Different Demographic, Genetic, and Longitudinal Traits in Language versus Memory Alzheimer's Subgroups

Jesse Mez[a,b,c,d,*], **Stephanie Cosentino**[a,b,c], **Adam M. Brickman**[a,b,c], **Edward D. Huey**[a,b,c,f], and **Richard Mayeux**[a,b,c,e,f]

[a]Gertrude H. Sergievsky Center, College of Physicians and Surgeons, Columbia University, New York, NY, USA

[b]Taub Institute for Research on Alzheimer's Disease and the Aging Brain, College of Physicians and Surgeons, Columbia University, New York, NY, USA

[c]Department of Neurology, College of Physicians and Surgeons, Columbia University, New York, NY, USA

[d]Department of Biostatistics, Joseph P. Mailman School of Public Health, Columbia University, New York, NY, USA

[e]Department of Epidemiology, Joseph P. Mailman School of Public Health, Columbia University, New York, NY, USA

[f]Department of Psychiatry, College of Physicians and Surgeons, Columbia University, New York, NY, USA

Abstract

The study's objective was to compare demographics, *APOE* genotypes, and rate of rise over time in functional impairment in neuropsychologically defined language, typical, and memory subgroups of clinical Alzheimer's disease (AD). 1,368 participants from the National Alzheimer's Coordinating Center database with a diagnosis of probable AD (CDR 0.5–1.0) were included. A language subgroup (*n* = 229) was defined as having language performance >1 SD worse than memory performance. A memory subgroup (*n* = 213) was defined as having memory performance >1 SD worse than language performance. A typical subgroup (*n* = 926) was defined as having a difference in language and memory performance of <1 SD. Compared with the memory subgroup, the language subgroup was 3.7 years older and more frequently self-identified as African American (OR = 3.69). Under a dominant genetic model, the language subgroup had smaller odds of carrying at least one *APOEε4* allele relative to the memory subgroup. While this difference was present for all ages, it was more striking at a younger age (OR = 0.19 for youngest tertile; OR = 0.52 for oldest tertile). Compared with the memory subgroup, the language subgroup rose 35% faster on the Functional Assessment Questionnaire and 44% faster on CDR sum of boxes over time. Among a subset of participants who underwent autopsy (*n* = 98), the language, memory, and typical subgroups were equally likely to have an AD pathologic diagnosis, suggesting that variation in non-AD pathologies across subtypes did not lead to the observed differences. The study demonstrates that a language subgroup of AD has different demographics, genetic profile, and disease course in addition to cognitive phenotype.

*Correspondence to: Jesse Mez, Gertrude H. Sergievsky Center, College of Physicians and Surgeons, Columbia University, 630 West 168th Street, New York, NY 10032, USA. Tel.: +1 212 305 8621; Fax: +1 212 305 2526; jbm2154@columbia.edu.

INTRODUCTION

The histological pathology of Alzheimer's disease (AD) is found across a wide clinical spectrum [1]. In this paper, 'clinical' AD refers to the clinical presentation of patients with AD histological pathology. While episodic memory loss is a classic early symptom of clinical AD [2], many patients also have early deficits in other cognitive domains such as language, executive function, or visuo-spatial function. As a result, the presentation of clinical AD can be quite heterogeneous [3]. The spectrum of early presentations ranges from isolated focal syndromes (including primary progressive aphasia, posterior cortical atrophy, a dysexecutive syndrome, or a pure amnestic syndrome [1, 4]) to a mixed syndrome with deficits in multiple cognitive domains [5]. Pathologic studies suggest that the heterogeneity in clinical presentation might be related to the relative anatomic distribution of tau pathology in the brain [6, 7].

It is well established that patients can meet clinical criteria for AD but demonstrate language dysfunction that is disproportionate to their memory dysfunction. Researchers have identified clinical AD patients during life whose major clinical characteristic is language dysfunction, who go on to have pathological AD at autopsy, but with prominent pathology in the cortical language networks [8, 9]. An extreme example is patients with primary progressive aphasia (PPA) with underlying AD pathology, a phenomenon that occurs in ~30–50% of PPA cases [10, 11]. PPA patients with underlying AD pathology have asymmetric atrophy of the language dominant hemisphere [10]. In one study of patients with pathologically proven AD, PPA patients had a larger ratio of neurofibrillary tangles in language-related neocortical areas relative to entorhinal cortex as compared with patients with an amnestic presentation [7].

While these findings are informative, there has been no large study of a language subgroup compared with a memory subgroup in AD. The majority of studies examining the heterogeneity of clinical presentations of AD have evaluated isolated focal syndromes. However, these syndromes account for the minority of cases as most clinical AD patients have a mixed syndrome with deficits in multiple cognitive domains [5]. Consequently, these studies tend to have small sample sizes and limited generalizability. By examining clinical AD patients with disproportionate language to memory deficits, while allowing for memory deficits to be present, one can study larger sample sizes and perhaps draw conclusions about AD patients with predominant language deficits that cannot be gleaned studying PPA. Here we take this approach to examine demographics, *APOE* status, and rise in functional impairment in clinical AD patients with predominant language dysfunction compared with clinical AD patients with predominant memory dysfunction.

METHODS

The National Alzheimer's Coordinating Center (NACC) developed and maintains a large relational database of standardized clinical research data collected from the 34 NIA-funded Alzheimer's Disease Centers (ADCs) nationwide. The study was approved by an institutional review board at each institution. The study is a secondary analysis of data collected between 2005 and 2011. Recruitment, participant evaluation, and diagnostic criteria for dementia and probable AD are detailed elsewhere [12]. Participants were

followed at approximately 12 month intervals with similar evaluations and reassessment of the diagnosis at each timepoint. Participants were either prevalent cases (i.e., were given an AD diagnosis at initial visit) or incident cases (i.e., were given an AD diagnosis at a follow-up visit). For incident cases, visits prior to the AD diagnosis were not included in this analysis and future mention of 'baseline' visit refers to the initial visit at which an AD diagnosis was made. Stratification by incident/prevalent status yielded similar effect sizes and thus incident and prevalent cases were combined in the analysis. Because we were interested in the early presentation of AD, we restricted our sample to participants who met criteria for probable mild AD (CDR 0.5 or 1) at baseline visit.

