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Cortical Amyloid Burden Differences Across Empirically-Derived Mild Cognitive Impairment Subtypes and Interaction with APOE ϵ 4 Genotype

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Abstract

We examined cortical amyloid- β (A β) levels and interactions with apolipoprotein (APOE) ϵ 4 genotype status across empirically-derived mild cognitive impairment (MCI) subgroups and cognitively normal older adults. Participants were 583 ADNI participants (444 MCI, 139 normal controls [NC]) with baseline florbetapir positron emission tomography (PET) amyloid imaging and neuropsychological testing. Of those with ADNI-defined MCI, a previous cluster analysis [1] classified 51% ($n = 227$) of the current sample as amnesic MCI, 8% ($n = 37$) as dysexecutive/mixed MCI, and 41% ($n = 180$) as cluster-derived normal (cognitively normal). Results demonstrated that the dysexecutive/mixed and amnesic MCI groups showed significantly greater levels of amyloid relative to the cluster-derived normal and NC groups who did not differ from each other. Additionally, 78% of the dysexecutive/mixed, 63% of the amnesic MCI, 42% of the cluster-derived normal, and 34% of the NC group exceeded the amyloid positivity threshold. Finally, a group by APOE genotype interaction demonstrated that APOE ϵ 4 carriers within the amnesic MCI, cluster-derived normal, and NC groups showed significantly greater amyloid accumulation compared to non-carriers of their respective group. Such an interaction was not revealed within the dysexecutive/mixed MCI group which was characterized by both greater cognitive impairment and amyloid accumulation compared to the other participant groups. Our results from the ADNI cohort show considerable heterogeneity in A β across all groups studied,

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even within a group of robust NC participants. Findings suggest that conventional criteria for MCI may be susceptible to false positive diagnostic errors, and that onset of A β accumulation may occur earlier in APOE ϵ 4 carriers compared to non-carriers.

Keywords

Amyloid; apolipoprotein E; APOE; biomarkers; florbetapir; mild cognitive impairment; neuroimaging; neuropsychology; PET; positron emission tomography

INTRODUCTION

Identification of risk factors and prevention targets for Alzheimer's disease (AD) has become a critical public health concern given its rapidly increasing prevalence [2, 3] coupled with the overwhelming failure of clinical trials designed to modify risk [4]. Embedded within this initiative is the need to accurately characterize mild cognitive impairment (MCI), an at-risk state that represents the transitional stage between normal aging and dementia [5–8]. While advances in research of neuroimaging and biofluid markers have improved our ability to detect and diagnose AD [9] and its preceding stages [10, 11], research focused on profiling mild forms of cognitive impairment have failed to reach this same level of sophistication. As a result, proper characterization of MCI has become a point of significant concern and controversy in both clinical and research settings [12].

Presently, MCI is commonly defined by objective evidence for cognitive impairment (i.e., performance less than or equal to 1.5 standard deviations below the normative mean on at least one neuropsychological measure), along with a subjective memory complaint, that occurs in the context of preserved overall cognition and ability to perform tasks of daily living [7, 8, 13]. Unfortunately, the application of these MCI criteria often involve: (1) crude cognitive screening measures rather than validated neuropsychological assessments that are more sensitive and specific to cognitive impairment; (2) subjective clinical judgment, in contrast to objective diagnostic decision-making; and (3) limited assessment protocols that fail to adequately tap domains of cognition outside of memory ability.

Recent research has provided a data-driven, empirical method of deriving MCI subtypes by using cluster analytic statistical techniques [1, 14–18]. Such studies have demonstrated that individuals with MCI can be meaningfully grouped together based on similarities in their patterns of performance across multiple cognitive domains. This research has revealed multiple subtypes of MCI, provided more nuanced MCI distinctions, and shown tighter associations with respect to biomarkers related to cognitive impairment as well as progression to dementia [1]. Additionally, recent research has demonstrated significant heterogeneity in MCI [14, 15, 19], considerable instability regarding the diagnosis of MCI, and highly variable prevalence rates across studies [20, 21]. All of this work has fueled efforts to improve the diagnostic rigor for MCI through employment of actuarial decision-making using a full range of neuropsychological test measures [20, 22, 23]. Such studies have consistently found evidence for distinct MCI phenotypic subgroups; however, one of the most provocative findings that has emerged from research employing actuarial decision-making has been the identification of a cluster-derived normal group which consists of a

large subset of individuals originally diagnosed with MCI but who performed within normal limits upon cognitive testing [1, 17, 18]. This “false positive” subgroup [1, 18] performs similarly to normal control (NC) participants on tests of cognition and show comparable cortical thickness values in areas typically affected by MCI and AD (Edmonds et al., under review). Additionally, cerebrospinal fluid (CSF) AD biomarker profiles do not differ between these groups. Moreover, as compared to other MCI subtypes, the cluster-derived normal group demonstrate an overall lower genetic risk for AD and contain fewer individuals who eventually progressed to dementia [1, 17, 18].

We aimed to extend our previous findings by examining levels of cortical amyloid- β (A β), an AD hallmark protein currently being targeted in clinical trials of disease-modifying agents in early AD, across empirically-derived MCI and cognitively normal subgroups. We examined group differences in mean cortical and regional amyloid load measured by florbetapir F 18 positron emission tomography (PET) imaging. Given the role of apolipoprotein E (APOE) in A β accumulation [24], we also examined the extent to which APOE ϵ 4 status (carrier versus non-carriers) influences amyloid accumulation within the cognitive groups. Based on our previous findings described above, we expected to find differences in cortical amyloid accumulation between empirically-derived MCI subgroups and cognitively normal groups, but no such differences between the cluster-derived normal and NC groups. In addition, we expected a cognitive group by APOE interaction whereby ϵ 4 carriers would demonstrate greater amyloid burden compared to non-carriers across the participant groups.

