Alzheimer's & Dementia: Diagnosis, Assessment & Disease Monitoring 10 (2018) 161-171

Cognitive & Behavioral Assessment

Temporal unfolding of declining episodic memory on the Free and Cued Selective Reminding Test in the predementia phase of Alzheimer's disease: Implications for clinical trials

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Abstract

Introduction: Free and Cued Selective Reminding Test (FCSRT) performance identifies patients with preclinical disease at elevated risk for developing Alzheimer's dementia, predicting diagnosis better than other memory tests.

Methods: Based on literature mapping FCSRT performance to clinical outcomes and biological markers, and on longitudinal preclinical data from the Baltimore Longitudinal Study of Aging, we developed the Stages of Objective Memory Impairment (SOMI) model. Five sequential stages of episodic memory decline are defined by Free Recall (FR) and Total Recall (TR) score ranges and years prior to dementia diagnosis. We sought to replicate the SOMI model using longitudinal assessments of 142 Einstein Aging Study participants who developed AD over 10 years.

Results: Time to diagnosis was at least seven years if FR was intact, at least four years if TR was intact, and two years if TR was impaired, consistent with SOMI model predictions. The SOMI identified incipient dementia with excellent sensitivity and specificity.

Discussion: The SOMI model provides an efficient approach for clinical trial cognitive screening in advance of more costly biomarker studies and ultimately in clinical practice, and provides a vocabulary for understanding AD biomarker patterns and for re-analysis of existing clinical trial data.

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Keywords: Free and Cued Selective Reminding Test; Preclinical AD; Dementia; Episodic memory impairment; Amnestic mild cognitive impairment; Prodromal AD; Biomarkers; Clinical trials

1. Introduction

Episodic memory is not a unitary phenomenon; encoding, storage, and retrieval are distinct processes that affect recall. Impairment of episodic memory, which is the hallmark of Alzheimer's disease (AD), begins well before the clinical diagnosis of dementia. To assess episodic memory, the International Working Group [1,2] recommends using the Free and Cued Selective Reminding Test (FCSRT) which, unlike other memory tests, controls the learning conditions to ensure encoding and distinguish retrieval deficits from storage deficits [3,4]. The earliest signs of memory impairment are found in free recall (FR), which reflects impaired retrieval of stored memories, progressively worsening in the prodromal stage. Storage remains unimpaired until the late prodromal stage when retrieval fails despite effective cued recall.

1.1. The Free and Cued Selective Reminding Test

The test begins with a study phase in which items (e.g., grapes) are identified in response to unique semantic cues (e.g., fruit) that are used in the test phase to prompt recall

Dr. Grober receives a small percentage of any royalties on the FCSRT 1 IR when it is used for commercial purposes. No conflict of interest exists for Drs. Veroff and Lipton.

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https://doi.org/10.1016/j.dadm.2017.12.004
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of items not retrieved by FR. In contrast to passively listening, as items are presented in conventional word list learning tests, the study phase requires active cognitive engagement and deep semantic processing. By coordinating the conditions of encoding and retrieval with category cues, the FCSRT [3] and its modification that includes immediate recall (FCSRT+IR) [4] optimizes encoding specificity and maximizes recall. The sum of free and cued recall is called total recall (TR). Test details are presented in Supplementary Material A.

Our use of FCSRT performance to define the stages of objective memory impairment (SOMI) in predementia AD is based on it outperforming typical cognitive screening measures for identifying preclinical and clinical AD including the Mini Mental State Exam [5], Selective Reminding Test [6,7], the California Verbal Learning Test [8], and Logical Memory [9,10]; its effectiveness at detecting amnestic mild cognitive impairment (aMCI) and dementia [11], predicting future dementia and AD [5,9,12–15], distinguishing AD from non-AD dementias [16], as an outcome measure in ongoing clinical trials [17,18]; and on the strong association of FR and TR with AD biomarkers summarized in Supplementary Material B.

1.2. TR impairment

Impairment of TR on the FCSRT + IR defines the core clinical phenotype of prodromal AD, which consists of a recall deficit that does not normalize with cuing [1].