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 future references to African Americans and whites imply non-Hispanic African Americans and non-Hispanic whites. Achieved years of education were ascertained by self-report.

Participants were administered the ADCs' Uniform Data Set (UDS) neuropsychological battery at each visit. 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) [13].

Functional status was assessed at each evaluation using the Functional Assessment Questionnaire (FAQ) by a research clinician based on informant interview. On the FAQ, functional status is divided into 10 different categories. For each category, a score of 0–3 corresponds to "normal," "has difficulty, but does by self," "requires assistance," or "dependent," respectively. A total functional score was calculated by summing the category scores. A higher score indicates more functional impairment [14]. Functional status was also assessed at each evaluation using the Clinical Dementia Rating (CDR) [15]. While every participant was assigned a global CDR at each visit, CDR sum of boxes was only recorded for a subset of participant visits.

APOE genotype was determined for a subset of participants and classified as having no *APOEε4* alleles, one *APOEε4* allele, or two *APOEε4* alleles.

1,368 (30%) of the 4,491 eligible participants were included in this study. Inclusion criteria are illustrated in the flow chart in Fig. 1. Participants were excluded from the full sample analysis if they lacked *APOE* genotyping or had incomplete neuropsychological data at the baseline visit. Compared with included participants, excluded participants had greater odds of being female (OR = 1.17, $p < 0.02$) and African American (OR = 2.01, $p < 0.001$), were 0.7 years younger ($p = 0.02$), and had 0.6 fewer years of education ($p < 0.001$).

Of the 1,368 eligible participants, 98 (7%) underwent autopsy (termed the autopsy subset in Fig. 1). Compared with the non-autopsy subset, the autopsy subset had lower odds of being African American (OR = 0.12, $p = 0.01$) and female (OR = 0.50, $p = 0.001$), was 3.4 years older ($p < 0.001$), and had 0.9 more years of education ($p = 0.01$). Each autopsy participant was given a primary pathologic diagnosis.

Of the 1,368 eligible participants, 954 (70%) also had complete FAQ data at baseline and at least 1 follow-up visit (termed the FAQ longitudinal subset in Fig. 1). For these participants, the mean number of visits was 3.1 (1.0 SD) and the mean length of time in the study was 2.3 years (1.1 SD). Compared with the non-FAQ longitudinal subset, the FAQ longitudinal subset had lower odds of being female (OR = 0.65, $p < 0.001$), had 0.5 more years of

education ($p = 0.009$), and was 0.5 years younger. They did not differ in odds of being African American, mean number of visits, or mean length of time in the study.

Of the 1,368 eligible participants, 547 (40%) had complete CDR sum of boxes at baseline and at least 1 follow-up visit (termed the CDR longitudinal subset in Fig. 1). For these participants, the mean number of visits was 3.1 (1.0 SD) and the mean length of time in the study was 2.3 years (1.1 SD). Compared with the non-CDR longitudinal subset, the CDR longitudinal subset had lower odds of being female (OR = 0.68, $p < 0.001$), had 0.5 more years of education ($p = 0.002$), and was 2.4 years younger ($p < 0.001$). They did not differ in odds of being African American, mean number of visits, or mean length of time in the study.

A recent factor analysis of the UDS cognitive battery in the NACC dataset identified four neuropsychological factors: executive, memory, language, and attention [16]. 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. In our current study, participants were classified into one of three subgroups: language, typical, or memory. Classification was carried out as follows: Among included participants, a mean and SD were calculated for each test in the UDS. These values were used to calculate Z scores on each test for each participant. Composite scores for each factor were calculated for each participant by averaging the z-scores on the tests that make up the factor. Participants were considered members of the language subgroup if their composite language score was 1 SD below their composite memory score. Participants were considered members of the memory subgroup if their composite memory score was 1 SD below their composite language score. Participants were considered members of the typical subgroup if their composite memory and language scores differed by <1 SD. We chose to call this subgroup 'typical' because the majority of cases fell into this phenotypic subgroup, reflecting the fact that AD patients generally present with both memory and language deficits [3].

Statistical analyses

Among the pathologic subset, a Fisher's exact test was used to compare the odds of an AD pathologic diagnosis in the language, typical, and memory subgroups.

In the full sample, a one-way ANOVA was used to compare mean age at baseline, years of education, and Mini-Mental State Exam (MMSE) at baseline in the language, typical and memory subgroups. An independent samples *t*-test was used for *post-hoc* pairwise analysis. A Pearson Chi Squared test was used to compare gender, race, and *APOEε4* status in the language, typical and memory subgroups, both across all three groups and pairwise. For all pairwise comparisons, Bonferroni corrected statistical significance was reached at $\alpha = 0.017$. Variables achieving significant results were included in regression models to determine the extent to which differences across subgroups remained after adjusting for variables hypothesized to contribute to the variance in the outcome variable. A dominant genetic model was used for *APOEε4* analysis because it demonstrated the largest OR compared with an additive or recessive model [17]. To account for the multiple models tested, Bonferroni corrected statistical significance was reached at $\alpha = 0.017$.