MATERIALS AND METHODS

The ADNI dataset

Data used for this study were obtained from the Alzheimer’s Disease Neuroimaging Initiative (ADNI) database (<http://adni.loni.usc.edu>). The ADNI was launched in 2003 by the National Institute on Aging (NIA), the National Institute of Biomedical Imaging and Bioengineering (NIBIB), the Food and Drug Administration (FDA), private pharmaceutical companies and non-profit organizations, as a \$60 million, 5-year public-private partnership. The primary goal of ADNI has been to test whether serial magnetic resonance imaging (MRI), 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, MD, VA Medical Center and University of California – San Francisco. ADNI is the result of efforts of many coinvestigators from a broad range of academic institutions and private corporations, and subjects have been recruited from over 50 sites across the U.S. and Canada. The initial goal of ADNI was to recruit 800 subjects but ADNI has been followed by ADNI-GO and ADNI-2. Subjects originally recruited for ADNI-1 and ADNI-GO had the option to be followed in ADNI-2. For up-to-date information, see <http://www.adni-info.org>.

Participants

Participants were 583 older adults who completed a comprehensive neuropsychological assessment and baseline florbetapir PET scan with processed data available for download as of December 2015 and also had available apolipoprotein (APOE) genotype data. This

included 444 individuals diagnosed with MCI and 139 cognitively normal older adults. Full criteria for ADNI eligibility and diagnostic classifications are described in detail at <http://www.adni-info.org>.

ADNI diagnostic criteria for MCI were as follows: (1) subjective memory complaints reported by participants, a study partner, or clinician, (2) objective memory loss defined as scoring below an education-adjusted cut-off score on delayed recall of Story A of the WMS-R Logical Memory Test, (3) global Clinical Dementia Rating (CDR) scale score of 0.5, and (4) general cognitive and functional performance sufficiently preserved such that a diagnosis of dementia could not be made by the site physician at the time of screening. The cognitively normal group for the present study included all participants who had at least one year of follow-up and who remained classified as normal throughout their participation in ADNI (range of 1–3 years of follow-up).

Empirically-derived MCI subtypes

We previously performed a cluster analysis using six neuropsychological scores from 846 MCI participants diagnosed using ADNI criteria [1]. The current study includes individuals from this initial sample who underwent florbetapir PET imaging at their baseline exam. The clusters derived in this initial study were used in the current study given that the cluster solution from the larger sample was more reliable. The cluster analysis methods used in this initial study have been previously described [1]. Briefly, a cluster analysis was performed using the following six measures of cognition: 1) Animal Fluency, total score; 2) 30-item Boston Naming Test (BNT) total score; 3) Trail Making Test, Part A; time to completion, 4) TMT, Part B; time to completion, 5) Rey Auditory Verbal Learning Test (AVLT) 30-minute delayed free recall; number of words recalled, and 6) AVLT recognition; number of words correctly recognized. These measures were selected because of their routine use in assessing early cognitive changes in AD, they were administered to all participants, and they assessed three different domains of cognitive ability – language (Animal Fluency, BNT), speed/executive function (Trail Making Test, Parts A and B), and episodic memory (AVLT recall & recognition).

Previous analyses revealed a three-cluster solution in which (1) amnesic MCI ($n = 477$), (2) dysexecutive/mixed MCI ($n = 104$), and (3) cluster-derived normal ($n = 265$) subgroups were identified [1]. The amnesic MCI subgroup demonstrated mildly impaired performance on memory measures (Rey AVLT delayed recall and recognition). The dysexecutive/mixed MCI subgroup performed in the severely impaired range on tasks of speed/executive function (Trail Making Test, Parts A and B) and had mildly impaired memory (Rey AVLT delayed recall and recognition) and language scores (BNT and Animal Fluency). Finally, the cluster-derived normal subgroup performed within normal limits across all six neuropsychological measures. For the present study, using cluster analysis, 51% ($n = 227$) of the current sample were classified as amnesic MCI, 8% ($n = 37$) dysexecutive/mixed MCI, and 41% ($n = 180$) belonged to the cluster-derived normal group. Fig. 1.

Clinical outcome

Participants had follow-up examinations (up to 3 years) following baseline assessment. Clinical out-comes were operationalized as: (1) “No change” for MCI participants who remained diagnosed as MCI; (2) “Reversion” for MCI participants who reverted back to a cognitively normal diagnosis on subsequent examination; and (3) “Progression” for MCI participants who progressed to a diagnosis of AD on subsequent examination.

Florbetapir PET data acquisition and processing

All participants underwent florbetapir PET imaging within two weeks of their baseline neuropsychological assessments. A detailed description of ADNI florbetapir PET imaging data acquisition and processing can be found online (http://adni.loni.usc.edu/wp-content/uploads/2010/05/ADNI2_PET_Tech_Manual_0142011.pdf; <http://adni.loni.usc.edu/methods/pet-analysis/pre-processing/>). Briefly, florbetapir scans were reviewed for quality control before being co-registered, averaged, reoriented into a standard $160 \times 160 \times 96$ voxel image grid with 1.5 mm cubic voxels, and smoothed to a uniform isotropic resolution of 8 mm full width at half maximum. Structural MR images were skull-stripped, segmented, parcellated using Freesurfer and subsequently co-registered to each participants' first florbetapir image.

