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Dysexecutive versus amnestic Alzheimer's disease subgroups: Analysis of demographic, genetic, and vascular factors

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Abstract

The objective of this study was to compare demographic and vascular characteristics and *APOE* genotypes of a dysexecutive subgroup of Alzheimer's disease (AD) with an amnestic subgroup of AD early in the disease course. 2,224 participants from the National Alzheimer's Coordinating Center (NACC) database who carried a diagnosis of MCI (n=1,188) or mild AD (clinical dementia rating ≤1) (n=1,036) were included in this study. A subset of the MCI (n=61) and mild AD (n=79) participants underwent autopsy. A dysexecutive subgroup (n=587) was defined as having executive performance >1 SD worse than memory performance and an amnestic subgroup (n=549) was defined conversely. Among the autopsy subset, the likelihood of an AD pathologic diagnosis was compared in the two subgroups. Demographics, *APOEε4* status, and vascular risk factors were compared in the two subgroups. Among the autopsy subset, the likelihood of having an AD pathologic diagnosis did not differ between the dysexecutive and amnestic subgroups. Under an additive model, participants in the dysexecutive subgroup possessed the *APOEε4* allele less frequently than those in the amnestic subgroup. The dysexecutive subgroup had a history of hypertension less frequently than the amnestic subgroup. These distinct characteristics add to accumulating evidence that a dysexecutive subgroup of AD may have a unique underlying pathophysiology.

INTRODUCTION

While episodic memory loss is a classic early symptom of Alzheimer's disease (AD),[1] the presentation of AD can be quite heterogeneous. Examples include primary progressive aphasia, posterior cortical atrophy/visual variant, and a dysexecutive variant.[2,3] Executive

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dysfunction refers to deficits in "planning, judgment, reasoning, problem solving, organization, attention, abstraction and mental flexibility."[4] A subset of mild AD patients (clinical dementia rating (CDR)[5] of 0.5 or 1) has been described with substantial executive dysfunction in addition to deficits in memory.[2]

Limited data exist regarding demographic characteristics of AD patients with predominant executive dysfunction compared with AD patients with predominant memory dysfunction. A study of mild cognitive impairment (MCI) and mild AD (CDR=0.5) participants suggested that the two subgroups do not differ in sex, age, or education.[6] In contrast, another study showed that AD patients (not restricted by CDR) with predominant executive dysfunction presented at a younger age and were disproportionately male.[7] Neither study evaluated ethnicity.

Significant biologic differences have been noted between AD patients with predominant executive dysfunction compared with typical AD. One study found disproportionate amyloid plaque burden[8] while another found disproportionate amyloid plaque and neurofibrillary tangle burden in the frontal lobes as compared to the typical distribution of pathology in AD.[9] Structural and functional imaging studies suggest that MCI and AD patients with predominant executive dysfunction have greater frontoparietal cortical thinning and hypometabolism than either controls or MCI and AD patients with predominant memory deficits.[6,10–12]

Assorted data exists regarding the frequency of the *APOE*ε4 allele in the dysexecutive subgroup of MCI and AD. Two studies showed that the *APOEε4* allele occurs significantly less frequently in MCI and AD patients with predominant executive dysfunction than in MCI and AD patients with predominant memory dysfunction.[6,7] In another study, the *APOEε4* allele occurred significantly more frequently in multi-domain (dysexecutive and amnestic) MCI patients than in pure amnestic MCI (aMCI) patients.[13]

Vascular risk factors may also contribute to executive dysfunction with or without AD. In normal aging, diabetes and hypertension have been associated with executive dysfunction.[14,15] In AD, an increase in the number of vascular comorbidities has been associated with greater impairments in verbal reasoning and set shifting.[16,17]

Here we compare demographic and clinical characteristics and *APOE* genotypes of a dysexecutive subgroup of AD with an amnestic subgroup of AD early in the disease course. We hypothesize that ethnic group, *APOE* genotype and vascular risk factors will differ in the dysexecutive subgroup compared with the amnestic subgroup.

METHODS

The National Alzheimer's Coordinating Center (NACC) developed and maintains a large relational database of standardized clinical research data collected from the 29 NIA-funded Alzheimer's disease Centers (ADCs) nationwide. The study was approved by an institutional review board at each institution. The current study is a secondary analysis of data previously collected. Recruitment, participant evaluation and diagnostic criteria for dementia, probable AD and MCI are detailed elsewhere.[18] Each participant with MCI was further classified as having memory impairment (aMCI) or not having memory impairment (non-amnestic MCI). Each participant with aMCI was further classified into single domain (memory impairment only) or multiple domain (attention/processing speed, executive function, language or visuo-spatial function)). Because we were interested in the early presentation of AD, we restricted our sample to participants who met criteria for probable mild AD (CDR ≤1) or for single or multiple domain aMCI (who are more likely to progress to AD than non-amnestic MCI[19]).

Race (white, African American, American Indian or Alaska native, Pacific Islander, Asian or other) and presence of Hispanic/Latino ethnicity were ascertained by self report using two separate questions. All references to African Americans and whites imply non-Hispanic African Americans and non-Hispanic whites. Achieved years of education was ascertained by self report.