Generalized estimating equations (GEE) [18] were used to model the relationship over time of each subgroup with two outcome variables: total FAQ score and CDR sum of boxes. GEE take into account multiple visits per subject and that characteristics of the same individual are likely correlated over time. The repeated measures for each subject are treated as a cluster. Predictor variables included: time (years from baseline), subgroup (language, memory, or typical), and the time × subgroup interaction. The following time stationary covariates were also included in the model: age at first evaluation, education, African

American race, and *APOE* genotype. We tested whether the outcome variables at baseline and the rate of change over time of the outcome variables differed in the language and typical subgroups as compared with the memory subgroup. All statistical analyses were carried out using SPSS [19].

RESULTS

Among the 1,368 participants, 229 met criteria for the language subgroup, 213 met criteria for the memory subgroup, and 926 met criteria for the typical subgroup. Participant demographic, clinical, and genetic characteristics are given in Table 1.

The mean composite language score was 0.818 ± 0.483, -0.063 ± 0.680, and -0.506 ± 0.891 for the memory, typical, and language subgroups, respectively. The mean composite memory score was -0.578 ± 0.392, -0.155 ± 0.649 and 1.165 ± 1.181 for the memory, typical, and language subgroups, respectively.

Comparing demographic characteristics in the full sample

Gender did not differ between the memory, typical, and language subgroups in the bivariate analysis. There were statistically significant differences between the subgroups in mean age at first visit, African American race, and mean years of education in the bivariate analyses. Therefore, multivariable regression analyses were used to model the relationship of these variables with subgroup type adjusting for covariates. Members of the language subgroup were on average 3.71 years older and were 3.69 times more likely to identify as African American than members of the memory subgroup after adjusting for covariates. Members of the typical subgroup were on average 2.07 years older and were 1.99 times more likely to identify as African American than members of the memory subgroup after adjusting for covariates. Mean years of education did not differ in the subgroups after adjusting for covariates (Tables 1 and 2).

Comparing APOEε4 status in the full sample

The odds of having at least one *APOEε4* allele differed between the memory, typical, and language subgroups in the bivariate analysis. Therefore, multivariable logistic regression was used to model the relationship of *APOEε4* with subgroup adjusting for covariates. An age by genotype interaction term was included in the model because a previous study indicated that the effect of *APOEε4* on memory and language function was more pronounced in early-onset AD compared with late-onset AD [20]. There was sufficient evidence to suggest that age was an effect modifier for genotype both for the language subgroup relative to the memory subgroup ($p = 0.01$) and for the typical subgroup relative to the memory subgroup ($p = 0.05$). To evaluate this interaction, we stratified the analysis by age tertiles. After adjusting for covariates, the OR for being an *APOEε4* carrier in the language subgroup relative to the memory subgroup was 0.19 for the youngest tertile (age <74.1) compared with 0.52 for the oldest tertile (age >80.7). After adjusting for covariates, the OR for being an *APOEε4* carrier in the typical subgroup relative to the memory subgroup was 0.37 for the youngest tertile compared with 0.77 for the oldest tertile (Tables 1 and 3).

Comparing MMSE at baseline in the full sample

There were statistically significant differences between the memory, typical, and language subgroups in baseline MMSE in the bivariate analyses. Therefore, multivariable linear regression was used to model the relationship of MMSE with subgroup type adjusting for covariates. Compared with the memory subgroup, the language subgroup scored 0.7 points higher on the MMSE at baseline after adjusting for covariates ($p = 0.02$). Compared with the

typical subgroup, the language subgroup scored 1.1 points lower on the MMSE at baseline after adjusting for covariates ($p < 0.001$). The typical subgroup did not differ from the memory subgroup at baseline after adjusting for covariates ($p = 0.10$). Covariates in this model included age, gender, African American race, years of education, and *APOEε4* carrier status.

Comparing baseline function and rate of change in function over time in the FAQ longitudinal subset

In the GEE model with outcome variable total FAQ score, typical and language subgroup effects were not significant indicating that compared with the memory subgroup, the typical subgroup and the memory subgroup did not differ in total FAQ score at baseline after adjusting for covariates. As expected, there was a significant time effect indicating that total FAQ score for the memory subgroup increased over time after adjusting for covariates. There was a significant interaction effect between time and the language subgroup indicating that compared with the memory subgroup, the language subgroup demonstrated a faster rise in total FAQ score. The language subgroup rose 35% faster than the memory subgroup. The rate of rise for the typical subgroup fell between that of the memory and language subgroups, but did not significantly differ from either of them (Table 4A and Fig. 2A).

Comparing baseline function and rate of change in function over time in the CDR longitudinal subset

When the above analysis was repeated using outcome variable CDR sum of boxes, the subgroups behaved similarly. There were no significant differences at baseline between the subgroups. Compared with the memory subgroup, the language subgroup rose 44% faster. While the standardized effect size was actually larger than the standardized effect size for total FAQ score, the difference was not statistically significant ($p = 0.10$) possibly due to the fewer number of participants with CDR sum of boxes data. The rate of rise for the typical subgroup fell between that of the memory and language subgroups, but did not significantly differ from either of them (Table 4B and Fig. 2B).

Comparing pathologic diagnosis

Among the 98 autopsy cases, 17 met criteria for the language subgroup, 12 met criteria for the memory subgroup, and 69 met criteria for the typical subgroup. The subgroups did not differ in odds of having a pathologic diagnosis of AD (Table 5).

DISCUSSION

While episodic memory deficits are a classic early symptom of clinical AD, the cognitive presentation can be quite heterogeneous. In this study, we compared demographics, *APOE* status, and functional decline in language, typical, and memory subgroups of clinical AD. We restricted our analysis to participants with initially mild AD (CDR 0.5 or 1) because identification of cognitive subgroups can be challenging later in the disease course.