The florbetapir mean of each subregion was weighted by its volume to account for difference in sizes of the subregions. The four regions of interest (ROI) were: (1) frontal, (2) anterior/posterior cingulate, (3) lateral parietal, and (4) lateral temporal cortex. A florbetapir mean cortical summary standardized uptake value ratio (SUVR) was calculated by averaging across the four main cortical regions and dividing by the mean florbetapir value of the whole cerebellum (white and gray matter). In addition, SUVRs for each of the four regions was calculated by dividing by the mean of that individual region by the mean for the whole cerebellum. Increased retention of florbetapir is thought to reflect increased cortical amyloid load. Amyloid positivity versus negativity was determined based on the recommended threshold for cross-sectional florbetapir analyses of 1.11 using the whole cerebellum as the reference region [25, 26].

Statistical analyses

A series of analysis of variance (ANOVAs) and analysis of covariance (ANCOVAs) adjusted for age and APOE genotype were performed to compare participant groups in terms of demographics, neuropsychological performance, and florbetapir SUVRs. Chi-square analyses were conducted to statistically compare the participants groups in terms of frequencies of APOE genotype ($\epsilon 4$ carrier versus noncarriers), A β threshold positivity, and clinical outcomes (no change versus reversion versus progression). Additional ANCOVAs adjusted for age were conducted to examine the interaction of diagnostic group and APOE $\epsilon 4$ status (carrier versus non-carrier) on amyloid burden. Bonferroni-corrected *post hoc* tests were conducted for significant omnibus tests ($\alpha = 0.05/6 = 0.008$). Logistic regression (adjusted for age, APOE genotype, and length of follow up) were conducted to assess the association between baseline amyloid burden and longitudinal clinical outcome. All analyses were performed in SPSS (version 20).

RESULTS

Characteristics of the MCI cluster and normal control groups

Participant demographics are presented in Table 1. ANOVA revealed that the 4 groups significantly differed in terms of age ($p < 0.001$). *Post hoc t*-tests revealed the dysexecutive/mixed MCI and NC groups were both significantly older than the cluster-derived normal group (p 's < 0.008). The groups significantly differed regarding APOE genotype ($\epsilon 4$ carriers versus non-carriers; $p < 0.001$), and *post-hoc* chi-square tests revealed that the amnesic MCI group had a greater proportion of APOE $\epsilon 4$ carriers in comparison to the NC ($p < 0.001$) and cluster-derived normal ($p = 0.004$) groups. The dysexecutive/mixed MCI group had a greater proportion of APOE $\epsilon 4$ carriers relative to the NC ($p < 0.001$) group. There were no significant group differences with respect to education ($p = 0.057$) or sex ($p = 0.058$).

Amyloid positivity across the MCI cluster and normal control groups

Overall, 50% ($n = 294$) of the entire sample met criteria for amyloid positivity and the proportion of individuals who met this diagnostic threshold significantly differed ($p < 0.001$) across the groups (Fig. 2). *Post hoc* chi-square tests showed that both the amnesic and dysexecutive/mixed MCI groups demonstrated a greater proportion of individuals who met criteria for amyloid positivity relative to both the NC (p 's < 0.001) and cluster-derived normal (p 's < 0.001) groups. The proportion of individuals who met criteria for amyloid positivity did not significantly differ between the amnesic and dysexecutive/mixed MCI groups ($p = 0.069$) or between the cluster-derived normal and NC groups ($p = 0.152$).

Cortical amyloid accumulation in the MCI cluster and normal control groups

ANCOVAs controlling for age and APOE genotype revealed that mean cortical florbetapir SUVR and regional amyloid accumulation (in frontal, temporal, cingulate, and parietal cortices) significantly differed across the groups (all p 's < 0.001 ; Table 1 and Figs. 3 and 4). With respect to mean cortical amyloid, *post hoc t*-tests showed that on average the dysexecutive/mixed MCI group had significantly greater amyloid burden ($p = 0.001$) than the amnesic MCI group; moreover, both the dysexecutive/mixed and amnesic MCI groups had significantly greater amyloid relative to the cluster-derived normal (p 's < 0.001) and NC (p 's < 0.001) groups. However, no significant differences were observed between the cluster-derived normal and NC groups ($p = 0.236$).

With respect to regional amyloid, *post hoc t*-tests revealed the following: (1) there were no significant differences between the dysexecutive/mixed and amnesic MCI groups ($p > 0.008$) in cingulate amyloid; however, frontal, parietal, and temporal amyloid burden was significantly greater in the dysexecutive/mixed MCI group relative to the amnesic MCI group (p 's < 0.008); (2) both MCI groups displayed significantly greater frontal, cingulate, parietal, and temporal amyloid accumulation relative to NC (p 's < 0.008) and cluster-derived normal groups (p 's < 0.008); and (3) across all ROIs investigated, there were no significant difference in amyloid burden between the NC and cluster-derived normal groups (p 's > 0.170).

Interaction between cognitive group and APOE genotype on amyloid accumulation

ANCOVAs adjusting for age demonstrated that there was a significant Group $\times$ APOE $\epsilon 4$ status interaction for mean cortical mean florbetapir SUVR ($F(3,574) = 3.98, p = 0.008, \eta_p^2 = 0.020$) and regional frontal ($F(3,574) = 4.56, p = 0.004, \eta_p^2 = 0.023$), cingulate ($F(3,574) = 4.23, p = 0.006, \eta_p^2 = 0.022$), parietal ($F(3,574) = 3.12, p = 0.026, \eta_p^2 = 0.016$), and temporal ($F(3,574) = 3.33, p = 0.019, \eta_p^2 = 0.017$) SUVRs (Fig. 5). Examination of simple main effects with Bonferroni correction revealed that, across all regions, APOE $\epsilon 4$ carriers within the amnesic MCI and cluster-derived normal groups had on average significantly greater amyloid accumulation in mean cortical and regional frontal, cingulate, parietal, and temporal cortices (all p 's < 0.001) when compared to APOE $\epsilon 4$ non-carriers of their respective group. Similarly, APOE $\epsilon 4$ carriers of the NC group had on average significantly greater mean cortical and regional frontal and cingulate (p 's < 0.008) amyloid accumulation compared to non-carriers of the same group. Within the dysexecutive/mixed MCI group, amyloid accumulation of APOE $\epsilon 4$ carriers did not significantly differ from non-carriers across any cortical ROI (all p 's > 0.008).