Stroke was defined according to the World Health Organization criteria, based on self-report and supplemented by a neurological examination. History of diabetes, hypertension, hyperlipidemia and myocardial infarction (MI) were ascertained by self-report at the first visit. A vascular risk score was assigned to each participant based on the number of vascular risk factors (0–5).

All participants were administered the ADCs' Uniform Data Set neuropsychological battery. The tests include Digit Span Forward (DSF), Digit Span Backward (DSB), Digit Symbol (DS), Trail Making Test (TMT) part A, TMT part B, Logical Memory Test story A (LMTA) immediate recall, LMTA delayed recall, Animal List Generation (ALG), Vegetable List Generation (VLG) and the Boston Naming Test (BNT).[20] Neuropsychological data were used from the first visit during which the diagnosis of MCI or AD was made.

APOE genotype was determined for each participant and classified as having no *APOEε4* alleles, one *APOEε4* allele or two *APOEε4* alleles.

2,224 (31%) of the 7,126 eligible participants were included in this study. Inclusion criteria are illustrated in the flow chart in figure 1. Participants were excluded if they had incomplete neuropsychological testing, lacked *APOE* genotyping or had incomplete vascular risk factor data. Included and excluded participants did not differ in sex or age. Compared with included participants, excluded participants were less educated by 0.4 years ($p<.001$), were disproportionately African American (OR=1.42, $p<.001$) and were disproportionately demented (OR=1.24, $p<.001$).

Of the 2,224 included participants, 140 underwent autopsy. Compared with the non-autopsy subset, the autopsy subset was 6.7 years older ($p<.001$), had 0.6 more years of education ($p=.017$), was less likely to be African American (OR=.13, $p=.004$) and was less likely to be female (OR=.67, $p=.022$). Each autopsy participant was given a primary pathologic diagnosis. If AD pathology was present and considered by the pathologist to be the primary diagnosis, but did not meet Reagan criteria,[21] the participant was still considered to have pathologic AD in our study.

Controls were diagnosed as normal at each annual NACC evaluation (n=6,385, first visit mean age=71.3). Using neuropsychological data from their first visit, a mean and SD were calculated for each test in the Uniform Data Set (UDS). These were used to calculate Z scores on each test for each participant with cognitive deficits. A global cognitive score was calculated for each participant by averaging the Z score on each of the UDS neuropsychological tests.

Classification of the 'dysexecutive' and 'amnestic' subgroups was made according to methods used by Dickerson et al.[6] in the AD Neuroimaging Initiative (ADNI) with modification due to test availability. The Logical Memory Test story A (LMTA) and the Trail Making Test (TMT) were used to evaluate memory and executive function respectively. This method was chosen because it utilizes neuropsychological tests (or variations on them) that are widely used so it can be easily replicated. The method has been shown to differentiate patients into subgroups who demonstrate consistent generalizable deficits in their respective cognitive domains on multiple neuropsychological tests.[6] In the LMTA, delayed recall was subtracted from immediate recall to account for learning ability.

This value was termed the memory score. In the TMT, TMT A was subtracted from TMT B to account for attention. This value was termed the executive score. Even though all participants needed to have cognitive impairment to be included in the study, they could have either positive or negative memory and executive scores because each of these scores was obtained by taking the difference between two neuropsychological tests. A mean and standard deviation for the executive and memory scores were calculated. These were used to calculate Z scores for each participant. Participants were considered members of the dysexecutive subgroup if their executive performance was ≥ 1 SD below their memory performance. Participants were considered members of the amnestic subgroup if their memory performance was ≥ 1 SD below their executive performance.

To determine if the dysexecutive and amnestic subgroups also differed in other aspects of cognition, we calculated several composite scores based on a recent factor analysis of the NACC cognitive battery in normal controls, MCI and dementia.[22] Specifically, we calculated scores for each of the four identified neuropsychological factors by averaging the z-scores for each participant on the tests that make up the factor. The executive factor consisted of TMT A, TMT B, and DS. The memory factor consisted of LMTA immediate recall and LMTA delayed recall. The language factor consisted of BNT, ALG and VLG. The attention factor consisted of DSF and DSB.

After controlling for variables that differed between the two subgroups (i.e. age, education, ethnicity, *APOEε4,* and global cognition as demonstrated in the results section), the AD dysexecutive subgroup performed worse than the AD amnestic subgroup on the executive factor, ($p<.001$), but performed better than the AD amnestic subgroup on the memory factor ($p<.001$) and the language factor ($p<.001$). They did not differ on the attention factor. After controlling for covariates, the MCI dysexecutive subgroup performed worse than the MCI amnestic subgroup on the executive factor ($p<.001$), but performed better than the AD amnestic subgroup on the memory factor ($p<.001$). They did not differ on the attention or language factors.