The memory subgroup accounted for about 1/6 of the study sample. While this might seem surprising because most patients with clinical AD have memory deficits, in fact many patients also have language dysfunction [3]. For this reason, a relative measure of language to memory function was used in this study. The memory subgroup does not represent "typical" AD, but rather a relatively focal presentation used to create a clear distinction from the language subgroup. Rather, the intermediate subgroup, that we term "typical," with relatively equivalent language and memory dysfunction, has the most common presentation, accounting for two-thirds of the study sample. While this subgroup is typical with respect to

memory and language, we acknowledge that it might include focal presentations like posterior cortical atrophy or a dysexecutive syndrome that are not considered typical clinical presentations of AD, but that lack a relative difference in memory and language function.

Even though all study participants had a clinical diagnosis of Probable AD, we investigated the possibility that the language subgroup might have disproportionate non-AD pathology (most likely frontotemporal lobar degeneration (FTLD)). However, in the subset of study participants who underwent autopsy, there was no difference in odds of AD pathology across the memory, typical, and language subgroups. Further, out of 98 autopsy cases, there were only 3 cases of FTLD, none of which was a member of the language subgroup. Interestingly, the language subgroup had a surprisingly large number of pathologic Lewy body cases (5 cases, 29%). On closer inspection, these 5 cases also had AD pathology contributing, although Lewy body disease was the primary pathologic diagnosis. These findings suggest that variation in non-AD pathologies across subtypes did not lead to the observed demographic, genetic, and longitudinal differences.

Multiple studies have suggested that early onset AD patients more commonly have an atypical presentation compared with late onset AD patients [21, 22]. The reverse—that atypical presentations tend to occur at a younger age—has been less studied, but may not be uniformly true. We and others have shown that a dysexecutive subgroup of AD presented at a younger age than a memory subgroup [23, 24]. However, Alladi et al. found no difference in age between typical and atypical presentations of pathologically proven AD [1]. Moreover, in the current study, the language subgroup was on average 3.7 years older than the memory subgroup and 1.6 years older than the typical subgroup after adjusting for covariates. Taken together, these studies suggest that distinct atypical clinical presentations of AD may present at different ages, some older and some younger than typical AD. Therefore, making generalizations about the age of onset of atypical clinical presentations of AD might not be informative.

While multiple studies have investigated the neuropsychological profiles of African Americans with AD, atypical clinical presentations in African Americans have hardly been studied. Our current finding, that African Americans have greater odds of presenting with a language presentation, is certainly interesting, but should be viewed with reasonable skepticism. In crude analyses in the literature, African Americans with AD demonstrated lower scores on tests of language compared with whites [25, 26]. However, these findings were significantly attenuated when the analysis was adjusted for literacy levels [27]. Replication studies that include literacy levels as a covariate would be worthwhile.

Two PPA studies have investigated whether *APOEε4* status impacts clinical presentation of patients with pathological AD. Rogalski et al. found that PPA patients have a lower frequency of the *APOEε4* allele compared with Probable AD patients. However, most of these patients did not have a pathological diagnosis. Given that at least 50% of PPA patients have non-AD pathology [10, 11], interpretation of this finding is limited in this context. In 31 PPA patients that did have a pathological diagnosis, *APOEε4* frequency did not differ between those with and without underlying AD pathology [28]. Gefen et al. found that *APOEε4* frequency did not differ when five PPA patients with underlying AD pathology were compared with normal controls [7]. Our study of only participants with Probable AD takes a different approach to investigate whether *APOEε4* impacts language function in AD. After adjusting for covariates, under a dominant genetic model, members of the language subgroup had lower odds of having at least one *APOEε4* allele relative to the memory subgroup. This finding further supports data indicating that *APOE* impacts the clinical presentation of AD. Indeed, multiple studies have shown that clinical AD patients who are

carriers of the *APOEε4* allele have more impairment in memory and less impairment in naming, mental speed, and executive function than non-carriers [20, 23, 24, 29–32].

Interestingly, we also found an *APOEε4*–age interaction. After adjusting for covariates, the OR for being an *APOEε4* carrier in the language subgroup relative to the memory subgroup for age <74.1 (youngest tertile) was nearly a third the OR for age >80.7 (oldest tertile). Similarly, the OR for being an *APOEε4* carrier in the typical subgroup relative to the memory subgroup for age <74.1 (youngest tertile) was less than half the OR for age >80.7 (oldest tertile). These findings are consistent with previous studies showing that the effect of *APOEε4* on memory and language function was more pronounced in early-onset AD compared with late-onset AD [20, 30].

After controlling for covariates, the language subgroup was less cognitively impaired on the MMSE at baseline compared with the memory subgroup, though with a small effect size (0.7 MMSE points). While this might suggest that the memory subgroup was later in their disease course, this is unlikely the case. When we compared a global cognition composite score based on all UDS neuropsychological tests, the language subgroup was no longer less impaired than the memory subgroup (data not shown). Further, there was no baseline difference between the subgroups on CDR sum of boxes or on the FAQ after controlling for covariates. More likely, the difference between the language and memory subgroups on the MMSE at baseline is due to intrinsic properties of the MMSE. Specifically, the MMSE language items are less sensitive for early dementia and have lower correlation with performance on neuropsychological testing compared with the MMSE memory item [33].

After controlling for covariates, compared with the memory subgroup, the language subgroup demonstrated a faster rise in functional impairment on both the FAQ and the CDR. On average, members of the language subgroup would take about 5 years to undergo a similar amount of cognitive decline as members of the memory subgroup would undergo in 7 years. The rate of rise for the typical subgroup fell between that of the memory and language subgroups. If the slope for the typical subgroup represents the typical rate of functional decline in AD, then our data suggests that an atypical memory variant will have slower than typical decline while an atypical language variant will have faster than typical decline. An analysis of rate of functional decline in a language subgroup of AD has not been performed previously. Age, *APOEε4* status, race, and years of education have all been implicated in the rate of decline in AD [34–38]. Differences in rate of decline between the language and memory subgroups persisted despite including these covariates, suggesting that these two groups differ not only in the cognitive phenotype, but in aspects of disease course as well.

