17	.018			
	APOE	.15	.047	.34	20.230	.000