STATISTICAL ANALYSES

All analyses were carried out in the entire sample and separately in MCI and AD participants. Among the pathologic subset, a chi squared test was used to compare the likelihood of an AD pathologic diagnosis in the dysexecutive subgroup, the amnestic subgroup and those in neither subgroup. In the full sample, we performed bivariate and multivariate analyses that included the following covariates: age, education, African American ethnicity, hypertension, hyperlipidemia, type 2 diabetes, MI, stroke, *APOEε4* carrier status, and global cognition. Logistic regression was used to compare the likelihood of categorical variables including demographic characteristics (sex and ethnicity) and the likelihood of various vascular risk factors (MI, stroke, hypertension, hyperlipidemia, type 2 diabetes) in the dysexecutive subgroup relative to the amnestic subgroup. Linear regression was used to compare the values of continuous variables including demographic characteristics (age and education level), performance on the neuropsychological factor scores, and the vascular risk score in the dysexecutive subgroup relative to the amnestic subgroup. Logistic regression was used to compare the likelihood that participants in the dysexecutive subgroup possessed the *APOEε4* allele relative to participants in the amnestic subgroup under an additive genetic model. This analysis was also carried out stratified by ethnicity. All statistical analyses were carried out using SPSS.[23]

RESULTS

Among the 1,188 participants with MCI, 294 met criteria for the dysexecutive subgroup, 283 met criteria for the amnestic subgroup and 611 met criteria for neither subgroup. Among the 1,036 patients with mild AD, 293 met criteria for the dysexecutive subgroup, 266 met criteria for the amnestic subgroup and 477 met criteria for neither subgroup. Participant demographic, clinical and genetic characteristics are given in table 1.

In the AD dysexecutive subgroup, the mean executive score was −1.04± 0.5 while in the AD amnestic subgroup, the mean executive score was +0.99± (0.5). In the MCI dysexecutive subgroup, the mean executive score was −1.21± 0.9 while in the MCI amnestic subgroup, the mean executive score was +0.68± 0.4. In the AD dysexecutive subgroup, the mean memory score was +0.76± 0.8 while in the AD amnestic subgroup, the mean memory score was −0.99± 0.8. In the MCI dysexecutive subgroup, the mean memory score was +0.70± 0.7 while in the MCI amnestic subgroup, the mean memory score was −1.17± 0.8. Although all participants were required to have memory impairment for inclusion in the current study, an independent sample T-test revealed that memory was significantly worse in the amnestic subgroup than in the dysexecutive subgroup ($p<.001$).

Comparing pathologic diagnosis

Among the 61 autopsy cases with MCI, 22 met criteria for the dysexecutive subgroup and 11 met criteria for the amnestic subgroup. Among the 79 autopsy cases with mild AD, 26 met criteria for the dysexecutive subgroup and 15 met criteria for the amnestic subgroup. Both in MCI and mild AD, the two subgroups (and those in neither subgroup) did not differ in likelihood of having a pathologic diagnosis of AD (Table 2). We also examined the rate of pathological AD at autopsy in MCI participants that were excluded from the current study because they were defined as non-amnestic. Individuals with non-amnestic MCI (36.3%) trended lower than a subset of the amnestic single domain MCI participants (60.9%).

Comparing demographic characteristics

Sex did not differ between the dysexecutive and amnestic subgroups in either MCI or mild AD. However, when stratified by diagnostic group across MCI and mild AD, other demographics of the cognitive subgroups differed substantially. After controlling for covariates, the MCI dysexecutive subgroup was older, had fewer years of education, and was more likely to identify as African American than the amnestic subgroup. After controlling for covariates, the AD dysexecutive subgroup was younger than the amnestic subgroup, but did not differ in years of education or ethnicity. (Table 3)

Comparing *APOEε4* status

Under an additive genetic model, after controlling for covariates, participants in the dysexecutive subgroup possessed the *APOEε4* allele less frequently than participants in the amnestic subgroup. The finding remained when stratified by diagnosis into MCI and mild AD groups. (table 4a)

The *APOEε4* allele frequencies in whites (.320) and African Americans (.322) were quite similar in the NACC cohort. Because the *APOEε4* – AD association is weaker among African Americans than whites,[24] and because there was a higher proportion of African American participants in the dysexecutive MCI subgroup as compared with the amnestic subgroup, we repeated the above analysis stratified by ethnicity. In African Americans, under an additive genetic model, after controlling for covariates, there was no difference in the frequency of the *APOEε4* allele. In whites, under an additive genetic model, after

controlling for covariates, participants in the dysexecutive subgroup possessed the *APOEε4* allele less frequently than participants in the amnestic subgroup. (Table 4b)

Comparing vascular risk factors

After controlling for covariates, the dysexecutive and amnestic subgroups did not differ in likelihood of history of diabetes, stroke, hyperlipidemia or MI. However, participants in the dysexecutive subgroup had a history of hypertension less frequently than participants in the amnestic subgroup (OR=0.73, p=0.040). Because of the possibility of additivity among vascular risk factors, we calculated a vascular score ranging from 1–5 based on the number of vascular risk factors. After controlling for covariates, the vascular risk score did not differ in the two subgroups. (Table 5)