Clinical outcome by cognitive group and amyloid accumulation

Longitudinal data (mean follow-up = 13.9 months; range 6–36 months) were available for 91.7% of the MCI sample. Overall, 10.1% of those diagnosed with MCI progressed to AD and 3.9% reverted back to a cognitively normal classification. The NC group was not included in these analyses given that they were selected on the basis of remaining cognitively normal (did not progress to MCI) throughout the course of their ADNI participation.

A chi-squared analysis revealed that the groups (i.e., amnesic MCI, dysexecutive/mixed MCI, cluster-derived normal) significantly differed in diagnostic status (i.e., MCI to AD [progression], MCI to cognitively normal [reversion], or no change) at follow-up assessment ($\chi^2 = 37.97, p < 0.001$). The groups significantly differed in frequency of progression to AD (see Table 1) with the dysexecutive/mixed MCI group showing the highest rate of progression to dementia (30.6%) compared to the amnesic MCI (13.5%) and cluster-derived normal groups (1.2%). Logistic regressions, adjusting for age, APOE genotype, and length of follow-up, revealed greater baseline mean cortical florbetapir SUVR was associated with later progression to dementia ($\chi^2 = 11.39, p = 0.001$; mean cortical SUVR: $B = 2.93, p = 0.001$). When regional florbetapir SUVRs were assessed separately, baseline SUVRs for frontal, cingulate, parietal, and temporal cortices were significantly associated with later progression to dementia (p 's ≤ 0.003).

DISCUSSION

Empirically-derived MCI subtypes from the ADNI cohort demonstrated considerable heterogeneity in A β accumulation as assessed by florbetapir PET. The cluster-derived normal group, all of whom were diagnosed as having MCI via ADNI protocols, did not differ from the NC group in terms of cortical florbetapir SUVRs. These results extend our previous finding of equivalence between cluster-derived normal and NC groups on AD biomarkers including CSF concentrations of hyperphosphorylated tau (p-tau_{181p}), A β ₁₋₄₂,

and the ratio of p-tau_{181p}/A β ₁₋₄₂ [18]; and frequency of the APOE ϵ 4 allele [1, 18] to PET A ϵ . Our present findings provide further support for the notion that conventional criteria for MCI may be susceptible to false positive diagnostic errors. In addition, even after adjusting for age and APOE genotype, MCI participants who were more severely cognitively impaired (i.e., showed impairments in multiple domains) demonstrated greater PET A β accumulation compared to the amnesic MCI, cluster-derived normal, and NC groups. This pattern of findings suggests that empirically-derived neuropsychological phenotypes correspond to differences in underlying fibrillar amyloid plaque density.

Our findings showed a pattern of progressive increase in A β positivity from 34% in cognitively normal older adults to 62% in amnesic MCI to 78% in dysexecutive/mixed MCI. The dysexecutive/mixed MCI showed greater A β accumulation in AD-vulnerable temporal and parietal regions relative to the amnesic MCI subgroup. The amnesic MCI subgroup demonstrated mildly impaired performance only on memory measures whereas the dysexecutive/mixed MCI subgroup performed in the severely impaired range on tasks of speed/executive function along with mild impairment on memory and language tests. Although this pattern of findings suggests that MCI represents a risk state for AD generally, it also further underscores the inherent heterogeneity within the ADNI MCI cohort. Indeed, approximately 40% and 20% of the amnesic and dysexecutive/mixed MCI participants, respectively, showed no evidence of A β positivity on florbetapir PET imaging suggesting that A β may be adding to or synergizing with other pathologies to produce progressive impairment.

An important finding in the current research is the presence of a cognitive group $\times$ APOE genotype interaction on A β accumulation. Among the amnesic MCI, cluster-derived normal, and NC groups, APOE ϵ 4 carriers had higher levels of cortical A β relative to non-carriers in their respective groups. In contrast, among individuals with dysexecutive/mixed MCI, there was no difference in cortical A β level between APOE ϵ 4 carriers and non-carriers. Although we do not have information about the onset of cognitive impairment among our MCI participants, the dysexecutive/mixed MCI group demonstrated greater A β accumulation, was more cognitively impaired at baseline, had a higher mean age at baseline (although this difference was not statistically significant), and was more likely to convert to dementia than the other MCI subgroups and, therefore, may have been farther along in the disease course than the other groups.

Previous studies suggest that, among APOE ϵ 4 carriers, there may be earlier onset of cortical A β accumulation compared to non-carriers [27–29]. A recent meta-analysis showed that compared to the APOE ϵ 3 allele, the APOE ϵ 4 allele is associated with amyloid positivity among cognitively normal older adults [30]. Previous studies demonstrated that the presence of the APOE ϵ 4 allele was significantly associated with higher PET-Pittsburgh compound B (PiB) retention independent of age and sex, however, APOE genotype did not affect A β change over time [29]. This pattern of findings raises the possibility that APOE ϵ 4 carriers may be farther along in the disease process, consistent with earlier onset of brain A β accumulation and providing a neurobiological basis for the effects of APOE genotype on the age of onset in AD [29]. Weak associations between cognitive decline and change in A β over time may suggest that other non-amyloid pathologies (e.g., cerebrovascular disease) or other

downstream factors may have a more direct effect on cognition as the disease progresses [31].

