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Trajectories of Alzheimer disease-related cognitive measures in a longitudinal sample

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Abstract

Background: The delineation of the relative temporal trajectories of specific cognitive measures associated with Alzheimer's disease (AD) is important for evaluating preclinical markers and monitoring disease progression.

Methods: We characterized the temporal trajectories of measures of verbal episodic memory, short-term visual memory, and mental status using data from 895 participants in the Baltimore Longitudinal Study of Aging.

Results: The California Verbal Learning Test (CVLT) immediate recall was the first measure to decline, followed by CVLT delayed recall. However, further along the disease progression scale, CVLT delayed recall and visual memory changed more rapidly than CVLT immediate recall.

Conclusions: Our findings reconcile reports of early changes in immediate recall with greater reliance on delayed recall performance in clinical settings. Moreover, the utility of cognitive markers in evaluating AD progression depends on the stage of cognitive decline, suggesting that optimal endpoints in therapeutic trials may vary across different stages of the disease process.

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Keywords: Disease progression score; California verbal learning test; Alzheimer's disease; Memory

1. Introduction

Examining the longitudinal progression of biomarkers implicated in Alzheimer's disease (AD) using data-driven methods is important for evaluating the early indicators of disease, monitoring disease progression at the individual level, and validating proposed disease progression models. A detailed study of longitudinal trajectories of functions affected earliest in AD is likely to benefit efforts in identifying measures sensitive to changes in the preclinical stage of disease, thus allowing for more appropriate selection of outcome measures in clinical trials.

Jedynak et al. recently proposed a method to investigate the temporal evolution of disease progression using selected cognitive and biological markers related to AD and applied this method to data from the Alzheimer's Disease Neuroimaging Initiative (ADNI) [1]. In addition to estimating the longitudinal trajectories that best describe the biomarker data for the entire sample, the method calculates an Alzheimer's Disease Progression Score (ADPS) for each participant based on the participant's own biomarker measurements.

Despite the versatility of the ADPS method in allowing for the characterization of the longitudinal changes in cognitive measures, the neuropsychological tests considered in the analysis performed on the ADNI data were limited to one test of verbal episodic memory (Rey Auditory Verbal Learning Test delayed recall) and two tests of overall mental status (Mini-Mental Status Examination and AD Assessment

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Scale-cognitive subscale), in addition to four anatomic and physiologic biomarkers. The analysis highlighted the Rey Auditory Verbal Learning Test delayed recall score as the earliest changing marker among the seven considered, indicating the importance of further analyzing the progression of measures of episodic memory in AD.

Episodic memory is involved in learning and retaining new pieces of information over a period of delay. Both cross-sectional and longitudinal studies show that episodic memory is the earliest and most severely affected cognitive domain in AD [2,3]. Although numerous studies have emphasized the importance of declines in learning with repeated trials (as reflected in a total learning score across immediate recall trials) and short and long delayed recall performance on tests of verbal episodic memory as early indicators of AD [4–9], there is no consensus as to whether immediate or delayed recall is affected earlier within the domain of verbal episodic memory. Furthermore, the temporal relationships among trajectories of measures of episodic memory have not been characterized in detail.

The purpose of our study was to define the relationships among longitudinal trajectories of early cognitive indicators of AD-related cognitive decline and to compare their rates of change over the course of cognitive impairment using the ADPS methodology proposed by Jedynak et al. To this end, we evaluated the AD-related measures of episodic memory performance, including immediate and delayed verbal episodic memory, short-term visual episodic memory, and indicators of mental status within the data-driven ADPS framework to construct a temporal model of cognitive performance in a group of older individuals from the Baltimore Longitudinal Study of Aging (BLSA). Our model provides information on the earliest cognitive changes and differences among indicators of episodic memory and other cognitive measures in rates of progression at different disease stages.