DISCUSSION

While episodic memory deficits are a classic early symptom of AD, the cognitive presentation of AD can be quite heterogeneous. In this study, we explored demographic, genetic, and vascular characteristics of a dysexecutive subgroup of AD early in the disease course and compared these characteristics to an amnestic subgroup of AD. Participants were included in the analysis if they had single domain aMCI, multiple domain aMCI or mild AD (CDR ≤ 1). Although it may have been informative to include those with non-amnestic executive MCI, we restricted our analyses to aMCI participants to increase our confidence that these individuals would progress to AD rather than a non-AD dementia. Existing studies have shown that aMCI is more likely to progress to AD than non-amnestic MCI.[19,25] Moreover, the rate of pathological AD at autopsy in a subset of the non-amnestic dysexecutive MCI participants in NACC (36.3%) trended lower than a subset of the amnestic single domain MCI participants (60.9%).

The dysexecutive and amnestic subgroups characterized in the current study did not differ in likelihood of having a pathologic diagnosis of AD. Although not significantly different, the AD dysexecutive subgroup had pathological AD in >80% of participants as compared to 60% of the amnestic subgroup, the latter of which also captured several individuals with hippocampal sclerosis. These findings, and that the amnestic subgroup accounted for only 27% of the current study sample, highlight the frequency of executive dysfunction in early AD.[26] Thus, the amnestic subgroup in the current study should not be considered typical AD, but rather a focal presentation used to create a clear distinction from the predominantly dysexecutive subgroup. A large portion of individuals in our study did not meet criteria for either of these “extreme” subgroups, and these individuals generally had demographic, genetic and vascular characteristics that were intermediate between the amnestic and dysexecutive subgroup characteristics.

While subgroup categorization was based on only two neuropsychological tests, the construction of the subgroups is nonetheless meaningful: Investigators have previously shown in ADNI that these subgroups, derived from very similar methodology, are biologically different, with the dysexecutive subgroup exhibiting greater frontoparietal cortical thinning on MRI that the amnestic subgroup.[6] Additionally, composite scores for recently derived NACC neuropsychological factors[22] differed in the two subgroups. Expectedly, the subgroups differ in the executive and memory factors. Given that the language factor is derived largely from tests of semantic fluency (that tend to be impaired in conjunction with memory secondary to compromise of the medial temporal lobe), it is not surprising that the AD amnestic subgroup was also more impaired on this factor. No differences were seen on the attention factor. These results support the definition of amnestic versus dysexecutive subgroups implemented in the current study as well as the existence of different subgroups within AD more broadly.

After controlling for covariates, African Americans were more likely to be members of the dysexecutive subgroup in MCI, but ethnicity did not differ between the subgroups in mild AD. Healthy African American elders obtain lower scores on tests of executive function compared with whites.[27] Perhaps, the finding in MCI reflects these differences in specificity of executive function measures among cognitively normal African Americans rather than a finding specific to AD pathology. Future longitudinal analyses would help clarify whether African Americans in the dysexecutive subgroup might convert to AD at a lower rate than African Americans in the amnestic subgroup as this data may intimate.

After controlling for covariates, the dysexecutive subgroup was older than the amnestic subgroup in MCI, but was younger than the amnestic subgroup in mild AD. The dysexecutive subgroup also had fewer years of education than the amnestic subgroup in MCI, but years of education did not differ between the subgroups in mild AD. Advanced age and fewer years of education are associated with lower scores on tests of executive function in healthy elders.[28] Perhaps the age and education findings in MCI reflect these differences among cognitively normal elders rather than a finding specific to AD pathology. Age of onset for focal, non-amnestic presentations of AD has been reported to be earlier than for typical presentations of AD.[29] The younger age of the dysexecutive subgroup in AD might echo these findings in the literature. Future longitudinal analyses would also help clarify whether an older or less educated subset of the dysexecutive subgroup might convert to AD at a lower rate than the amnestic subgroup as this data may intimate.

We decided to look at *APOEε4* frequency in the amnestic and dysexecutive subgroups because AD *APOEε4* carriers have been found to have greater memory deficits and greater medial temporal atrophy than non-carriers.[30,31] Additionally, AD non-carriers have been found to have greater executive impairment and greater frontoparietal atrophy than carriers.[31,32] In our study, after controlling for covariates, under an additive genetic model, participants with the *APOEε4* allele were underrepresented in the dysexecutive subgroup compared with the amnestic subgroup. These findings were still present when stratified into MCI and mild AD. This result replicates data from ADNI[6] in a considerably larger sample using a superior genetic model. Unlike previous studies, our additive model controls for potential effect modulators and demonstrates a dose-effect based on the number of *APOEε4* alleles.