A possible weakness of the study was that participant demographics and clinical criteria may have lacked uniformity given the heterogeneity of the 34 ADCs contributing to the NACC database. However, the heterogeneity allows for greater generalizability to other populations. Another possible weakness is the lack of non-verbal memory tests in the UDS. Deficits on verbal memory tests could result from language deficits. Our use of a relative measure of language to memory deficits, at least in part, addresses this issue.

This study illustrates that demographic, genetic, and longitudinal characteristics of a language subgroup of AD differ from a memory subgroup. We suspect that *APOE* as well as other unknown genetic and environmental factors impact the anatomic distribution of AD pathology, which in turn influences the neuropsychological presentation. These factors may also affect age-of-onset and disease course. Future studies should investigate additional non-*APOE* mediated susceptibility factors that contribute to language dysfunction in AD. 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.

Acknowledgments

References

1. Alladi S, Xuereb J, Bak T, Nestor P, Knibb J, Patterson K, Hodges JR. Focal cortical presentations of Alzheimer's disease. Brain. 2007; 130:2636–2645. [PubMed: 17898010]

2. Dubois B, Feldman HH, Jacova C, Dekosky ST, Barberger-Gateau P, Cummings J, Delacourte A, Galasko D, Gauthier S, Jicha G, Meguro K, O'Brien J, Pasquier F, Robert P, Rossor M, Salloway S, Stern Y, Visser PJ, Scheltens P. Research criteria for the diagnosis of Alzheimer's disease: Revising the NINCDS-ADRDA criteria. Lancet Neurol. 2007; 6:734–746. [PubMed: 17616482]

3. Bondi MW, Jak AJ, Delano-Wood L, Jacobson MW, Delis DC, Salmon DP. Neuropsychological contributions to the early identification of Alzheimer's disease. Neuropsychol Rev. 2008; 18:73–90. [PubMed: 18347989]

4. Binetti G, Magni E, Padovani A, Cappa SF, Bianchetti A, Trabucchi M. Executive dysfunction in early Alzheimer's disease. J Neurol Neurosurg Psychiatr. 1996; 60:91–93. [PubMed: 8558161]

5. Stopford CL, Snowden JS, Thompson JC, Neary D. Variability in cognitive presentation of Alzheimer's disease. Cortex. 2008; 44:185–195. [PubMed: 18387548]

6. Murray ME, Graff-Radford NR, Ross OA, Petersen RC, Duara R, Dickson DW. Neuropathologically defined subtypes of Alzheimer's disease with distinct clinical characteristics: A retrospective study. Lancet Neurol. 2011; 10:785–796. [PubMed: 21802369]

7. Gefen T, Gasho K, Rademaker A, Lalehzari M, Weintraub S, Rogalski E, Wieneke C, Bigio E, Geula C, Mesulam M-M. Clinically concordant variations of Alzheimer pathology in aphasic versus amnestic dementia. Brain. 2012; 135:1554–1565. [PubMed: 22522938]

8. Croot K, Hodges JR, Xuereb J, Patterson K. Phonological and articulatory impairment in Alzheimer's disease: A case series. Brain Lang. 2000; 75:277–309. [PubMed: 11049669]

9. Price BH, Gurvit H, Weintraub S, Geula C, Leimkuhler E, Mesulam M. Neuropsychological patterns and language deficits in 20 consecutive cases of autopsy-confirmed Alzheimer's disease. Arch Neurol. 1993; 50:931–937. [PubMed: 8363447]

10. Mesulam M, Wicklund A, Johnson N, Rogalski E, Léger GC, Rademaker A, Weintraub S, Bigio EH. Alzheimer and frontotemporal pathology in subsets of primary progressive aphasia. Ann Neurol. 2008; 63:709–719. [PubMed: 18412267]

11. Knibb JA, Xuereb JH, Patterson K, Hodges JR. Clinical and pathological characterization of progressive aphasia. Ann Neurol. 2006; 59:156–165. [PubMed: 16374817]

12. Morris JC, Weintraub S, Chui HC, Cummings J, Decarli C, Ferris S, Foster NL, Galasko D, Graff-Radford N, Peskind ER, Beekly D, Ramos EM, Kukull WA. The Uniform Data Set (UDS): Clinical and cognitive variables and descriptive data from Alzheimer Disease Centers. Alzheimer Dis Assoc Disord. 2006; 20:210–216. [PubMed: 17132964]

13. Weintraub S, Salmon D, Mercaldo N, Ferris S, Graff-Radford NR, Chui H, Cummings J, DeCarli C, Foster NL, Galasko D, Peskind E, Dietrich W, Beekly DL, Kukull WA, Morris JC. The Alzheimer's Disease Centers' Uniform Data Set (UDS): The neuropsychologic test battery. Alzheimer Dis Assoc Disord. 2009; 23:91–101. [PubMed: 19474567]

14. Pfeffer RI, Kurosaki TT, Harrah CH Jr, Chance JM, Filos S. Measurement of functional activities in older adults in the community. J Gerontol. 1982; 37:323–329. [PubMed: 7069156]

15. Morris JC. The Clinical Dementia Rating (CDR): Current version and scoring rules. Neurology. 1993; 43:2412–2414. [PubMed: 8232972]

16. Hayden KM, Jones RN, Zimmer C, Plassman BL, Browndyke JN, Pieper C, Warren LH, Welsh-Bohmer KA. 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; 25:128–137. [PubMed: 21606904]

