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Short Reports

Serial position effects are sensitive predictors of conversion from MCI to Alzheimer's disease dementia

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Abstract

Background: It is unclear whether the predictive strength of established cognitive variables for progression to Alzheimer's disease (AD) dementia from mild cognitive impairment (MCI) varies depending on time to conversion. We investigated which cognitive variables were best predictors, and which of these variables remained predictive for patients with longer times to conversion.
Methods: Seventy-five participants with MCI were assessed on measures of learning, memory, language, and executive function. Relative predictive strengths of these measures were analyzed using Cox regression models.
Results: Measures of word-list position—namely, serial position scores—together with Short Delay Free Recall of word-list learning best predicted conversion to AD dementia. However, only serial position scores predicted those participants with longer time to conversion.
Conclusions: Results emphasize that the predictive strength of cognitive variables varies depending on time to conversion to dementia. Moreover, finer measures of learning captured by serial position scores were the most sensitive predictors of AD dementia.

Keywords: Alzheimer's disease; Mild cognitive impairment; Serial position effects; Dementia; Verbal episodic memory; Aging

1. Introduction

Studies show that several neuropsychological variables and biomarkers can predict progression from presymptomatic Alzheimer's disease (AD) or mild cognitive impairment (MCI) to AD dementia (e.g., [1]). Episodic memory measures are examples of reliably predictive measures (e.g., [2]) and are known to be associated with the functional integrity of mesiotemporal brain regions (e.g., [3]) typically affected in incipient AD [4]. In addition, nonmemory measures can also be predictive (e.g., [2]). These measures implicate greater pathology extending to additional temporal regions as well as frontal and parietal association cortices [4] and may be indicative of a longer duration of disease [5]. Therefore, when considering the predictive value of cognitive measures, it may be critical to consider time to conversion from presymptomatic or MCI stages to AD dementia.

The study aims were (*i*) to determine the relative strengths of different, established cognitive predictors in patients with MCI; and (*ii*) to compare the predictive power of these measures in a subsample of patients who converted to dementia after a relatively longer period.

2. Methods

2.1. Participants

Seventy-five patients with MCI from the Memory Clinic, University Center for Medicine of Aging, Basel, Switzerland, participated. Thirty-seven were members of a longitudinal observational study and the remaining 38 were clinic

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patients. All underwent comprehensive neuropsychological, geriatric, neurological, and structural neuroimaging assessments [6]. Diagnosis of MCI followed Winblad et al. [7]; operationalization and exclusion criteria are presented in the supplementary materials. This study was approved by the ethics committee.

2.2. Selection of cognitive predictors of conversion to AD dementia

A PubMed literature search yielded cognitive variables that had previously predicted progression to AD dementia either in presymptomatic persons or in patients with MCI (Supplementary Materials). Nine variables, which overlapped with our assessment, emerged from this search: California Verbal Learning Test (CVLT)–Encoding (cumulative trials 1–5) [2,8], the CVLT–Short Delay Free Recall (SDFR) (e.g., [5]), the CVLT–Long Delay Free Recall (LDFR) (e.g., [1]), the CVLT–Percent Savings from Trial 5 to LDFR (e.g., [9]), the CVLT–Standard Recency Score across trials 1 through 5 (e.g., [10]), the CVLT–Regional Primacy Score across trials 1 through 5 (e.g., [11]), the Rey Osterrieth Complex Figure–Delayed Recall (ROCF-DR) (e.g., [10]), the Trail Making Test–Part B (e.g., [2]), and Semantic Fluency (e.g., [5]). All variables were transformed into demographically adjusted z-scores [12].

2.3. Statistical analyses

2.3.1. Analysis 1: cognitive variables predicting time to conversion to AD dementia

To avoid multicollinearity in the regression analyses, Pearson product moment correlations were performed on the z-scores of all nine variables, and coefficients of $-0.5 > r > +0.5$, denoting a large effect size [13], were used as cutoff points for high-risk intercorrelations. Variables showing a high correlation strength were entered into separate regression analyses.

To assess the relationship of multiple predictors to a right-censored, time-to-event outcome, Cox regression analyses were conducted, with time to conversion to AD dementia as the dependent variable, and age, education, and gender as covariates. A stepwise backward method was applied and continued until the removal of a variable would have resulted in a decrease in the P value of the likelihood ratio test to less than 0.1. To examine the proportional hazards assumption, time-dependent covariates were calculated for each cognitive variable that survived the regression analyses.

2.3.2. Analysis 2: cognitive variables predicting longer time to conversion to AD dementia

To determine a subsample of patients who converted to dementia over a longer time period, we applied a data-driven method to define the time point for longer time to conversion using log-log survival curves of all the cognitive variables that survived regression analysis 1. In the resulting subsample, Cox regression analyses with backward elimination were rerun on the variables that had survived regression analysis 1, including the same covariates mentioned earlier.

3. Results

Of the sample, 68 participants (91%) met criteria for amnestic MCI (Table 1). Twenty-nine participants (39%) converted to probable AD by the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association criteria [14] (i.e., MCI converters). Demographic characteristics of MCI converters and MCI nonconverters differed significantly only by age.

3.1. Analysis 1

Four measures of verbal episodic memory (Encoding, SDFR, LDFR, and Savings) strongly intercorrelated, as did the two serial position variables. In addition, Encoding

Table 1
Demographic characteristics of MCI converters and MCI nonconverters (n = 75)

Characteristic	MCI converters (n = 29)	MCI nonconverters (n = 46)	Test$_{(df)}$*
Age ± SD, y	73.0 ± 7.6	66.3 ± 9.2	$t_{(68)} = -3.42^{\dagger}$
Gender, % men	44.8	56.5	$\chi^2_{(1)} = 0.98$
Education ± SD, y	13.2 ± 3.5	13.7 ± 3.1	$t_{(54)} = 0.54$
Mini-Mental State Examination ± SD, pt	28.5 ± 1.1	28.7 ± 1.0	$t_{(56)} = 0.94$
Amnestic MCI, nonamnestic MCI	28 (97%), 1 (3%)	40 (87%), 6 (13%)	$\chi^2_{(1)} = 1.94$
Single amnestic MCI, multiple amnestic MCI	12 (43%), 16 (57%)	17 (43%), 23 (57%)	$\chi^2_{(1)} = 0.00$
Time of follow-up ± SD, mo	23.5 ± 13.4	28.7 ± 17.8	$t_{(71)} = 1.45$
Time to conversion ± SD, mo	23.5 ± 13.4	NA	—

Abbreviations: MCI, mild cognitive impairment; SD, standard deviation; NA, not applicable.*t Tests of inhomogeneous variances were applied to test for group differences in age, education, Mini-Mental State Examination score, and time of follow-up.
$^{\dagger}P < .05$.