In the NACC sample used for this study, there were 1,861 whites (83.7%) and 219 African Americans (9.8%). Given that whites make up most of the sample, it is not surprising that the results of the full-sample *APOE* analysis were replicated in the whites when analyses were stratified by race. When we performed this analysis in African Americans, there was no significant difference in the proportion of individuals with the *APOEε4* allele. Nonetheless, the OR in African Americans was similar to the OR in whites. Given the small number of African Americans, our study might lack the power to detect a true difference. Alternatively, this might reflect the historically weaker *APOEε4* – AD association in African Americans.[24]

After controlling for covariates, participants in the dysexecutive subgroup had a history of hypertension less frequently than participants in the amnestic subgroup. The two subgroups did not differ in likelihood of history of hyperlipidemia, diabetes, stroke or MI. When a vascular score was calculated based on the number of vascular risk factors, the two subgroups did not differ after controlling for covariates. These findings suggest that the dysexecutive subgroup is not associated with increased vascular risk factors either individually or additively compared with the amnestic subgroup. Multiple studies suggest that AD patients with vascular risk factors have more executive impairment than those without vascular risk factors.[16,17] Multiple studies also suggest that AD patients with

vascular risk factors including hypertension have more memory impairment than those without vascular risk factors.[16,33] While it may be a widely held belief that increased vascular risk factors lead to relatively more executive dysfunction than memory dysfunction in AD, the literature does not address this question directly. Our findings suggest that vascular risk factors do not impose a disproportionate executive to memory burden in AD, and in fact, hypertension may impose a disproportionate memory to executive burden in AD. Our findings might also suggest that executive dysfunction might have another underlying etiology besides subcortical white matter disease such as increased plaque and tangle pathology in the prefrontal cortex.

The study has several limitations. Participant demographics and clinical criteria may have lacked uniformity given the heterogeneity of the 29 ADCs contributing to the NACC database. Nonetheless, the large NACC sample size should have reduced the likelihood that false positives contaminated the results. Further, the heterogeneity allows for greater generalizability to other populations.

Another limitation is the limited utility of Trails B in individuals with poor education or who lack familiarity with the English alphabet. While one may argue that our findings in African Americans may be disproportionately affected by this limitation, we control for education in our model.

Within MCI, the requirement that all participants have memory impairment might suggest that the dysexecutive subgroup (that must be multidomain MCI) had more advanced disease than the amnestic subgroup (that could be either single or multidomain MCI), confounding the comparison. However, it was not the case that both groups had comparable memory loss, with additional executive dysfunction in the dysexecutive group. Rather, memory was more impaired in the amnestic subgroup than the dysexecutive subgroup, suggesting that the two groups were qualitatively different presentations rather than similar presentations at different points on a continuum. Further, to be sure that disease severity did not drive the current results, we controlled for global cognition in our regression analyses.

This study illustrates the distinct demographic, genetic, and vascular characteristics of a dysexecutive subgroup of AD. Specifically, it further supports data indicating that *APOE* impacts the clinical presentation of AD through effects on the anatomic distribution of the disease.[31] Future studies should investigate additional non-*APOE* mediated susceptibility factors that participate in executive dysfunction in AD, as well as potential differences in rate of decline across various AD subgroups. Well defined AD clinical phenotypes likely will have value in differential diagnosis and prognostication in clinical practice and in uniform patient recruitment for genetic studies and clinical trials.

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References

1. Dubois B, Feldman HH, Jacova C, et al. Research criteria for the diagnosis of Alzheimer’s disease: revising the NINCDS-ADRDA criteria. Lancet Neurol. 2007; 6(8):734–746. [PubMed: 17616482]
2. Binetti G, Magni E, Padovani A, et al. Executive dysfunction in early Alzheimer’s disease. J Neurol Neurosurg Psychiatr. 1996; 60(1):91–93. [PubMed: 8558161]
3. Alladi S, Xuereb J, Bak T, et al. Focal cortical presentations of Alzheimer’s disease. Brain. 2007; 130(Pt 10):2636–2645. [PubMed: 17898010]