17. Lewis CM. Genetic association studies: Design, analysis and interpretation. Brief Bioinformatics. 2002; 3:146–153. [PubMed: 12139434]

18. Zeger SL, Liang KY, Albert PS. Models for longitudinal data: A generalized estimating equation approach. Biometrics. 1988; 44:1049–1060. [PubMed: 3233245]

19. SPSS for Windows. SPSS Inc; Chicago: 2010.

20. Marra C, Bizzarro A, Daniele A, De Luca L, Ferraccioli M, Valenza A, Brahe C, Tiziano FD, Gainotti G, Masullo C. Apolipoprotein E epsilon4 allele differently affects the patterns of neuropsychological presentation in early-and late-onset Alzheimer's disease patients. Dement Geriatr Cogn Disord. 2004; 18:125–131. [PubMed: 15211066]

21. Koss E, Edland S, Fillenbaum G, Mohs R, Clark C, Galasko D, Morris JC. Clinical and neuropsychological differences between patients with earlier and later onset of Alzheimer's disease: A CERAD analysis, Part XII. Neurology. 1996; 46:136–141. [PubMed: 8559362]

22. Koedam ELGE, Lauffer V, van der Vlies AE, van der Flier WM, Scheltens P, Pijnenburg YAL. Early-versus late-onset Alzheimer's disease: More than age alone. J Alzheimers Dis. 2010; 19:1401–1408. [PubMed: 20061618]

23. Snowden JS, Stopford CL, Julien CL, Thompson JC, Davidson Y, Gibbons L, Pritchard A, Lendon CL, Richardson AM, Varma A, Neary D, Mann D. Cognitive phenotypes in Alzheimer's disease and genetic risk. Cortex. 2007; 43:835–845. [PubMed: 17941342]

24. Mez J, Cosentino S, Brickman AM, Huey ED, Manly JJ, Mayeux R. Dysexecutive versus amnestic Alzheimer disease subgroups. Alzheimer Dis Assoc Disord. 201210.1097/WAD. 0b013e31826a94bd

25. Fillenbaum GG, Huber M, Taussig IM. Performance of elderly White and African American community residents on the abbreviated CERAD Boston Naming Test. J Clin Exp Neuropsychol. 1997; 19:204–210. [PubMed: 9240480]

26. Welsh KA, Fillenbaum G, Wilkinson W, Heyman A, Mohs RC, Stern Y, Harrell L, Edland SD, Beekly D. Neuropsychological test performance in African-American and white patients with Alzheimer's disease. Neurology. 1995; 45:2207–2211. [PubMed: 8848195]

27. Chin AL, Negash S, Xie S, Arnold SE, Hamilton R. Quality, and not just quantity, of education accounts for differences in psychometric performance between african americans and white non-hispanics with Alzheimer's disease. J Int Neuropsychol Soc. 2012; 18:277–285. [PubMed: 22300593]

28. Rogalski EJ, Rademaker A, Harrison TM, Helenowski I, Johnson N, Bigio E, Mishra M, Weintraub S, Mesulam M-M. ApoE E4 is a susceptibility factor in amnestic but not aphasic dementias. Alzheimer Dis Assoc Disord. 2011; 25:159–163. [PubMed: 21346518]

29. Lehtovirta M, Soininen H, Helisalmi S, Mannermaa A, Helkala EL, Hartikainen P, Hänninen T, Ryynänen M, Riekkinen PJ. Clinical and neuropsychological characteristics in familial and sporadic Alzheimer's disease: Relation to apolipoprotein E polymorphism. Neurology. 1996; 46:413–419. [PubMed: 8614504]

30. Van der Vlies AE, Pijnenburg YAL, Koene T, Klein M, Kok A, Scheltens P, van der Flier WM. Cognitive impairment in Alzheimer's disease is modified by APOE genotype. Dement Geriatr Cogn Disord. 2007; 24:98–103. [PubMed: 17596691]

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 U S A. 2010; 107:10256–10261. [PubMed: 20479234]

32. 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; 82:45–51. [PubMed: 20562467]

33. Feher EP, Mahurin RK, Doody RS, Cooke N, Sims J, Pirozzolo FJ. Establishing the limits of the Mini-Mental State. Examination of "subtests. Arch Neurol. 1992; 49:87–92. [PubMed: 1728269]

34. Cosentino S, Scarmeas N, Helzner E, Glymour MM, Brandt J, Albert M, Blacker D, Stern Y. APOE epsilon 4 allele predicts faster cognitive decline in mild Alzheimer disease. Neurology. 2008; 70:1842–1849. [PubMed: 18401023]

35. Scarmeas N, Albert SM, Manly JJ, Stern Y. Education and rates of cognitive decline in incident Alzheimer's disease. J Neurol Neurosurg Psychiatr. 2006; 77:308–316. [PubMed: 16484637]

36. Sachs-Ericsson N, Blazer DG. Racial differences in cognitive decline in a sample of community-dwelling older adults: The mediating role of education and literacy. Am J Geriatr Psychiatry. 2005; 13:968–975. [PubMed: 16286440]

37. Barnes LL, Wilson RS, Li Y, Aggarwal NT, Gilley DW, McCann JJ, Evans DA. Racial differences in the progression of cognitive decline in Alzheimer disease. Am J Geriatr Psychiatry. 2005; 13:959–967. [PubMed: 16286439]

