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Alzheimer's & Dementia 10 (2014) 84–92

Alzheimer's & Dementia

The neuropsychology of normal aging and preclinical Alzheimer's disease

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Abstract

Objective: A National Institute on Aging–sponsored work group on preclinical Alzheimer's disease (AD) articulated the need to characterize cognitive differences between normal aging and preclinical AD.

Methods: Seventy-one apolipoprotein E (*APOE*) ε4 homozygotes, 194 ε3/ε4 heterozygotes, and 356 ε4 noncarriers age 21 to 87 years who were cognitively healthy underwent neuropsychological testing every 2 years. Longitudinal trajectories of test scores were compared between *APOE* subgroups.

Results: There was a significant effect of age on all cognitive domains in both *APOE* ε4 carriers and noncarriers. A significant effect of *APOE* ε4 gene dose was confined to the memory domain and the Dementia Rating Scale. Cross-sectional comparisons did not discriminate the groups.

Conclusions: Although cognitive aging patterns are similar in *APOE* ε4 carriers and noncarriers, preclinical AD is characterized by a significant ε4 gene dose effect that impacts memory and is detectable longitudinally. Preclinical neuropsychological testing strategies should emphasize memory-sensitive measures and longitudinal design.

Keywords: Preclinical Alzheimer's disease; Cognitive aging; Age-related memory loss; Mild cognitive impairment; Apolipoprotein E; Longitudinal testing

1. Introduction

Interest in preclinical Alzheimer's disease (AD) is driven by the need for earlier therapeutic intervention. The National Institute on Aging–Alzheimer's Association (NIA-AA) work group on diagnostic guidelines for the preclinical stages of AD drew a distinction between the pathophysiological disease process (AD-P) that begins before symptoms are evident and the clinical manifestations (AD-C) of mild cognitive impairment (MCI) and dementia [1] that ultimately ensue. In previous work, we showed that apolipoprotein E (*APOE*) ε4 carriers, a powerful genetic risk factor for AD [2], experienced accelerating memory decline that correlated with ε4 gene dose, and preceded MCI by more than a decade [3], identical to the preclinical stage envisioned

Richard J. Caselli, Co-principal Investigator, designed the study, analyzed neuropsychological data, and wrote the main draft of the manuscript. Dona E. C. Locke collected neuropsychology data, provided groundwork for using the paired self- and informant questionnaires, and contributed critical revisions to the manuscript. Amylou C. Dueck, Biostatistician, performed all statistical analyses, contributed statistical sections to the manuscript, and provided critical revisions. David Knopman, Associate Editor of *Neurology*, provided critical revisions to the manuscript and content expertise. Bryan K. Woodruff and Charlene Hoffman-Snyder helped collect and analyze data, and provided critical revisions to the manuscript. Rosa Rademakers performed genetic testing for apolipoprotein E, and provided genetic data and critical revisions to the manuscript. Adam S. Fleisher contributed critical revisions to the manuscript. Eric M. Reiman, Principal Investigator, contributed critical revisions to the manuscript.

Bryan K. Woodruff receives research funding support from Genetech.

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http://dx.doi.org/10.1016/j.jalz.2013.01.004

by the NIA-AA work group. Howieson and colleagues [4] showed that 3 to 4 years before the diagnosis of MCI, decline accelerates further in memory as well as in some executive and spatial measures. The preclinical stage of AD is characterized by the progressive accumulation of cerebral amyloid [5,6], which amyloid–positron emission tomographic studies have shown is maximal, not in medial temporal regions, but in prefrontal and posterior cingulate regions [7–12]. In a subsequent study, we compared performances on neuropsychological measures of executive function (that are known to depend on the normal function of the prefrontal cortices) in *APOE* ε4 carriers who are expected to have an elevated prefrontal amyloid burden with noncarriers (NCs), but despite the wealth of evidence that executive measures are sensitive to aging [13–15], we found the differences between *APOE* ε4 carriers and NCs surprisingly limited, in contrast to the more robust memory differences [16] presumably mediated by medial temporal tau-based pathology in ε4 carriers [17].