Although caution must be taken given the cross-sectional design of the current study, our findings of greater A β accumulation among APOE ϵ 4 carriers compared to non-carriers in the amnesic MCI, cluster-derived normal, and NC groups coupled with no APOE genotype-related differences in A β accumulation in the dysexecutive/mixed MCI subgroup which showed the greatest A β accumulation and greatest cognitive impairment may support these previous studies indicating early onset of A β accumulation among APOE ϵ 4 carriers. Another possibility is that early in the disease course, among APOE ϵ 4 carriers, A β may play a larger role in symptom development compared to non-carriers who may have other non-amyloid pathologies (e.g., cerebrovascular disease) and for whom the early disease process may not necessarily involve amyloid to as great of an extent. When A β burden increases among APOE ϵ 4 non-carriers, cognitive decline may progress leading to more severe cognitive impairment and greater breadth of cognitive domains affected.

Neuropathological and multimodal clinical studies have shown that clinically diagnosed MCI and even amnesic MCI specifically [32, 33], is a pathologically heterogeneous disorder. The etiology of cognitive impairment in A β -negative individuals with MCI may relate to age-related pathologies including cerebrovascular disease, hippocampal sclerosis, Lewy body disease, or mixed pathologies [30, 32, 34]. This possibility is further underscored by a recent meta-analysis that showed that roughly 12% of clinically diagnosed AD participants showed a negative amyloid PET scan [34]. This finding may be explained by a mix of age-related pathologies, such as hippocampal sclerosis, argyrophilic grain disease, or tangle predominant dementia, that target the limbic system and may result in an “AD phenotype” predominated by memory impairment [34], or by co-occurring cerebrovascular disease. In a sample of autopsy-confirmed AD patients, we found that the presence of even mild cerebrovascular disease was associated with lower Braak stage, yet there were no differences in severity of cognitive impairment between the AD patients with and without cerebrovascular changes [35]. The fact that the AD patients with cerebrovascular disease showed the same degree of cognitive impairment as the AD patients without cerebrovascular disease, despite having a significantly lower burden of AD pathology, suggests that vascular pathology may have an additive effect on cognitive impairment, even in patients with autopsy-confirmed AD and relatively mild cerebrovascular disease [35].

Interestingly, more than a third of our rigorously screened, stable NC group who did not progress to MCI over 1–3 years of follow-up met criteria for A β positivity. Conversely, roughly 20% of our most impaired sample (those with prominent memory and executive dysfunction) did not meet the threshold for A β positivity. These findings further underscore recent work that has called into question the amyloid cascade hypothesis [36, 37]. Specifically, our results dovetail with neuropathological studies that have demonstrated that 33–50% of individuals without cognitive impairment show a significant amount of AD pathology at autopsy [38–41], and 10–30% of cognitively normal participants have considerably high brain levels of A β (PiB and florbetapir studies) [42, 43]. Importantly, the overall burden of amyloid in the AD brain is not associated with the severity of cognitive

decline [44–46], and amyloid plaques are not situated near neurons or synapses that degenerate in early AD [47]. Although clearly an important component that contributes to the disease process in AD, the pathogenesis of amyloid and how it relates to the clinical expression of AD is complex and unfortunately still very unclear. However, our current finding of a cognitive group $\times$ APOE genotype interaction on A β accumulation taken together with previous studies demonstrating that the presence of the ϵ 4 allele relates to earlier onset of disease [29] suggests that APOE genotype may influence the onset/course of disease. Nonetheless, the amyloid hypothesis is rapidly coming under increasing scrutiny as more clinical trials continue to fail in the face of new data that are not consistent with the hypothesis [36]. Clearly, additional studies examining the complex interaction of amyloid accumulation, synaptic loss, neurofibrillary tangle formation and accumulation, neurodegeneration, and microglial activation are needed in order to understand this complex disease and therefore lead to improved therapeutic strategies to combat AD.

A recent meta-analysis demonstrated that the age-related prevalence of amyloid positivity in cognitively normal individuals parallels the age-related prevalence of AD in the general population in APOE genotype specific patterns with a 20–30 year lag [30]. Given this pattern, Jansen and colleagues speculate that there may be 20–30 years between amyloid positivity and the expression of clinical AD [30]. Participants in the current study had follow-up between one and three years and, therefore, if they had been followed for a longer period of time, some of these individuals may have developed clinical AD. However, these participants demonstrated normal cognition in the context of significant burden of amyloid pathology suggesting that other factors, at least in a sizable proportion of older adults, likely contribute to the expression of cognitive impairment. Indeed, a recent study demonstrated that hippocampal volume and memory abilities are decoupled from amyloid burden in cognitively normal individuals with reductions in hippocampal volume and worsening memory occurring at earlier ages than abnormal PET amyloid [48]. Alternatively, although groups were similar on educational attainment, perhaps many of these individuals were able to benefit from greater levels of cognitive or neural reserve so that a greater burden of AD pathology was not coupled with overt cognitive decline [39, 49].

