Journal of Psychiatric Research 96 (2018) 33–38

Contents lists available at ScienceDirect

Journal of Psychiatric Research

journal homepage: www.elsevier.com/locate/psychires

A novel cognitive assessment paradigm to detect *Pre-mild cognitive impairment* (*PreMCI*) and the relationship to biological markers of Alzheimer's disease

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ARTICLE INFO

Article history:
Received 17 April 2017
Received in revised form
20 June 2017
Accepted 18 August 2017

Keywords:
Preclinical Alzheimer's
MCI
LASSI-L
MRI
Semantic interference

ABSTRACT

Objective: A number of older adults obtain normal scores on formal cognitive tests, but present clinical concerns that raise suspicion of cognitive decline. Despite not meeting full criteria for Mild Cognitive Impairment (MCI), these PreMCI states confer risk for progression to Alzheimer's disease (AD). This investigation addressed a pressing need to identify cognitive measures that are sensitive to PreMCI and are associated with brain biomarkers of neurodegeneration.

Method: Participants included 49 older adults with a clinical history suggestive of cognitive decline but normal scores on an array of neuropsychological measures, thus not meeting formal criteria for MCI. The performance of these PreMCI participants were compared to 117 cognitively normal (CN) elders on the LASSI-L, a cognitive stress test that uniquely assesses the failure to recover from proactive semantic interference effects (frPSI). Finally, a subset of these individuals had volumetric analyses based on MRI scans.

Results: PreMCI participants evidenced greater LASSI- L deficits, particularly with regards to frPSI and delayed recall, relative to the CN group. No differences on MRI measures were observed. Controlling for false discovery rate (FDR), frPSI was uniquely related to increased dilatation of the inferior lateral ventricle and decreased MRI volumes in the hippocampus, precuneus, superior parietal region, and other AD prone areas. In contrast, other LASSI-L indices and standard memory tests were not related to volumetric findings.

Conclusions: Despite equivalent performance on traditional memory measures, the frPSI distinguished between PreMCI and CN elders and was associated with reductions in brain volume in numerous AD-relevant brain regions.

1. Introduction

In 2011, the National Institutes on Aging and Alzheimer's Association (NIA-AA) established broad research criteria for the diagnosis of preclinical Alzheimer's disease (AD). The focus of these guidelines was to address the to define AD in terms of its underlying pathophysiological disease process rather than NIA-AA guidelines for clinical stages of the disease relative to individuals with mild cognitive impairment (MCI) who had MRI or amyloid PET evidence of AD pathology (Albert et 2011) or dementia related to Alzheimer's Disease (McKhann et al., 2011).

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https://doi.org/10.1016/j.jpsychires.2017.08.015
0022-3956/

From a cognitive standpoint, accurately identifying individuals on the Alzheimer's disease (AD) continuum during the preclinical stages is challenging given that there are older adults who may have suspected cognitive deficits, score within normal limits on neuropsychological evaluation and do not meet formal criteria for mild cognitive impairment (MCI). These individuals, classified as PreMCI, *experienced a much greater likelihood* of experiencing a decline to formal MCI or dementia *longitudinally than cognitively normal older adults* (Loewenstein et al., 2012). In fact, the neuropsychological test performance of persons with PreMCI has also been associated with biomarkers of AD pathology (Duara et al., 2011; Loewenstein et al., 2016; Loewenstein, Curiel, Buschke and Duara 2017a).

The ability to identify individuals with PreMCI is important since many persons evaluated may not have access to advanced neuroimaging such as amyloid PET scans and that emerging therapies, *both* now and in the future, are likely to be more efficacious before multisystem brain deterioration has occurred.

Recent findings have suggested that cognitive "stress tests" may be sensitive to the earliest changes in AD (Loewenstein et al., 2016). These measures are analogous to an exercise EKG that may reveal cardiac deficits that simply cannot be identified in a resting state. One such test, the LASSI-L, requires learning of 15 words belonging to three semantic categories and taps vulnerability to semantic proactive interference by presenting a competing semantically similar set of targets. A unique feature of the LASSI-L is a second presentation of the second target list that taps failure to recover from proactive semantic interference (frPSI). The LASSI-L frPSI measure has been found to be: highly related to total and regional amyloid load in neuropsychologically normal community-dwelling elders (Loewenstein et al., 2016); has differentiated between aMCI patients with suspected AD from cognitively unimpaired elderly controls (CN) (Curiel et al., 2013; Crocco et al., 2014; Matías-Guiu et al., 2016); and has been associated with volumetric loss in AD prone areas among elders with amnestic MCI (Loewenstein et al., 2017b).