4. Stuss DT, Alexander MP. Is there a dysexecutive syndrome? Philos Trans R Soc Lond, B, Biol Sci. 2007; 362(1481):901–915. [PubMed: 17412679]
5. Morris JC. The Clinical Dementia Rating (CDR): current version and scoring rules. Neurology. 1993; 43(11):2412–2414. [PubMed: 8232972]
6. Dickerson BC, Wolk DA. Dysexecutive versus amnesic phenotypes of very mild Alzheimer's disease are associated with distinct clinical, genetic and cortical thinning characteristics. J Neurol Neurosurg Psychiatr. 2011; 82(1):45–51. [PubMed: 20562467]
7. Snowden JS, Stopford CL, Julien CL, et al. Cognitive phenotypes in Alzheimer's disease and genetic risk. Cortex. 2007; 43(7):835–845. [PubMed: 17941342]
8. Johnson JK, Head E, Kim R, Starr A, Cotman CW. Clinical and pathological evidence for a frontal variant of Alzheimer disease. Arch Neurol. 1999; 56(10):1233–1239. [PubMed: 10520939]
9. Johnson JK, Vogt BA, Kim R, Cotman CW, Head E. Isolated executive impairment and associated frontal neuropathology. Dement Geriatr Cogn Disord. 2004; 17(4):360–367. [PubMed: 15178954]
10. Bracco L, Bessi V, Piccini C, et al. Metabolic correlates of executive dysfunction. Different patterns in mild and very mild Alzheimer's disease. J Neurol. 2007; 254(8):1052–1065. [PubMed: 17385079]
11. Pa J, Boxer A, Chao LL, et al. Clinical-neuroimaging characteristics of dysexecutive mild cognitive impairment. Ann Neurol. 2009; 65(4):414–423. [PubMed: 19399879]
12. Chao LL, Pa J, Duarte A, et al. Patterns of cerebral hypoperfusion in amnestic and dysexecutive MCI. Alzheimer Dis Assoc Disord. 2009; 23(3):245–252. [PubMed: 19812467]
13. Chang Y-L, Jacobson MW, Fennema-Notestine C, et al. Level of executive function influences verbal memory in amnestic mild cognitive impairment and predicts prefrontal and posterior cingulate thickness. Cereb Cortex. 2010; 20(6):1305–1313. [PubMed: 19776343]
14. Desmond DW, Tatemichi TK, Paik M, Stern Y. Risk factors for cerebrovascular disease as correlates of cognitive function in a stroke-free cohort. Arch Neurol. 1993; 50(2):162–166. [PubMed: 8431135]
15. Robbins MA, Elias MF, Elias PK, Budge MM. Blood pressure and cognitive function in an African-American and a Caucasian-American sample: the Maine-Syracuse Study. Psychosom Med. 2005; 67(5):707–714. [PubMed: 16204428]
16. Goldstein FC, Ashley AV, Endeshaw Y, et al. Effects of Hypertension and Hypercholesterolemia on Cognitive Functioning in Patients with Alzheimer's Disease. Alzheimer Dis Assoc Disord. 2008; 22(4):336–342. [PubMed: 19068499]
17. Lamar M, Libon DJ, Ashley AV, et al. The impact of vascular comorbidities on qualitative error analysis of executive impairment in Alzheimer's disease. J Int Neuropsychol Soc. 2010; 16(1):77–83. [PubMed: 19835657]
18. Morris JC, Weintraub S, Chui HC, et al. The Uniform Data Set (UDS): clinical and cognitive variables and descriptive data from Alzheimer Disease Centers. Alzheimer Dis Assoc Disord. 2006; 20(4):210–216. [PubMed: 17132964]
19. Fischer P, Jungwirth S, Zehetmayer S, et al. Conversion from subtypes of mild cognitive impairment to Alzheimer dementia. Neurology. 2007; 68(4):288–291. [PubMed: 17242334]
20. Weintraub S, Salmon D, Mercaldo N, et al. The Alzheimer's Disease Centers' Uniform Data Set (UDS): the neuropsychologic test battery. Alzheimer Dis Assoc Disord. 2009; 23(2):91–101. [PubMed: 19474567]
21. Hyman BT, Trojanowski JQ. Consensus recommendations for the postmortem diagnosis of Alzheimer disease from the National Institute on Aging and the Reagan Institute Working Group on diagnostic criteria for the neuropathological assessment of Alzheimer disease. J Neuropathol Exp Neurol. 1997; 56(10):1095–1097. [PubMed: 9329452]
22. Hayden KM, Jones RN, Zimmer C, et al. Factor Structure of the National Alzheimer's Coordinating Centers Uniform Dataset Neuropsychological Battery: An Evaluation of Invariance Between and Within Groups Over Time. Alzheimer Dis Assoc Disord. 2011; 25(2):128–137. [PubMed: 21606904]
23. SPSS for Windows. Chicago: SPSS Inc; 2010.
24. Farrer LA, Cupples LA, Haines JL, et al. Effects of age, sex, and ethnicity on the association between apolipoprotein E genotype and Alzheimer disease. A meta-analysis. APOE and

Alzheimer Disease Meta Analysis Consortium. JAMA. 1997; 278(16):1349–1356. [PubMed: 9343467]

25. Yaffe K, Petersen RC, Lindquist K, Kramer J, Miller B. Subtype of mild cognitive impairment and progression to dementia and death. Dement Geriatr Cogn Disord. 2006; 22(4):312–319. [PubMed: 16940725]
26. Bondi MW, Jak AJ, Delano-Wood L, et al. Neuropsychological Contributions to the Early Identification of Alzheimer's Disease. Neuropsychol Rev. 2008; 18(1):73–90. [PubMed: 18347989]
27. Schwartz BS, Glass TA, Bolla KI, et al. Disparities in cognitive functioning by race/ethnicity in the Baltimore Memory Study. Environ Health Perspect. 2004; 112(3):314–320. [PubMed: 14998746]
28. Tombaugh TN. Trail Making Test A and B: normative data stratified by age and education. Arch Clin Neuropsychol. 2004; 19(2):203–214. [PubMed: 15010086]
29. Koedam ELGE, Lauffer V, van der Vlies AE, et al. Early-versus late-onset Alzheimer's disease: more than age alone. J Alzheimers Dis. 2010; 19(4):1401–1408. [PubMed: 20061618]
30. Geroldi C, Pihlajamaki M, Laakso MP, et al. APOE-epsilon4 is associated with less frontal and more medial temporal lobe atrophy in AD. Neurology. 1999; 53(8):1825–1832. [PubMed: 10563634]
31. Wolk DA, Dickerson BC. Apolipoprotein E (APOE) genotype has dissociable effects on memory and attentional-executive network function in Alzheimer's disease. Proc Natl Acad Sci US A. 2010; 107(22):10256–10261.
32. Pievani M, Rasser PE, Galluzzi S, et al. Mapping the effect of APOE epsilon4 on gray matter loss in Alzheimer's disease in vivo. Neuroimage. 2009; 45(4):1090–1098. [PubMed: 19349226]
33. Reitz C, Patel B, Tang M-X, et al. Relation between vascular risk factors and neuropsychological test performance among elderly persons with Alzheimer's disease. J Neurol Sci. 2007; 257(1–2): 194–201. [PubMed: 17328914]