Our previous work suggests that a significant proportion of individuals in the ADNI MCI sample are cognitively normal once detailed testing and a more sensitive and reliable diagnostic scheme is employed [1, 18]. Our current findings indicate that these individuals do not differ from a robust normal control sample in terms of A β accumulation, further supporting the notion that these individuals likely do not represent prodromal AD. False positive diagnostic errors may have adverse consequences not only for those individuals from a clinical perspective, but they may negatively impact outcomes of biomarker studies and clinical trials. If a large number of cognitively normal older adults without significant amyloidosis or neurodegeneration are incorrectly classified as having MCI in studies of potential biomarkers or potential treatments, results could be significantly diluted and the apparent utility of these markers or treatments could be greatly diminished. Of course, an alternative strategy of recruitment based on amyloid positivity, as in the current A4 trial [50], will continue to miss many individuals as well, given the significant percentages of individuals with MCI without amyloid positivity, as shown in our study.

Strengths of this study include a large, well-characterized sample of older adults who have been followed longitudinally as part of a national study on aging and AD. Additionally, we employed an empirical data-driven statistical approach to the identification of MCI phenotypes, and use of a robust control group that excluded individuals with pre-clinical dementia at any time point of follow-up. A limitation of our study is the absence of assessing other cognitive domains, such as visuospatial functions, particularly since we have previously identified a visuospatial MCI subtype [17] and baseline MCI diagnoses based on visuospatial deficits reliably predict development of dementia with Lewy bodies [51]. The follow-up period was relatively short (up to 3 years) and the shorter follow-up time may explain the lower frequency of conversion from MCI to dementia in our current study compared to our previous studies that involved up to 7 years of follow-up [1, 18]. Although our observed MCI-to-dementia conversion rate of 10.1% over a mean follow-up of 13.9 months is relatively similar to the 12% annual conversion rate reported in the literature [13], future studies should aim for a longer follow-up period. Another limitation of our study is our inability to assess false negative diagnostic errors given our decision to use a ‘robust’ normal control sample. That is, individuals misclassified as cognitively normal but found to have cognitive impairment upon more extensive neuropsychological testing or who later declined were not included in the cognitively normal sample. In addition, given the relatively small number of participants in some subgroups (i.e., dysexecutive/mixed MCI) taken together with the low frequency of APOE $\epsilon 4$ homozygosity, we were unable to examine gene-dose effects. Future studies should explore whether incorporating more or different neuropsychological measures modifies cluster solutions and identifies additional individuals at risk for progression to AD. Future work should also incorporate novel tau tracers to assess both amyloidosis and neurodegeneration measured by PET. Improved diagnostic accuracy and characterization of prodromal AD phenotypes will assist clinicians and researchers in identifying those individuals who will develop AD. This work has important implications for biomarker studies, clinical trials, and treatment.

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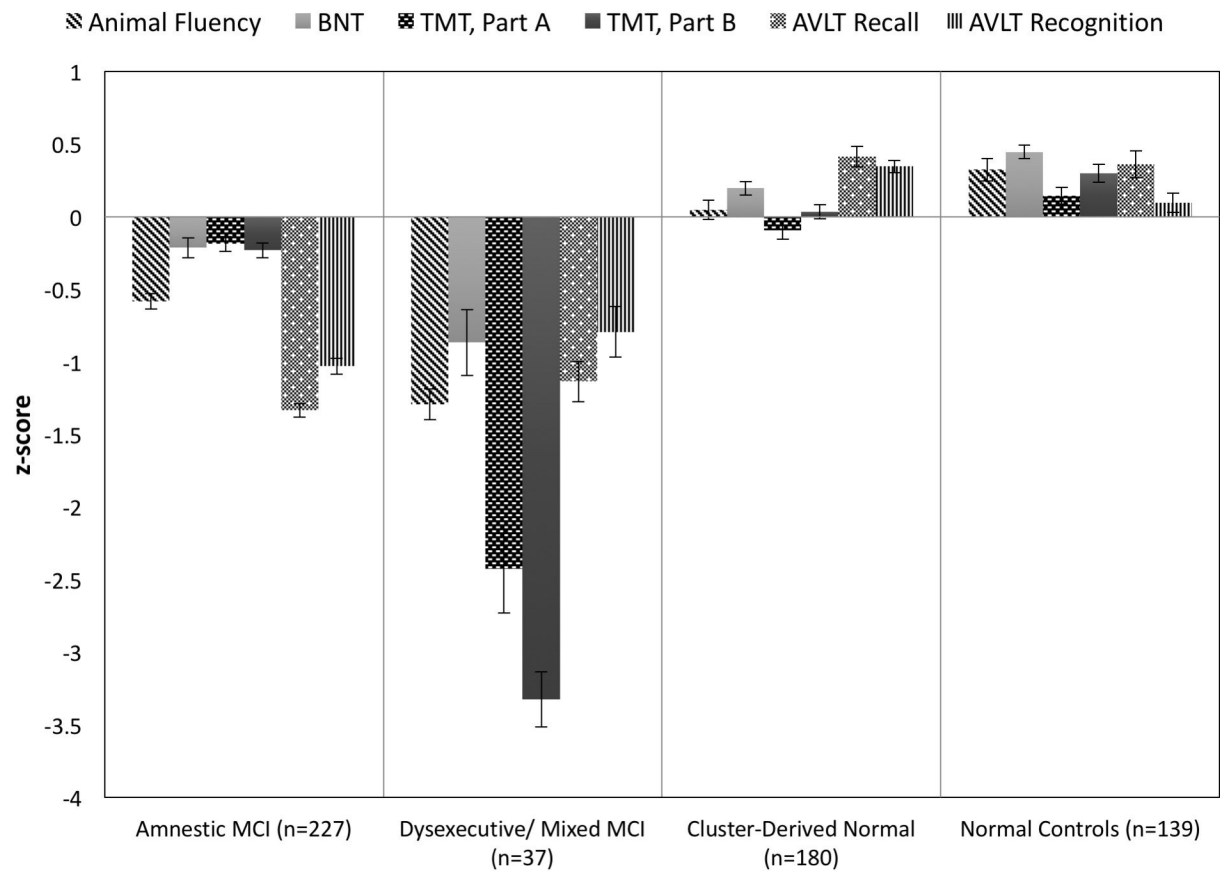
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**Fig. 1.**

Mean z-scores for the three MCI subgroups on neuropsychological measures included in the cluster analysis of conventional Petersen/Winblad ADNI criteria. Error bars denote standard error of the mean.