The current investigation is unique in that it represents a first attempt to determine whether failure to recover from proactive semantic interference (frPSI) differentiates between older adults with PreMCI and those who are cognitively normal (CN). A further goal was to determine the extent to which frPSI was associated with volumetric structural MRI changes in AD related brain regions (Dickerson et al., 2011; Holland et al., 2009; Loewenstein et al., 2017b) among our participants.

2. Methods

2.1. Participants

The sample included 166 older adult participants from an NIH funded and IRB approved DETECT-pAD study at the University of Miami School of Medicine designed to measure the longitudinal trajectories of decline in PreMCI participants, *A major focus of the longitudinal investigation was to determine the extent to which novel cognitive stress tests versus traditional neuropsychological measures could predict different trajectories of decline among persons who were cognitively normal, those diagnosed with MCI other diagnosed with PreMCI.*

All participants were independent community-dwellers, with the vast majority having knowledgeable collateral informants. None of these individuals met DSM-V criteria for Major Neurocognitive Disorder, active Major Depression or any other neuropsychiatric disorder *after an extensive clinical interview which included the Neuropsychiatric Inventory (NPI:)*. Participants were evaluated using a standard clinical assessment protocol consisting of the Mini-mental State Examination (MMSE) (Folstein et al., 1975) and Clinical Dementia Rating Scale (CDR) (Morris, 1993). Neuropsychologists or post-doctoral fellows, who had formal training in the administration of the CDR, assessed the memory and the presence of other cognitive complaints among the participants and also conducted the CDR interview with a collateral informant that knew the patient well. *Over 95% of participants had collateral informants such as a spouse, children, sibling or close friend who could rate any changes in the individuals cognitive status in the previous year and years prior as well as a structured interview about the ability to perform different cognitive and functional tasks*. A standard neuropsychological battery was subsequently administered after the clinical examination. The neuropsychological battery included the Hopkins Verbal Learning Test-Revised (HLVT-R: Benedict et al., 1998), National Alzheimer's Coordinating Center (NACC) delayed paragraph recall (Beekly et al., 2007), Category Fluency (Lucas et al., 1998), Block Design of the WAIS-IV (Wechsler, 2008), and the Trail Making Test (Parts A and B) (Reitan, 1958). *The LASSI-L was not used for diagnostic determination. All tests including the LASSI-L had been translated and back-translated into Spanish using methods that we have previously reported and those persons who reported Spanish as their primary language were tested in Spanish (*Acevedo et al, 2007, 2009*). We have an extensive normative database for English and Spanish-speaking subjects in all the neuropsychological tests administered*.

On the basis of the independent clinical interview and performance on the neuropsychological tests, an individual was considered to have PreMCI if all of the following conditions were met: a) subjective memory complaints by the participant and/or or collateral informant; b) evidence by clinical evaluation or history of memory or other cognitive decline *determined after the extensive CDR interview*); c) Global CDR scale of 0.5; d) the neuropsychological battery was deemed normal (DL) and generally, no measures in the neuropsychological battery fell 1.0 SD or more below normal limits relative to age and education related normative data. PreMCI represents more than a mere subjective memory complaint. It requires a careful interview with both the participant and a collateral informant and the determination by the clinician is that there has been cognitive decline beyond that expected for age. For example, a participant might not notice any changes in their memory or other cognitive functions, yet a knowledgeable informant provides concrete examples of decline in recent memory during the previous year. This decline is not sufficient to interfere with social/occupational functioning and independent traditional neuropsychological testing is within normal limits for age, education and primary language (perhaps due to cognitive reserve). Because the clinician judges that there has been cognitive decline in spite of normal neuropsychological testing, this participant is classified as having PreMCI.

Participants were diagnosed as cognitively normal (CN) if: a) there was no subjective memory complaints by the participant and/or or collateral informant; b) no evidence by clinical evaluation or history of memory or other cognitive decline; c) Global Clinical Dementia Rating scale of 0; d) Global CDR scale of 0.5; d) the neuropsychological battery was deemed normal (DL) and generally, no measures in the neuropsychological battery fell 1.0 SD or more below normal limits relative to age and education related normative data.

As indicated in Table 1, there were no differences between PreMCI and CN participants with regards to age, educational attainment, average MMSE scores or performance on the HVLT-R *immediate or delayed recall.* Individuals with PreMCI were more likely to be Hispanic and thus, this factor was employed in covariate analyses when evaluating potential differences between study groups and the gender distribution was predominantly female but