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Response speed, contingent negative variation and P300 in Alzheimer's disease and MCI

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ABSTRACT

Background: Decreased speed of information processing is a hallmark of Alzheimer's disease (AD) and mild cognitive impairment (MCI). Recent studies suggest that response speed (RS) measures are very sensitive indicators of changes in longitudinal follow-up studies. Insight into the psycho-physiological underpinnings of slowed RS can be provided by measuring the associated event-related potentials (ERP).
Aims: The current study aims to investigate the relation between RS and its psycho-physiological correlates in AD and MCI.
Methods: Fifteen psychoactive drug-naïve AD patients, 20 MCI patients and twenty age-matched, healthy control subjects participated. Response speed was measured during a simple (SRT) and choice reaction time task (CRT). An oddball and contingent negative variation (CNV) paradigm were used to elicit ERP. To evaluate test-retest reliability (TRR), subjects underwent a similar assessment one week after the first.
Results: The SRT and CRT distinguished the patient groups significantly. The P300 amplitude and latency also distinguished the groups and showed a significant correlation with response speed. The CNV amplitude did not reveal a significant difference between groups and also showed a low TRR. The TRR of the SRT, CRT and P300 amplitude and latency in general was moderate to high. The current study suggests that response speed measures on a behavioural and psycho-physiological level deserve attention as a possible marker in the diagnosis and follow-up of AD.

1. Introduction

Decreased speed of information processing is one of the hallmarks of cognitive aging. Several studies have shown an age-related increase of reaction times (RT) in a variety of cognitive tasks (Salthouse, 2000). Typically response speed (RS) is measured during tasks measuring simple reaction time (SRT), choice reaction time (CRT), rapid visual information processing, speed of scanning working memory, or similar processes. The SRT primarily reflects sensory encoding and psychomotor speed, whereas the CRT captures an additional decision-making component (Gordon & Carson, 1990). Furthermore, the speed of response is associated with focussed and sustained attention (Salthouse, 1996, 2000; Verhaeghen & De Meersman, 1998). Augmented slowing of RS is a characteristic of Alzheimer's disease and distinguishes patients from elderly controls (Gordon & Carson, 1990; Levinoff, Saumier, & Chertkow, 2005; Storandt & Beaudreau, 2004).

The clinical diagnosis of AD is based on the outcome of an extensive medical and neuropsychological evaluation. However, when monitoring the progression of the disease, or the evaluation of treatment intervention, the Alzheimer's disease assessment scale – cognitive subscale (ADAS-cog) is routinely used (Rosen, Mohs, & Davis, 1984; Verhey et al., 2004). The ADAS-cog measures a variety of cognitive functions but does not include any measure of attention or RS (Wesnes, 2008). A 12-week follow-up study on the effects of Galantmine on cognitive performance in AD, showed that RS measurements were more sensitive indicators of changes than the ADAS-cog (Caramelli et al., 2004). A recent neuroimaging study showed that adding attentional or speed measures to ADAS-cog, improves this instrument's sensitivity as a means to predict white matter changes in an elderly population (Ylikoski et al., 2007). These findings suggest that RT measures could also improve the sensitivity of the ADAS-cog in the behavioural domain.

Response speed is the behavioural endpoint of a cascade of neural processes. These processes can be unravelled by measuring psycho-physiological brain activity with the aid of event-related potentials (ERP). The ERP typically associated with RS and stimulus classification are contingent negative variation (CNV) and P300. Measuring these ERP simultaneously with RS can provide more insight into the neural underpinnings of slowed RS in AD. The CNV is

