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Research Article

Can a novel computerized cognitive screening test provide additional information for early detection of Alzheimer's disease?

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Abstract

Background: Virtual reality testing of everyday activities is a novel type of computerized assessment that measures cognitive, executive, and motor performance as a screening tool for early dementia. This study used a virtual reality day-out task (VR-DOT) environment to evaluate its predictive value in patients with mild cognitive impairment (MCI).

Methods: One hundred thirty-four patients with MCI were selected and compared with 75 healthy control subjects. Participants received an initial assessment that included VR-DOT, a neuropsychological evaluation, magnetic resonance imaging (MRI) scan, and event-related potentials (ERPs). After 12 months, participants were assessed again with MRI, ERP, VR-DOT, and neuropsychological tests.

Results: At the end of the study, we differentiated two subgroups of patients with MCI according to their clinical evolution from baseline to follow-up: 56 MCI progressors and 78 MCI nonprogressors. VR-DOT performance profiles correlated strongly with existing predictive biomarkers, especially the ERP and MRI biomarkers of cortical thickness.

Conclusions: Compared with ERP, MRI, or neuropsychological tests alone, the VR-DOT could provide additional predictive information in a low-cost, computerized, and noninvasive way.

Keywords: Computerized cognitive assessment; Computerized testing; Early detection; Dementia; Psychometrics

1. Introduction

Age is a strong risk factor for the most common cause of dementia, sporadic Alzheimer's disease (AD) [1,2]. Because of the growing numbers of older individuals in many societies, the prevalence of AD is increasing at an alarming rate [3,4]. It is believed that, by the time AD is diagnosed, sufficient neuronal injury has occurred to the extent that reversal of the disease is unlikely [5]. This has therefore raised considerable interest in the prodromal stage of AD involving subjects with mild cognitive impairment (MCI), who are in the predementia stage of cognitive dysfunction and could therefore be targeted for early interventions that may potentially provide beneficial effects [6].

MCI, which indicates early cognitive aging beyond the normal range according to respective age and level of education, is a clinical syndrome that commonly arises as a result of neurodegenerative pathology [7]. In clinical trials and epidemiologic studies, the annual rate of conversion of MCI subjects to dementia was found to be in the range of 6% to 25%, which is much higher than the incidence rate of dementia of 1% to 2% seen in the general population [8]. Recently described MCI diagnostic criteria require

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evidence of: (1) cerebral amyloidosis (amyloid positron emission tomography [PET] or cerebrospinal fluid [CSF] amyloid-β); and (2) neurodegeneration (magnetic resonance imaging [MRI]–derived atrophy, fluorodeoxyglucose PET–derived hypometabolism, or CSF tau) [9].

Currently, there is interest in developing reliable and sensitive biomarkers of early cognitive impairment [10]. A number of studies have shown that, within a group of subjects with MCI, the presence and prominence of such biomarkers were predictive of AD dementia within a few years [10–18]. Combining cutoff CSF biomarkers, neuroimaging data, and noninvasive biomarkers, such as endogenous evoked potential, has also shown great promise in identifying prodromal AD with high sensitivity and specificity [19–23]. Recent studies have also validated the relevance of event-related potentials (ERPs) alone as a marker for detecting early cognitive changes associated with MCI [24], or predicting the evolution of patients with MCI [25]. Other recent studies addressed the temporal utility of biomarkers and identified that the rapid progression (i.e., over 1 year) from MCI to AD dementia is better predicted by markers of neurodegeneration rather than the presence of amyloid [26], whereas the long-term progression from MCI to dementia (i.e., 3 years) is best predicted by the presence of abnormal levels of brain amyloid [27,28].

Despite recent advances in the identification of MCI-related biomarkers, neuropsychological assessment remains a critical component of evaluation to ensure the cognitive correlates of biomarker abnormalities and to assist in detecting and tracking progression of MCI to early AD. Current challenges in the neuropsychological evaluation of MCI include: test selection; the availability of normative databases; the effect of different base rates of MCI and AD in different settings; establishing cutoff points for impairment; and developing measures more sensitive to early AD while having sufficient specificity to distinguish between etiologically different conditions [29,30]. Another challenge in the evaluation is the issue of cognitive reserve [31], which allows use of compensatory mechanisms that may mask overt manifestations of disease [32]. Possible solutions to the problem of diagnosing cognitive impairment in highly intelligent people are to apply appropriate norms for these subgroups and to develop more cognitively challenging measures in which compensation is more difficult.

Within this context, computerized assessment may be uniquely suited for early detection of changes in cognition. Included among the multiple advantages cited [33], computer tests can cover a wider range of ability, minimize floor and ceiling effects, are given in a standardized format, and can precisely record accuracy and speed of response with a level of sensitivity not possible in standard assessment. Computerized testing also has many advantages when analyzing test data. One particular kind of computerized assessment is virtual reality simulation of everyday tasks in naturalistic settings, which proved particularly sensitive in assessing not only brain-damaged patients [34–36] but also the more pronounced changes occurring in the early stages of dementia [37].

In previous work, we found that a novel virtual reality simulation of a complex day-out task (VR-DOT) has 97% sensitivity and 100% specificity when used as a screening tool for early dementia with the introduction of a psychomotor and cognitive performance–based rate-of-change score [38]. However, tracking progression from MCI to dementia and an eventual prognosis of AD require the correlation of VR-DOT performance scores with neurodegenerative markers at different intervals. In this study, we attempted to investigate the sensitivity of VR-DOT in predicting the evolution of patients with MCI and in particular the rapid progression from MCI to AD (within 1 year). To accomplish this goal, we compared VR-DOT with standard neuropsychological evaluation, as well as sensitive biomarkers for short-term prognosis in MCI such as AD signature cortical thickness marker [39] and the noninvasive ERPs. We chose those two markers because they are noninvasive and have a large number of studies behind them as sensitive and specific markers of very early progression from MCI to AD [17,19,20].

2. Methods

2.1. Participants

Participants were recruited at the 3rd Neurological Clinic of the Aristotle University of Thessaloniki, Greece, and from the memory clinics of the Greek Association for Alzheimer Disease and Related Disorders, belonging to the 3rd Neurological Clinic of the Aristotle University of Thessaloniki. The study was carried out in accordance with the Declaration of Helsinki, and was approved by the local ethics committee. Written informed consent was obtained before study participation. One hundred fifty-two patients with a diagnosis of MCI according to the criteria of Petersen et al. [8,40] were selected for the study. The diagnosis was made if the patient met the following criteria: (1) memory complaint; (2) abnormal memory for age; (3) normal activities of daily living; (4) normal general cognitive function; and (5) not demented. Structural MRI data were also available in all MCI cases to exclude conspicuous brain abnormalities. Seventy-five age-matched control subjects without cognitive complaints were recruited. Furthermore, it was ascertained that all participants had normal or corrected-to-normal vision. All participants, except one older adult, were right-handed according to the Edinburgh Handedness Inventory [41]. Three subjects from the original sample were excluded from the analysis because subsequent chart review revealed a prior diagnosis of dementia. Three additional subjects did not complete the evaluation, and data from 12 subjects were lost due to software error. The final sample size analyzed included 134 MCI patients and 75 healthy controls. Final sample groups did not differ in years of education [$F(3, 206) = 1.29$, $P = .31$] or distribution of gender