2. Methods

2.1. Participants

The analyses were based on data from 895 participants (mean age 70.1, standard deviation [SD] 8.4) enrolled in the BLSA with at least two longitudinal visits. Visits without Mini-Mental State Examination (MMSE) [10] scores were not considered. All available visits meeting these requirements were included in the analysis, including data acquired after the onset of cognitive impairment and AD. The cognitively impaired (CI, n = 149) group includes all subjects who had a cognitive deficit in at least one cognitive domain but were not affected in their social or functional abilities, e.g., participants with mild cognitive impairment (MCI) and those who subsequently met the *Diagnostic and Statistical Manual of Mental Disorders 3-R* criteria [11] for dementia and the National Institute of Neurological and Communicative Disorders and Stroke–Alzheimer's Disease and Related Disorders Association criteria [12] for AD based on neuropsychological diagnostic tests and clinical data. The number of subjects in the CI group who were cognitively normal (CN) at baseline but eventually developed MCI or AD is 93 and 12, respectively. The CI group additionally included 18 participants with MCI at baseline who developed AD, 20 participants with stable MCI and 6 with stable AD diagnoses throughout the visits considered in this study. The interval between baseline and onset of cognitive impairment for the CI subjects who started as CN was 6.45 ± 3.86 years. Sample characteristics are presented in Table 1.

2.2. Cognitive outcome measures

We studied cognitive markers that provide measures of episodic memory and mental status. We used the California

Table 1
Participant demographics and scores on cognitive tests at baseline, grouped by final cognitive status

Final cognitive status	CN, n = 746	CI, n = 149	Entire sample*, n = 895
Age at baseline, mean (SD), y	68.4 (7.7)	78.3 (7.1)	70.1 (8.4)
Education, mean (SD), y	16.4 (2.5)	16.4 (2.4)	16.4 (2.5)
Male, no. (%)	425 (57.0)	86 (57.7)	511 (57.1)
White, no. (%)	540 (72.4)	132 (88.6)	672 (75.1)
BMI, mean (SD)	27.1 (4.3)	25.7 (3.7)	26.8 (4.3)
Smoking status, no. (%)			
Never	311 (41.7)	60 (40.3)	371 (41.5)
Former	386 (51.7)	80 (53.7)	466 (52.1)
Current	28 (3.8)	7 (4.7)	35 (3.9)
Alcohol intake, no. (%)			
None	287 (38.5)	46 (30.9)	333 (37.2)
<1 drink per day	222 (29.8)	51 (34.2)	273 (30.5)
≥1 drink per day	217 (29.1)	50 (33.6)	267 (29.8)
Hypertension, no. (%)			
No	445 (59.6)	88 (59.1)	533 (59.6)
Yes	281 (37.7)	59 (39.6)	340 (38.0)
Diabetes, no. (%)			
No	672 (90.1)	141 (94.6)	813 (90.8)
Yes	54 (7.2)	6 (4.0)	60 (6.7)
Prior cardiovascular disease†, no. (%)			
No	689 (92.4)	139 (93.3)	828 (92.5)
Yes	37 (5.0)	8 (5.4)	45 (5.0)
Number of visits, mean (SD)	5.3 (3.2)	5.1 (2.9)	5.3 (3.2)
Interval between visits, mean (SD), y	1.89 (1.0)	1.74 (1.0)	1.87 (1.0)
Scores on cognitive tests at baseline, mean (SD)			
MMSE	28.7 (1.5)	27.7 (2.2)	28.5 (1.7)
BMS	1.3 (1.7)	2.1 (2.5)	1.4 (1.9)
CVLT immediate recall	52.5 (10.9)	43.3 (11.3)	51.0 (11.5)
CVLT short delayed free recall	10.4 (3.2)	7.7 (3.4)	10.0 (3.4)
CVLT long delayed free recall	11.0 (3.2)	8.4 (3.4)	10.6 (3.4)
BVRT error	5.4 (3.8)	8.8 (4.3)	6.0 (4.1)

Abbreviations: CN, cognitively normal; CI, cognitively impaired; SD, standard deviation; BMI, body mass index; MMSE, Mini-Mental State Examination; BMS, Blessed Information Memory Concentration Score; CVLT, California Verbal Learning Test; BVRT, Benton Visual Retention Test.

*Education information was missing for 4 participants, BMI for 29, and smoking status for 23. A total of 22 participants had missing values for alcohol intake, hypertension, diabetes, and prior cardiovascular disease.

†Defined as myocardial infarction or congestive heart failure.

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