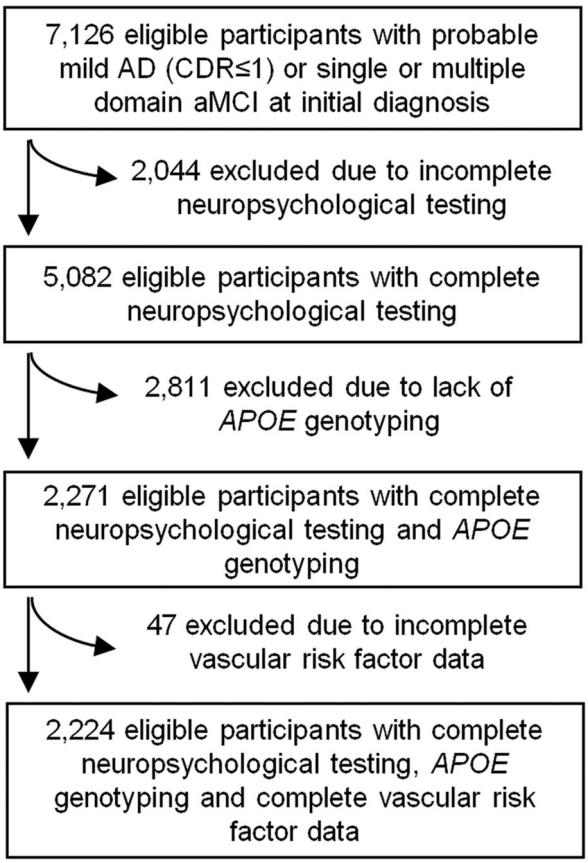

Figure 1.
Flow chart for participant inclusion

Table 1

Demographic, genetic and vascular characteristics of the participants

	MCI			AD		
	dysexecutive subgroup	**amnestic subgroup**	**neither subgroup**	**dysexecutive subgroup**	**amnestic subgroup**	**neither subgroup**
Females (%)	151 (51.4)	145 (51.2)	315 (51.6)	156 (53.2)	143 (53.8)	253 (53.0)
mean age (SD)	78.5 (8.9)	73.3 (9.7)	75.6 (9.7)	76.1(9.1)	75.1 (7.9)	77.2 (8.2)
whites (%)	209 (71.1)	257 (90.8)	503 (82.3)	242 (82.6)	240 (90.2)	410 (86.0)
African Americans (%)	55 (18.7)	18 (6.4)	73 (11.9)	26 (8.9)	16 (6.0)	31 (6.5)
mean years of education (SD)	13.5 (3.5)	15.8 (2.9)	15.2 (3.1)	14.0 (3.5)	15.2 (2.8)	14.5 (3.2)
APOEε4 carriers (%)	116 (39.5)	165 (58.3)	281 (46.0)	159 (54.3)	174 (65.4)	268 (56.2)
APOEε4 homozygotes (%)	15 (5.1)	37 (13.1)	51 (8.3)	27 (9.2)	46 (17.3)	62 (13.0)
hypertension (%)	173 (58.8)	147 (51.9)	319 (52.2)	163 (55.6)	146 (54.9)	230 (48.2)
hyperlipidemia (%)	159 (54.1)	156 (55.1)	329 (53.8)	178 (60.8)	146 (54.9)	251 (52.6)
diabetes (%)	42 (14.3)	29 (10.2)	77 (12.6)	34 (11.6)	24 (9.0)	47 (9.9)
stroke (%)	26 (8.8)	10 (3.5)	33 (5.4)	12 (4.1)	10 (3.8)	16 (3.4)
myocardial infarction (%)	26 (8.8)	16 (5.7)	43 (7.0)	28 (9.6)	20 (7.5)	27 (5.7)
total	294	283	611	293	266	477

Table 2

Frequency and percentage of pathologic diagnoses among the dysexecutive, amnestic or neither subtypes stratified by diagnosis into MCI and dementia at initial diagnosis

Pathologic diagnosis	MCI			dementia		
	dysexecutive subgroup	amnestic subgroup	neither subgroup	dysexecutive subgroup	amnestic subgroup	neither subgroup
Normal (%)	2 (9)	1 (9)	0	0	1 (7)	0
AD (%)	13 (59)	6 (55)	17 (61)	21 (81)	9 (60)	31 (82)
Lewy Body disease (%)	1 (5)	0	1 (4)	2 (8)	1 (7)	4 (11)
Vascular dementia (%)	4 (18)	2 (18)	4 (14)	0	0	0
Frontotemporal lobar degeneration (%)	0	0	1 (4)	1 (4)	1 (7)	0
Hippocampal sclerosis (%)	1 (5)	0	0	2 (8)	3 (20)	1 (3)
Prion disease (%)	0	0	0	0	0	0
Other (%)	1 (5)	2 (18)	5 (18)	0	0	2 (5)
total	22	11	28	26	15	38

There was no association between phenotype and AD pathologic diagnosis in MCI (p=.94) or mild AD (p=.21).