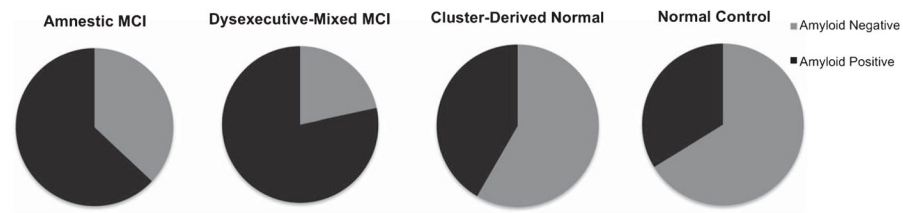


Fig. 2.

Distribution of amyloid positivity for the three MCI subgroups and normal controls based on the recommended threshold for cross-sectional florbetapir analyses of 1.11 using the whole cerebellum as the reference region.

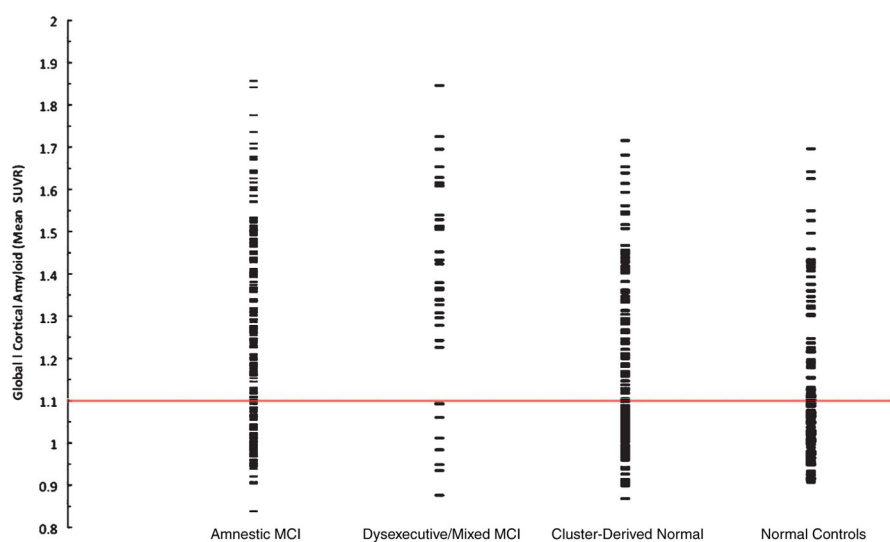
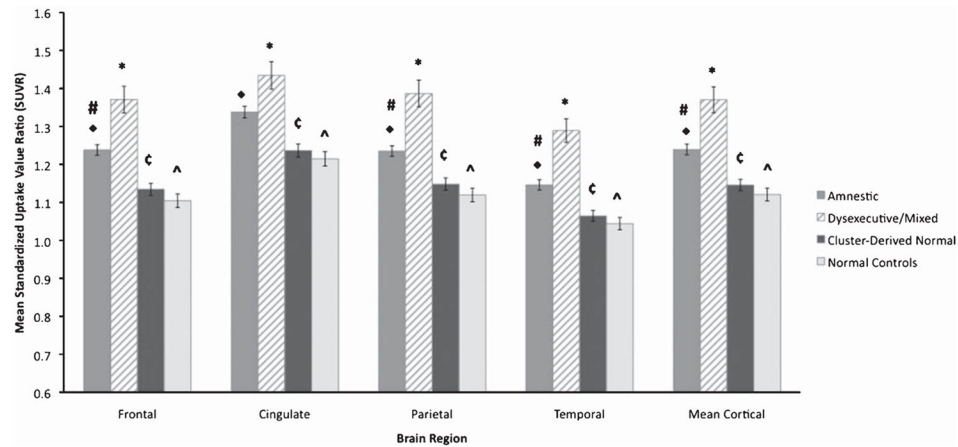


Fig. 3.
Distribution of mean cortical amyloid standard uptake value ratios (SUVRs) for the three MCI subgroups and normal controls.

**Fig. 4.**

Mean cortical and regional florbetapir standard uptake value ratios (SUVRs) for MCI and cognitively normal groups. Error bars denote standard error of the mean. Symbols denote significant ($p < 0.008$) pairwise comparisons: Amnesic MCI versus Cluster Derived Normal; ^ Amnesic MCI versus Normal Controls; ^ Dysexecutive/Mixed MCI versus Cluster Derived Normal; * Dysexecutive/Mixed MCI versus Normal Controls; # Amnesic MCI versus Dysexecutive/Mixed MCI; No significant Cluster Derived Normal versus Normal Controls findings were observed. All models were adjusted for age and APOE genotype ($\epsilon 4$ carrier versus noncarrier).