38. Jacobs D, Sano M, Marder K, Bell K, Bylsma F, Lafleche G, Albert M, Brandt J, Stern Y. Age at onset of Alzheimer's disease: Relation to pattern of cognitive dysfunction and rate of decline. Neurology. 1994; 44:1215–1220. [PubMed: 8035918]
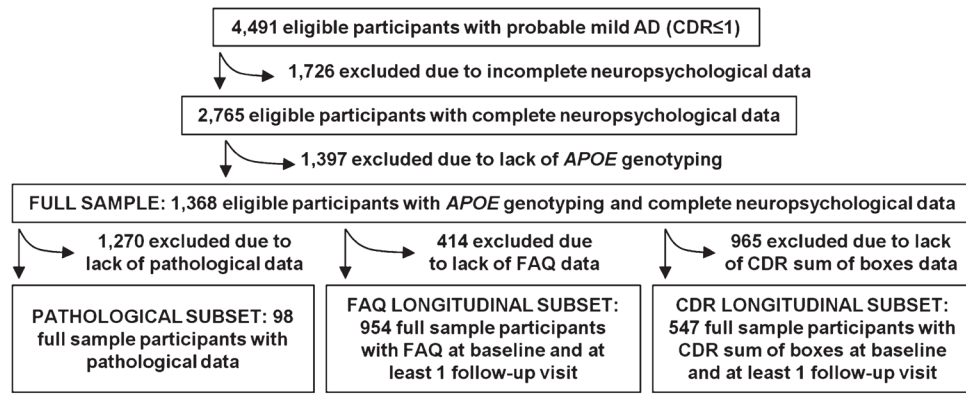
Fig. 1.
Flow chart for participant inclusion.
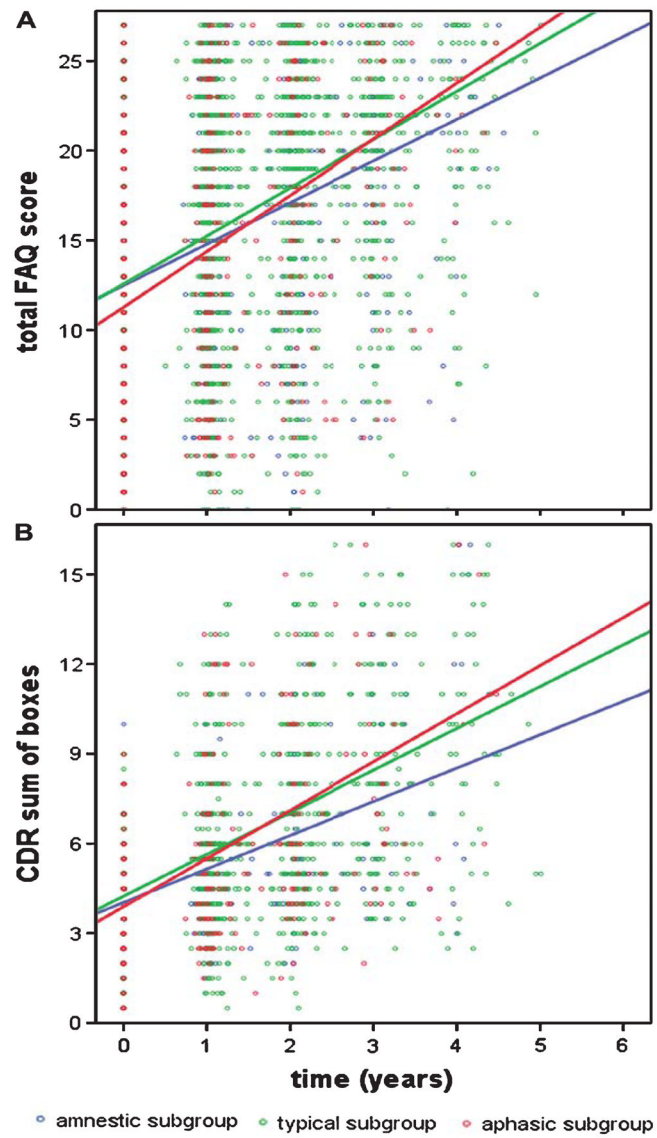
Fig. 2.
Rise in total FAQ score (A) and CDR sum of boxes (B) over time in years in the language, typical and memory subgroups.

Table 1

Demographic and clinical characteristics of the subgroups

	Memory subgoup (n = 213)	Typical subgroup (n = 926)	Language subgroup (n = 229)	p-values			
				Overall[1]	Memory vs. typical[2,3]	Language vs. typical[2,3]	Memory vs. language[2,3]
Females (%)	121 (56.8)	490 (52.9)	109 (47.6)	0.15	0.30	0.15	0.05
Mean age at baseline (SD)	74.2 (8.4)	76.9 (8.5)	78.5 (7.9)	<0.001	<0.001	0.01	<0.001
Whites (%)	189 (88.7)	798 (86.2)	193 (84.3)	0.39	0.32	0.46	0.17
African Americans (%)	8 (3.8)	67 (7.2)	23 (10.0)	0.04	0.07	0.16	0.01
Mean years of education (SD)	14.8 (2.9)	14.6 (3.3)	15.2 (3.2)	0.05	0.36	0.02	0.23
$APOE\varepsilon4$ carriers (%)	159 (74.6)	539 (58.2)	102 (44.5)	<0.001	<0.001	<0.001	<0.001
Folstein MMSE at baseline (SD)	24.0 (2.8)	23.5 (3.2)	24.6 (3.4)	<0.001	0.02	<0.001	0.04
Total FAQ at baseline (SD)	12.5 (6.9)	12.3 (7.0)	11.1 (7.5)	0.05	0.64	0.03	0.04
CDR sum of boxes at baseline (SD)[4]	4.1 (1.7)	4.3 (1.9)	4.1 (2.1)	0.41	0.33	0.28	0.93

[1] For continuous variables (age, education, MMSE, FAQ CDR sum of boxes), overall comparisons used 1-way ANOVA. For categorical variables (females, African Americans, whites, $APOE\varepsilon4$ carriers), overall comparisons used Pearson's Chi squared test.