Table 3

Demographic regression models stratified by diagnosis

	Model	diagnosis	beta	p
age[1]	unadjusted	MCI	5.18	<.001
		mild AD	0.99	.17
	controlling for years of education, African American ethnicity, *APOEε4* carrier status, global cognition & vascular risk factors	MCI	4.42	<.001
		mild AD	−2.23	.02
education[2]	unadjusted	MCI	−2.23	<.001
		mild AD	−1.29	<.001
	controlling for age, African American ethnicity, *APOEε4* carrier status, global cognition & vascular risk factors	MCI	−0.75	.02
		mild AD	−0.27	.46

	model	diagnosis	OR	p
African American[3]	unadjusted	MCI	3.39	<.001
		mild AD	1.52	.20
	controlling for age, education, *APOEε4* carrier status, global cognition & vascular risk factors	MCI	2.68	.007
		mild AD	0.40	.06

[1] Linear regression model showing age at first evaluation in the dysexecutive phenotype relative to the amnestic phenotype

[2] Linear regression model showing years of education in the dysexecutive phenotype relative to the amnestic phenotype

[3] Logistic regression model showing likelihood of being African American in the dysexecutive phenotype relative to the amnestic phenotype

Vascular risk factors include history of myocardial infarction, type 2 diabetes, hypertension, hyperlipidemia, and stroke

Table 4a

Genetic regression models stratified by diagnosis

	Model	diagnosis	OR	p
APOEε4	unadjusted	MCI	0.52	<.001
		mild AD	0.66	.001
		combined	0.59	<.001
	additive model controlling for demographics, global cognition & vascular risk factors	MCI	0.65	.01
		mild AD	0.65	.03
		combined	0.58	<.001

Logistic regression models showing likelihood of possessing an *APOEε4* allele in the dysexecutive phenotype relative to the amnestic phenotype, under an additive genetic model

Demographics include age, education and African American ethnicity

Vascular risk factors include history of myocardial infarction, type 2 diabetes, hypertension, hyperlipidemia, and stroke

Table 4b

Genetic regression models stratified by ethnicity

	model	ethnicity	OR	p
APOEε4	unadjusted	white	0.65	<.001
		African Americans	0.40	.76
	additive model controlling for age, years of education, global cognition & vascular risk factors	white	0.60	<.001
		African Americans	0.63	.29

Logistic regression models showing likelihood of possessing an *APOEε4* allele in the dysexecutive phenotype relative to the amnestic phenotype, under an additive genetic model, stratified by ethnicity

Vascular risk factors include history of myocardial infarction, type 2 diabetes, hypertension, hyperlipidemia, and stroke

Table 5

Vascular risk factor regression models

	model	OR	p
hypertension[1]	unadjusted	1.17	.19
	controlling for *APOEε4* carrier status, global cognition and demographics	0.73	.04
hyperlipidemia[2]	unadjusted	1.10	.42
	controlling for *APOEε4* carrier status, global cognition and demographics	1.11	.51
diabetes[3]	unadjusted	1.39	.08
	controlling for *APOEε4* carrier status, global cognition and demographics	1.10	.69
stroke[4]	unadjusted	1.83	.03
	controlling for *APOEε4* carrier status, global cognition and demographics	1.06	.88
MI[5]	unadjusted	1.44	.10
	controlling for *APOEε4* carrier status, global cognition and demographics	1.02	.95

	model	beta	p
vascular risk score[6]	unadjusted	0.15	.01
	controlling for *APOEε4* carrier status, global cognition & demographics	−0.03	.65

[1] Logistic regression model showing likelihood of having history of hypertension in the dysexecutive phenotype relative to the amnestic phenotype

[2] Logistic regression model showing likelihood of having history of hyperlipidemia in the dysexecutive phenotype relative to the amnestic phenotype

[3] Logistic regression model showing likelihood of having history of type 2 diabetes in the dysexecutive phenotype relative to the amnestic phenotype

[4] Logistic regression model showing likelihood of having history of stroke in the dysexecutive phenotype relative to the amnestic phenotype

[5] Logistic regression model showing likelihood of having history of myocardial infarction (MI) in the dysexecutive phenotype relative to the amnestic phenotype

[6] Linear regression model showing vascular risk score in the dysexecutive phenotype relative to the amnestic phenotype

Demographics include age, education and African American ethnicity