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Encoding deficits in low-educated individuals with non-amnestic Mild Cognitive Impairment. Analysis of memory processes using the Item Specific Deficit Approach

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ABSTRACT

This work aims to analyze encoding impairments using new assessment scores in patients with naMCI who present to memory clinics with subjective cognitive complaints. The sample included 102 participants, of whom 28 were classified as healthy controls (HC), 24 as amnestic MCI (aMCI), 24 as naMCI and 26 patients as Alzheimer's disease (AD). Research outcomes were the Encoding, Consolidation and Retrieval deficit indices from the Item Specific Deficit Approach, and traditional indices (immediate total recall, delayed cued recall, delayed total recall) derived from the Free and Cued Selective Reminding Test (FCSRT). We found no differences in immediate recall or delayed recall between HC and naMCI on the FCSRT, both scoring higher than aMCI and AD. naMCI showed encoding deficits in between HC and aMCI, with no differences between naMCI and HC on consolidation or retrieval deficit indices. The ISDA indices were better than traditional indices to discriminate between HC and naMCI (sensitivity: 70.8%, specificity: 78.6%), whereas the opposite pattern was found between naMCI and aMCI (sensitivity: 70.8%, specificity: 91.7%). New indices derived from neuropsychological tests may help to identify objective memory impairments in naMCI. Whether these new indices are useful for predicting conversion to AD needs further research.

1. Introduction

Pure Alzheimer's Disease (AD) pathology has been recognized as the most frequent underlying pathology in non-amnestic Mild Cognitive Impairment (naMCI) (Schneider et al., 2009). Supporting this data, Dugger et al. (2015) found that neurofibrillary tangles, neuritic plaques and Lewy Bodies loads were similar in persons with amnestic MCI (aMCI) and naMCI, with the temporal lobe showing a differential propensity of neurofibrillary tangles for aMCI and of Lewy-type alpha-synucleinopathy for naMCI. Conversely, naMCI has been associated with cerebrovascular disease more often than aMCI (Hughes et al., 2011), and it has been reported that naMCI patients are more likely to progress to other forms of dementia than AD (Ferman et al., 2013). However, Vos et al. (2013) reported that although progression rate to AD was higher in aMCI compared to naMCI and aMCI had more abnormal biomarker scores such as CSF Aβ1-42, tau, Aβ1-42/tau ratio, HCV and APOE ε4, biomarkers predicted memory decline only in participants with naMCI. Thus, there may be no single underlying etiology dichotomizing aMCI from naMCI (Dugger et al., 2015). The fact that less AD pathology along with comorbid vascular lesions are needed for naMCI to develop clinical AD at follow-up suggests that patients with naMCI may be in an earlier stage of AD (Vos et al., 2013).

Persons with naMCI often complain about memory impairments. Recent findings suggest that subjective memory complaints (SMC) in naMCI reflect an underestimation of their otherwise normal memory ability (Lehrner et al., 2015), so average performance would reflect a normal memory functioning. Under this condition, the presence of SMC as indicative of MCI diagnosis would produce an increased rate of false positives (Lenehan et al., 2012). An alternative hypothesis is that SMC represents a pre-clinical stage of AD (Jessen et al., 2014); thus, average performance would reflect a lack of an adequate sensitivity to detect very mild impairments. This notion is supported by findings that

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persons with naMCI show decreased activation in frontal, occipital and parietal regions (Machulda et al., 2009) but perform within normal limits on memory tasks. It has been reported recently that older people with SMC are twice as likely to develop dementia, have higher rates of progression to dementia and have significant cortical thinning in brain regions related to AD compared to persons without SMC (Luck et al., 2015; Mitchell et al., 2014; Schultz et al., 2015).

If AD pathology is common in naMCI, impairments in encoding of new information might be expected as those found in AD (Oltra-Cucarella et al., 2014) and aMCI (Chechko et al., 2014). As performance in standardized memory tests is within normal ranges, new methods of interpreting cognitive tests are needed to identify subtle but clinically relevant impairments. We examined verbal memory using the Item Specific Deficit Approach (ISDA) (Wright et al., 2009, 2010). The ISDA was developed as a way of characterizing memory process deficits in list-learning tasks. The ISDA showed acceptable internal consistency (0.58–0.77) and predicted neurological status with higher precision than traditional memory process indices derived from the California Verbal Learning Test (CVLT) in participants with either HIV+ or traumatic brain injury (Wright et al., 2009). The ISDA evaluates encoding, consolidation and retrieval at the item level, contrary to the traditional indices that focus on the sum of scores (e.g., immediate recall, recognition-recall discrepancy). The ISDA has been applied to characterize memory impairments in traumatic brain injury (Wright et al., 2009; Wright and Schmitter-Edgecombe, 2011), closed-head injury (Wright et al., 2010), HIV (Cattie et al., 2012), Amyotrophic Lateral Sclerosis (Christidi et al., 2012) and AD (Oltra-Cucarella et al., 2014), but to our knowledge it has never been used in MCI.

