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Featured Article

Cognitive subtypes of probable Alzheimer's disease robustly identified in four cohorts

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Abstract

Introduction: Patients with Alzheimer's disease (AD) show heterogeneity in profile of cognitive impairment. We aimed to identify cognitive subtypes in four large AD cohorts using a data-driven clustering approach.

Methods: We included probable AD dementia patients from the Amsterdam Dementia Cohort ($n = 496$), Alzheimer's Disease Neuroimaging Initiative ($n = 376$), German Dementia Competence Network ($n = 521$), and University of California, San Francisco ($n = 589$). Neuropsychological data were clustered using nonnegative matrix factorization. We explored clinical and neurobiological characteristics of identified clusters.

Results: In each cohort, a two-clusters solution best fitted the data (cophenetic correlation >0.9): one cluster was memory-impaired and the other relatively memory spared. Pooled analyses showed that the memory-spared clusters (29%–52% of patients) were younger, more often APOE e4 negative, and had more severe posterior atrophy compared with the memory-impaired clusters (all $P < .05$).

Conclusions: We could identify two robust cognitive clusters in four independent large cohorts with distinct clinical characteristics.

Keywords: Alzheimer's disease; Cognition; Heterogeneity; Subtypes; Atypical; Neuropsychology

[1]Data used in preparation of this article were obtained from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database (adni.loni.usc.edu). As such, the investigators within the ADNI contributed to the design and implementation of ADNI and/or provided data but did not participate in analysis or writing of this report. A complete listing of ADNI investigators can be found at http://adni.loni.usc.edu/wp-content/uploads/how_to_apply/ADNI_Acknowledgement_List.pdf.

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1. Introduction

Alzheimer's disease (AD) dementia is characterized by progressive cognitive impairment in multiple cognitive domains, for example, memory, language, visuospatial and executive functioning, and attention. Typically, AD is characterized by early and prominent memory loss [1]. A minority of patients has a prominent and relatively focal cognitive presentation, such as logopenic-variant primary progressive aphasia, posterior cortical atrophy, or a behavioral/dysexecutive subtype [2–5]. Atypical variants have been associated with specific demographic, genetic, and neuroimaging/biomarker findings that are distinct from those of typical amnestic patients (e.g., age at onset, apolipoprotein E [APOE] genotype, distribution of cortical atrophy, hypometabolism, tau deposition, cerebrospinal fluid (CSF) biomarker concentrations, and pathologic findings) [6–10]. However, even patients who do not display a defined subtype also show a considerable variation in patterns of cognitive impairment. Earlier studies demonstrated the potential to capture cognitive heterogeneity in AD using a data-driven clustering approach [11–14]. Studies differed in sample size, clinical diagnosis of included patients, available neuropsychological (NP) test results, available neurobiological characteristics to compare clusters with, and clustering technique. This has resulted in different numbers of clusters, with different cognitive and neurobiological characteristics. Although those studies were clearly suggestive of variability in underlying pathologic mechanisms, it is difficult to generalize the findings, because they result from single studies that show considerable variability in patient population and methodological approaches.

In the present study, we aimed to identify cognitive subtypes and to study whether these subtypes could be replicated in three independent AD dementia cohorts. For the identification of cognitive AD subtypes, we used nonnegative matrix factorization (NMF) [15–18]. On the basis of the earlier descriptions of cognitive heterogeneity, we expected NMF to identify at least a cluster including patients with typical amnestic AD and one or more other clusters including patients with nonamnestic features [15–18].

2. Methods

2.1. Patients

We selected AD patients from four large cohorts: the Amsterdam Dementia Cohort (ADC), the Alzheimer's Disease Neuroimaging Initiative (ADNI), the German Dementia Competence Network (DCN), and the University of California, San Francisco Memory and Aging Center research cohort (UCSF). Patients were selected based on (1) clinical diagnosis of probable AD dementia, (2) availability of NP test results, and (3) Mini–Mental State Examination (MMSE) score >16/30 [19]. In the ADC and UCSF cohort, patients with focal presentations logopenic-variant primary progressive aphasia, posterior cortical atrophy, and the behavioral/dysexecutive subtype of probable AD dementia were included, whereas such subjects were explicitly excluded from participation in the ADNI and DCN studies.

From the ADC we selected 496 patients with probable AD [20]. Patients visited the outpatient memory clinic of the VU University Alzheimer Center between 2008 and 2013. Standard dementia screening included for most patients medical history and medication use, physical and neurologic examination, extensive NP evaluation, screening laboratory tests, APOE genotyping, magnetic resonance imaging (MRI), and lumbar puncture (LP). In the ADC, level of education was defined according to a rating scale ranging from 1 (low, primary school not finished) to 7 (high, university degree) [21]. All participants provided written informed consent to use their clinical data for research purposes. The local ethical committee approved the study.

From the ADNI database (adni.loni.usc.edu) we selected 376 probable AD patients. Patients were recruited from more than 50 sites across the US and Canada (www.adni-info.org). Standard workup included medical history, physical and neurologic examination, extensive NP evaluation, screening laboratory tests, APOE genotyping, neuroimaging including MRI, and LP. For the present study, we used data of screening and baseline visits acquired for ADNI-1 or ADNI-2 between 2005 and 2013. All patients gave written informed consent at screening.

From the DCN cohort database (http://www.kompetenznetz-demenzen.de) we selected 521 probable AD patients [22]. The DCN is a collaboration of 14 specialized German memory clinics from university hospitals. All patients were offered a uniform dementia screening at first visit between 2003 and 2007, including medical history, physical and neurologic examination, extensive NP evaluation, screening laboratory tests, MRI scan, and LP. The DCN study protocol was approved by the institutional review boards of all participating study centers [22]. All patients, or their legal guardians, provided written informed consent.

From the UCSF research cohort we selected 589 probable AD patients [23]. Patients were either seen in the outpatient memory clinic or for a research assessment in the UCSF Alzheimer's Disease Research Center. All patients were assessed at first visit between 1998 and 2013. Standardized dementia screening included medical history, physical and neurologic examination, NP evaluation, screening laboratory tests, APOE genotyping, and neuroimaging including MRI. A core screening NP battery was performed in both the clinical and research settings. All patient and informants provided written informed consent. Surrogate consent was accepted when patients lacked capacity to provide consent themselves. The local medical ethical committee approved the study.

2.2. NP tests

NP data included tests covering the major cognitive domains in each cohort, but the exact composition of NP test batteries differed across cohorts. NP tests included for analysis in this study are shown in Supplementary