[2] For continuous variables, pairwise comparisons used independent sample t-tests. For categorical variables, pairwise comparisons used Pearson's Chi squared test.

[3] For pairwise comparisons, after Bonferroni correction for multiple comparisons, significance was achieved at $\alpha = 0.017$.

[4] CDR sum of boxes was available for a reduced number of participants (memory: 127; typical: 541; language: 141).

Table 2

Regression models for demographics

A[1]

Outcome	Covariates	Predictor	b	*p*
Mean age at baseline	Gender, years of education, African American race, *APOEε4* carrier status, MMSE	Typical subgroup	2.07	0.001
		Language subgroup	3.71	<0.001

B[2]

			OR	*p*
African American	Age, gender, years of education, *APOEε4* carrier status, MMSE	Typical subgroup	1.99	0.08
		language subgroup	3.69	0.003

C[3]

			b	*p*
Mean years of education	Age, gender, African American race, *APOEε4* carrier status, MMSE	Typical subgroup	−0.08	0.73
		Language subgroup	0.26	0.37

[1] Linear regression model: $b_{typical}$ is the difference in mean age at baseline of the typical subgroup compared with the memory subgroup after adjusting for covariates. $b_{language}$ is the difference in mean age at baseline of the language subgroup compared with the memory subgroup after adjusting for covariates.

[2] Logistic regression model: $OR_{typical}$ is the odds members of the typical subgroup identify as African American relative to the odds members of the memory subgroup identify as African American after adjusting for covariates. $OR_{language}$ is the odds members of the language subgroup identify as African American relative to the odds members of the memory subgroup identify as African American after adjusting for covariates.

[3] Linear regression model: $b_{typical}$ is the difference in mean years of education of the typical subgroup compared with the memory subgroup adjusting for covariates. $b_{language}$ is the difference in mean years of education of the language subgroup compared with the memory subgroup adjusting for covariates.

Table 3

Regression model for *APOEε4*

Outcome	Covariates	Predictor	Age tertile	OR	p
Language subgroup	Gender, years of education, African American race, MMSE	*APOEε4*	1st tertile (age: <74.1)	0.19	<0.001
			2nd tertile (age: 74.1–80.7)	0.36	0.007
			3rd tertile (age: >80.7)	0.52	0.08
Typical subgroup	Gender, years of education, African American race, MMSE	*APOEε4*	1st tertile (age: <74.1)	0.37	0.001
			2nd tertile (age: 74.1–80.7)	0.57	0.07
			3rd tertile (age: >80.7)	0.77	0.42

Multinomial logistic regression model stratified by age tertile: OR|language is the odds members of the language subgroup relative to the memory subgroup are carriers of at least one *APOEε4* allele adjusting for covariates. OR|typical is the odds members of the typical subgroup relative to the memory subgroup are carriers of at least one *APOEε4* allele adjusting for covariates.

Table 4

GEE models for Functional Assessment Questionnaire (FAQ) and Clinical Dementia Rating (CDR) sum of boxes.

Effect	b	*p*
A) Total FAQ score[1]		
Time	2.31	<0.001
Typical subgroup	0.09	0.89
Language subgroup	−1.21	0.14
Time × typical subgroup	0.37	0.16
Time × language subgroup	0.81	0.02
B) CDR sum of boxes[2]		
Time	1.12	<0.001
Typical subgroup	0.21	0.32
Language subgroup	−0.14	0.66
Time × typical subgroup	0.28	0.20
Time × language subgroup	0.49	0.10

[1] b_{time} is the rate of change in total FAQ score (points/year) for the memory subgroup. $b_{typical}$ is the difference in total FAQ score in the typical subgroup compared with the memory subgroup at base-line (time = 0). $b_{language}$ is the difference in total FAQ score in the language subgroup compared with the memory subgroup at baseline (time = 0). $b_{time \times typical}$ is the difference in rate of change in total FAQ score in the typical subgroup compared with the memory subgroup. $b_{time \times language}$ is the difference in rate of change in total FAQ score in the language subgroup compared with the memory subgroup. The following covariates are adjusted for in the model: age at first visit, years of education, *APOEε4* status and African American race.

[2] b_{time} is the rate of change in CDR sum of boxes (points/year) for the memory subgroup. $b_{typical}$ is the difference in CDR sum of boxes in the typical subgroup compared with the memory subgroup at base-line (time = 0). $b_{language}$ is the difference in CDR sum of boxes in the language subgroup compared with the memory subgroup at baseline (time = 0). $b_{time \times typical}$ is the difference in rate of change in CDR sum of boxes in the typical subgroup compared with the memory subgroup. $b_{time \times language}$ is the difference in rate of change in CDR sum of boxes in the language subgroup compared with the memory subgroup. The following covariates are adjusted for in the model: age at first visit, years of education, *APOEε4* status and African American race.

Table 5

Primary pathologic diagnoses within each subgroup for the pathologic subset

Pathologic diagnosis	Memory subgroup (*n* = 12)	Neither subgroup (*n* = 69)	Language subgroup (*n* = 17)
Normal (%)	1 (8)	1 (1)	1 (6)
AD (%)	8 (67)	53 (77)	11 (65)
Lewy body disease (%)	0	3 (4)	5 (29)
Vascular dementia (%)	0	2 (3)	0
Frontotemporal lobar degeneration (%)	1 (8)	2 (3)	0
Hippocampal sclerosis (%)	0	6 (9)	0
Prion disease (%)	0	0	0
Other (%)	2 (17)	2 (3)	0

The odds of a pathologic diagnosis of AD did not differ in the 3 subgroups (*p* = 0.48) using Fisher's exact test.