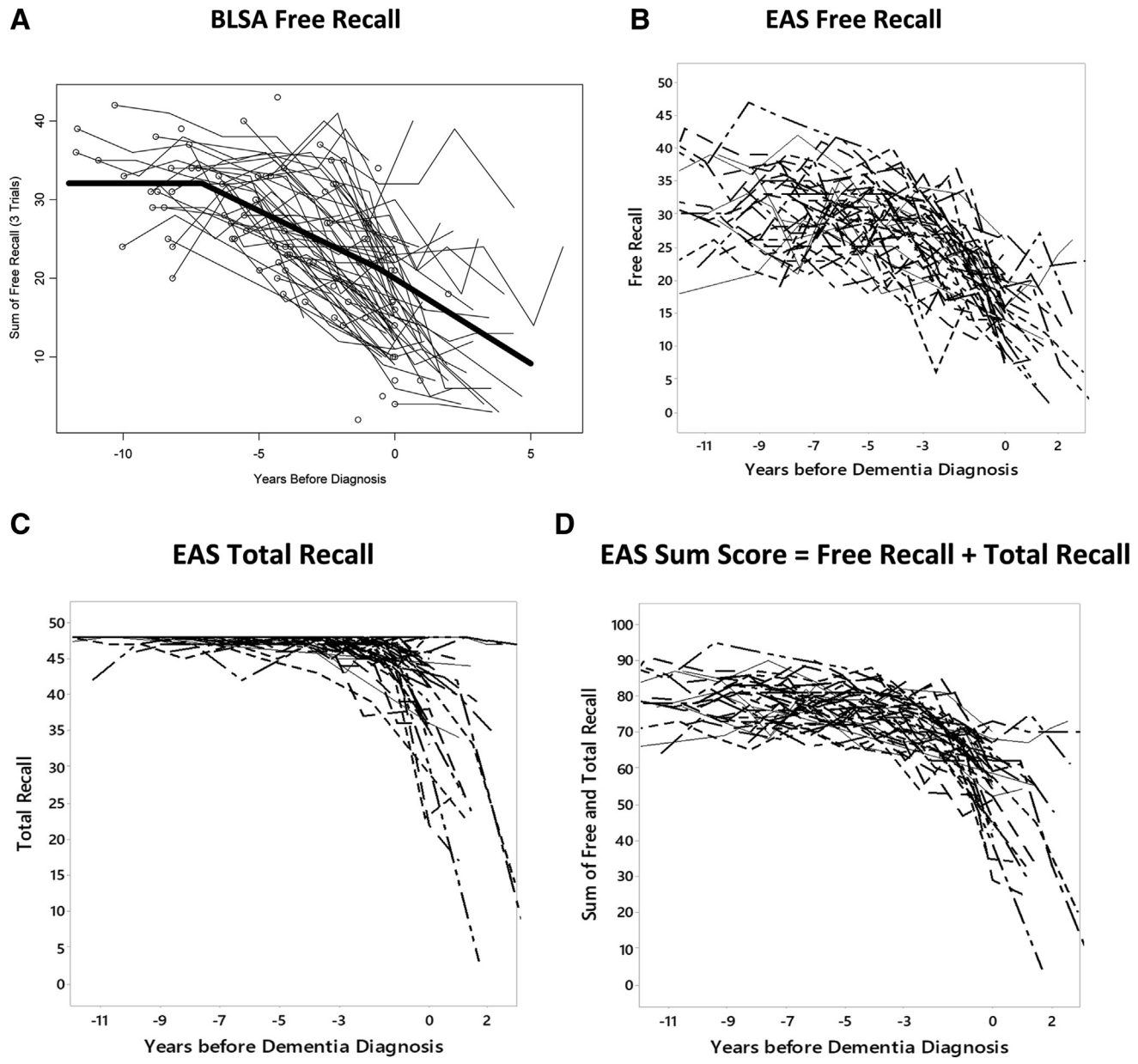

Fig. 1. Spaghetti plots from the Baltimore Longitudinal Study of Aging (BLSA) and Einstein Aging Study (EAS) of cases diagnosed with Alzheimer's disease (AD): (A) BLSA free recall, (B) EAS free recall, (C) EAS total recall, (D) EAS sum score = free recall + total recall.

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