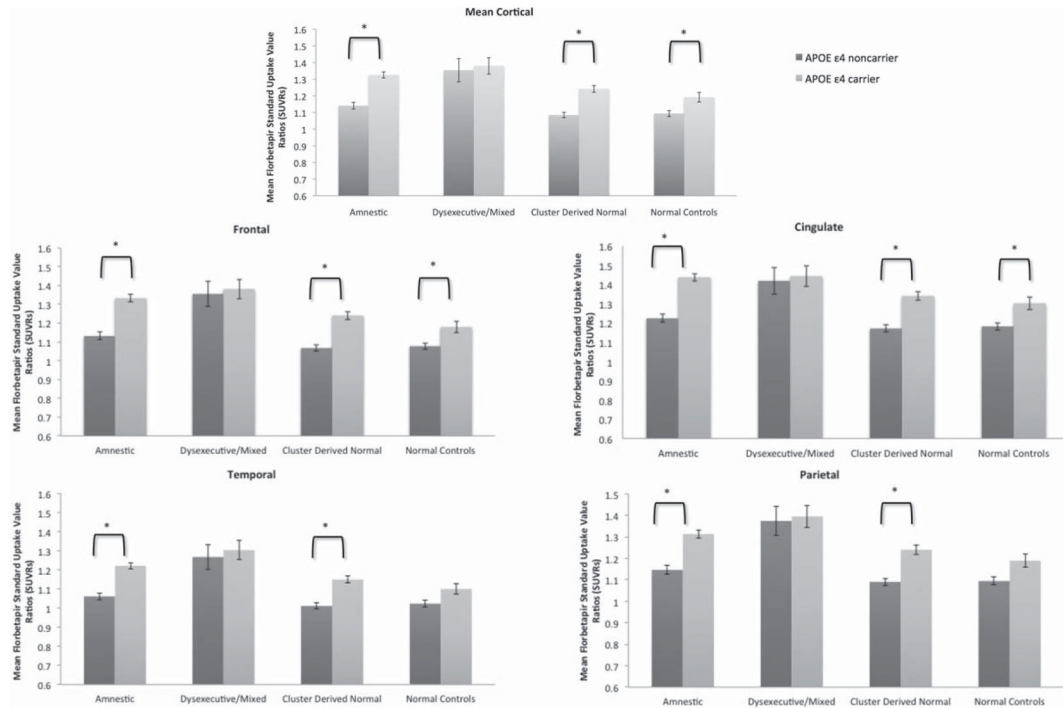


Fig. 5. Interaction of cognitive status (Amnestic MCI, Dysexecutive/Mixed MCI, Cluster-Derived Normal, Normal Control) and APOE genotype (ε4 carrier versus noncarrier) on regional florbetapir standard uptake value ratios (SUVRs). Error bars denote standard error of the mean. * p < 0.008

Table 1

Demographic and amyloid characteristics of the cluster and normal control groups

	Amnesic MCI (n = 227)	Dysexecutive MCI (n = 37)	Cluster-Derived Normal (n = 180)	Normal Control (n = 139)	F or χ^2	Sig.	Effect Size
<i>Demographics*</i>	Mean (SD)						
Age (years)	71.79 (7.06)	74.78 (8.47)	70.68 (7.78)	73.61 (6.09)	F = 6.27	p < 0.001	$\eta_p^2 = 0.031$
Education (years)	16.00 (2.66)	15.97 (2.87)	16.50 (2.59)	16.69 (2.53)	F = 2.52	p = 0.057	$\eta_p^2 = 0.013$
Sex (% male)	59.9%	62.2%	47.8%	51.1%	$\chi^2 = 7.47$	p = 0.058	$\phi = 0.113$
APOE $\epsilon 4$ (% yes)	53.3%	62.2%	38.9%	27.3%	$\chi^2 = 30.48$	p < 0.001	$\phi = 0.229$
Amyloid Positive (% yes)	63.0%	78.4%	41.7%	33.8%	$\chi^2 = 46.78$	p < 0.001	$\phi = 0.283$
<i>Regional Amyloid[#]</i>							
Cortical Summary	1.24 (0.22)	1.37 (0.24)	1.15 (0.19)	1.12 (0.19)	F = 13.34	p < 0.001	$\eta_p^2 = 0.065$
Frontal	1.24 (0.24)	1.37 (0.25)	1.13 (0.20)	1.10 (0.19)	F = 14.59	p < 0.001	$\eta_p^2 = 0.070$
Cingulate	1.34 (0.24)	1.43 (0.26)	1.24 (0.20)	1.21 (0.20)	F = 9.36	p < 0.001	$\eta_p^2 = 0.046$
Parietal	1.24 (0.22)	1.39 (0.25)	1.15 (0.20)	1.12 (0.20)	F = 13.61	p < 0.001	$\eta_p^2 = 0.066$
Temporal	1.15 (0.20)	1.29 (0.24)	1.06 (0.17)	1.04 (0.17)	F = 14.30	p < 0.001	$\eta_p^2 = 0.069$
<i>Clinical Outcome[^]</i>							
Progression (MCI to dementia)	28 (13.5%)	11 (30.6%)	2 (1.2%)	n/a	$\chi^2 = 32.45$	p < 0.001	$\phi = 0.288$
Reversion (MCI to cognitively normal)	4 (1.9%)	1 (2.8%)	11 (6.7%)	n/a	$\chi^2 = 4.23$	p = 0.121	$\phi = 0.108$

* Data are summarized as mean (standard deviation), unless otherwise indicated;

[#] units are standardized uptake value ratio (SUVR) with whole cerebellum (gray and white) as reference region and models are adjusted for age and APOE genotype ($\epsilon 4$ carrier versus noncarrier);[^] Number of participants for progression/reversion analysis: amnesic MCI: n = 207; dysexecutive/mixed MCI: n = 36; and cluster-derived normal: n = 164. Follow-up ranged from 6–36 months. Clinical outcome was not assessed for the Normal Control group given that they were selected on the basis of remaining cognitively normal (did not progress to MCI) throughout the course of their ADNI participation.