At what point should AD-C be defined? The work group felt that MCI was the appropriate starting point, a stage that would follow their proposed preclinical AD stage 3, but the cognitive profile distinguishing this stage from normal aging was felt to require further clarification. More specifically, the work group hypothesized that patients may have objective "decline from their own baseline," especially on challenging episodic memory measures, and possibly subjective impairment or some combination of objective and subjective changes [1]. Building on our previous work, we therefore sought to characterize more comprehensively the longitudinal changes in neuropsychological performance that may distinguish normal from pathological (AD-P) cognitive aging in *APOE* ε4 carriers (who are at higher risk for both AD-P and AD-C) and ε4 NCs.

2. Methods

2.1. Study participants and enrollment

Since January 1, 1994, cognitively normal residents of Maricopa County age 21 years and older were recruited through local media advertisements into a longitudinal study of cognitive aging (the Arizona *APOE* Cohort) requiring *APOE* genotyping [16]. Demographic, family, and medical history data were obtained, and identity was coded by a study assistant. All individuals gave their written, informed consent to participate in the study, which was approved by the institutional review boards of all participating institutions. The participants agreed to have the results of the *APOE* test withheld from them as a precondition to their participation in this study. Genetic determination of *APOE* allelic status was performed using a polymerase chain reaction-based assay.

The recruitment strategy for the Arizona *APOE* Cohort involved recruiting all identified ε4 homozygotes (HMZs), matching them by age, gender, and education with one heterozygote (HTZ; all with the ε3/ε4 genotype), and two NCs. We identified many more HTZs and NCs than HMZs—especially those persons older than 70 years, reflecting the greater number of HMZs developing MCI and AD by this age—who were also eligible for enrollment so that the final match paradigm involved matching two ε4 carriers to two NCs, with priority given to HMZs.

Each potential participant had screening tests to confirm their neuropsychiatrically normal state, which included a neurological examination, the Folstein Mini-Mental State Examination [18], the Hamilton Depression Rating Scale [19], the Functional Activities Questionnaire, the Instrumental Activities of Daily Living, and the Structured Psychiatric Interview from the *Diagnostic and Statistical Manual for Mental Disorders*, 3rd edition, revised [20]. There were no potentially confounding medical (e.g., end organ failure), neurological (e.g., stroke), or psychiatric problems (e.g., psychotic disorder). None met the published criteria for MCI [21], AD [22], other forms of dementia, or major depressive disorder [20] at entry or during subsequent follow-up. (To ensure ours was a true preclinical cohort and that the data would not be skewed by a few potentially impaired individuals, individuals developing MCI during follow-up were identified either because they had sought medical attention for cognitive impairment that was then evaluated by the patient's physician with results reviewed by R.J.C., or else were identified on the basis of their study results.) Entry criteria for all participants included a score of at least 27 points on the Mini-Mental State Examination (and a score of at least 1 point out of 3 points on the recall subtest), a score of 10 points or less on the Hamilton Depression Rating Scale at the time of their first visit, and no indication of loss of function according to the Functional Activities Questionnaire and Instrumental Activities of Daily Living. The resulting study population was identical to that previously reported [16]. Those fulfilling these requirements were administered an extensive standardized battery of neuropsychological tests, repeated every 1 to 2 years.

2.2. Neuropsychological testing

The neuropsychological tests within our battery are detailed elsewhere [18] and encompass four broadly defined cognitive domains [19]. The scores used are as follows:

Memory

- Auditory Verbal Learning Test Total Learning and Long-Term Memory scores
- Buschke Free and Cued Selective Reminding Test, total free (SRT-free) and cued (SRT-cued) recall scores
- Rey-Osterrieth Complex Figure Test Absolute Recall (CFT-recall) and Percent Recall (CFT-%) scores
- Benton Visual Retention Test, total number correct