The aim of this work is to test whether new memory indices are useful to identify objective memory impairments in naMCI. We expected to find encoding deficits in naMCI compared to healthy controls despite age- and education-corrected memory scores within the normal range (Wang et al., 2012), which would suggest that standard scores are not sensitive enough to identify subtle deficits. Moreover, because performance on the memory test was within normal ranges for both HC and naMCI, we expected that the ISDA indices would discriminate between these two groups better than standard scores; on the other hand, because performance on the memory test was within normal ranges for naMCI and in the impaired range for aMCI, we expected that traditional scores would discriminate between these two groups better than ISDA indices.

2. Methods

Participants were part of a longitudinal study of test-retest reliability of memory tasks in a Spanish population and their utility for identifying objective memory impairments in naMCI. All participants were assessed with a comprehensive neuropsychological battery covering general cognitive functioning (Mini-Mental State Examination, MMSE) (Folstein et al., 1975), the Clinical Dementia Rating scale (CDR) (Hughes et al., 1982), information processing speed (Trail Making Test, Part A) (Strauss et al., 2006), executive functioning (phonetic fluency), visual memory (the ROCF-immediate and delayed recall) (Rey, 1987), visuospatial perception (Judgment of Line Orientation) (Strauss et al., 2006), constructional praxis (Rey-Osterrieth Complex Figure – copy; Block Design) (Wechsler, 1999), naming (Boston Naming Test abbreviated form version C) (Casals-Coll et al., 2014), verbal memory (Free and Cued Selective Reminding Test, Buschke's FCSRT. Copyright, 1996–2000. Albert Einstein College of Medicine of Yeshiva University, New York) (Peña-Casanova et al., 2009a), and semantic knowledge (Peña-Casanova et al., 2009b). Neuropsychological profile is presented in Supplemental material.

Functionality was assessed with the CDR (Hughes et al., 1982) and the Instrumental Activities of Daily Living questionnaire (IADL) (Lawton and Brody, 1969). Higher scores on the IADL indicate higher levels of independence in instrumental ADLs. Some level of impairment was allowed because it has been found that individuals with MCI have impairments in IADLs such as shopping or driving (Jekel et al., 2015). All participants with MCI scored 6 or higher out of 8.

For diagnosis purposes, all neuropsychological tasks (except the Block design subtest) were interpreted using age- and education-corrected scaled scores (SS) from normative values for Spanish population.

2.1. Participants

Participants in the healthy control group (HC) were 28 healthy elder volunteers living independently in the community. Inclusion criteria were a) no history of neurological, psychiatric or metabolic diseases, b) independent for activities of daily living (ADL's), c) no subjective memory complaints (mandatory CDR Memory box = 0), and d) no cognitive impairment (CDR = 0).

Participants in the MCI (naMCI = 24, aMCI = 24) and the AD (n = 26) groups were outpatients from the Unit of Cognitive Impairments and Movement Disorders at the Hospital Universitario Santa María del Rosell (Cartagena, Spain). Both MCI and AD patients were diagnosed by consensus (neurologists, neuropsychologists and neuroradiologists) after carefully gathering data from neurological examination, neuropsychological assessment, neuroimaging (CT or MR) and laboratory analyses (e.g., B12). MCI was diagnosed according to established criteria (Winblad et al., 2004), including a) presence of subjective cognitive complaints corroborated by an informant (mandatory CDR Memory box = 0.5), b) evidence of objective cognitive impairment on at least one cognitive test, c) CDR = 0.5, e) absence or minimal impairment on ADL's corroborated by an informant, f) absence of other psychiatric or neurological disease that could cause cognitive impairment (e.g., mental retardation, depression, movement disorders, stroke, TBI, epilepsy) and g) failure to meet diagnostic criteria for dementia and probable or possible AD according to the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) criteria (McKhann et al., 2011). The criterion for defining participants as not normal/not demented was the CDR = 0.5 global score, irrespective of MMSE scores. Objective impairment was defined as age- and education-corrected SS equal to or lower than 6 (i.e., 7th percentile). MCI patients were diagnosed as naMCI if both FCSRT and ROCF delayed recall scaled scores were > 6. AD was diagnosed according to NINCDS-ADRDA criteria (McKhann et al., 2011).

Written informed consent to use clinical data for research was obtained from all participants. Approval to conduct this study was obtained from the hospital's ethical committee according to the Declaration of Helsinki.

2.2. Traditional and ISDA indices

The Spanish adaptation of the FCSRT was administered according to standard instructions. Traditional indices were derived from the FCSRT to assess encoding (*total immediate recall*: trial 1 to 3 total recall), consolidation (*total delayed recall*), and retrieval (*delayed cued recall*) (Wright et al., 2009). These three scores were selected to equate the number of scores with the ISDA.

The ISDA method provides three indices:

1. The Encoding Deficit Index (EncDI) is the proportion of information deficiently encoded during learning. Contrary to the traditional indices, the EncDI has no associations with impaired attention (Wright et al., 2009). In prior works, deficient encoding of each item was identified as recall < 3 during the 5 learning trials of the CVLT (Wright et al., 2009). For the current study, we categorized deficient encoding as recall < 3 during the 3 FCSRT learning trials. This was deemed the closest possible approximation given the internal task structure (i.e., 5 free recall trials on the CVLT versus 3 free plus 3 cued recall trials on the FCSRT). EncDI values range from 0 to 1. The