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a slow negative potential that precedes a response to an anticipated stimulus. The typical CNV paradigm consists of a warning stimulus (S1) followed by the imperative (S2) stimulus four seconds later (Walter, Cooper, Aldridge, McCallum, & Winter, 1964). The amplitude of the CNV complex is believed to reflect attention, expectancy, intention to respond and motor preparation. The amplitude of the CNV component seems to be related to RS: larger CNV amplitudes precede shorter reaction times (Brunia & Vingerhoets, 1980; Brunia & Vingerhoets, 1981; Haagh & Brunia, 1985). Early studies showed decreased CNV amplitudes in Alzheimer's disease and MCI but it has to be noted that very small sample sizes were used (O'Connor, 1980; Zappoli et al., 1991). Therefore, a comparison with larger sample sizes of CNV activity in these patient groups is necessary. The P300 is elicited in response to deviant stimuli in simple auditory or visual discrimination tasks. The amplitude of the P300 is considered as the manifestation of brain activity that reflects attention to incoming stimulus information when representations are updated (Polich, 2007). In general, passive stimulus processing produces smaller P300 amplitudes than active stimulus processing. The P300 latency is considered as stimulus classification speed and is sensitive to task processing demands and cognitive abilities (Polich, 2007). Previous studies have reported decreased P300 amplitudes and increased latencies in AD (Boutros, Torello, Burns, Wu, & Nasrallah, 1995; Golob & Starr, 2000; Ito, Yamao, Fukuda, Mimori, & Nakamura, 1990; Patterson, Michalewski, & Starr, 1988; Polich, Ladish, & Bloom, 1990; Szelies, Mielke, Grond, & Heiss, 1995). Despite these consistent findings, there are also studies that did not show a difference between AD and healthy controls on P300 amplitude and latency (Verleger, Kompf, & Neukater, 1992). Other studies showed a difference between AD and healthy controls for P300 amplitude only (Duffy, Albert, & McAnulty, 1984) or on P300 latency only (Ito, 1990). For an extensive review, see Polich & Herbst (2000). There is some evidence that suggests that a larger P300 amplitude and slower latency is related to faster responses. However, this relation has only been shown in healthy subjects and in MCI but not yet in AD (Dimoska, Johnstone, & Barry, 2006; Williams, Jones, Briscoe, Thomas, & Cronin, 1991).

Most ERP studies in AD have been performed with patients on cholinesterase inhibiting drug treatment. These drugs have a profound effect on ERP amplitudes and latencies (Katada et al., 2003; Werber, Gandelman-Marton, Klein, & Rabey, 2003). It is therefore of importance to study the relationship between RS and ERP in a drug-naïve population.

A relatively underexposed aspect of ERP recordings is their reliability when it comes to monitoring cognitively impaired patients. If RS measures or ERP are to be used as markers in the diagnosis and follow-up of AD and MCI in the future, it is important to test their reliability. Therefore, the TRR of the RS tasks and the ERP have been a point of focus in the current study. The current study examines the relation between RS and the psycho-physiological correlate in cases of AD and in cases of MCI, as well as in healthy elderly control subjects.

2. Materials and methods

2.1. Subjects

The study involved three different groups of subjects. The first group consisted of fifteen patients who were psychoactive drug-naïve and diagnosed with probable AD according to the NINCDS-ADRDA criteria (McKhann et al., 1984). Standard blood workup and neuroimaging (CT of MRI) were carried out on this group, and the diagnosis was supported by abnormal performance on neuropsychological testing.

The second group consisted of twenty patients who were psychoactive drug-naïve and diagnosed with MCI according to the Petersen criteria (Petersen et al., 2001). These MCI subjects also received standard blood workup, neuroimaging and neuropsychological testing. The diagnosis AD or MCI was made during a weekly consensus meeting of different specialists. All MCI patients showed objective cognitive disturbances and were divided in the following sub-classifications: Five of the MCI patients had single domain amnestic MCI; eight patients had multiple domain amnestic MCI; two patients had single domain non-amnestic MCI; and five had multiple domain non-amnestic MCI (Petersen, 2004).

The third group consisted of twenty healthy control subjects who were recruited from the Maastricht Aging Study (MAAS), a longitudinal study of the determinants of healthy cognitive aging (van Boxtel et al., 1998). None of the healthy controls used psychoactive medication. Their medical history was screened by a medical health questionnaire. The cognitive status of the control subjects was screened with the Mini Mental State Examination (MMSE), using a cut-off score of >28 (Folstein, Folstein, & McHugh, 1975). The test scores on the ADAS-cog were also used to ensure that the control group had normal cognitive abilities. Main exclusion criteria were: a history of stroke, head trauma, and/or any other neurological or psychiatric disorders. Additional exclusion criteria were: severe cardiovascular disease, a Hachinski ischemic scale (HIS) (Hachinski, Lassen, & Marshall, 1974; Rosen, Terry, Fuld, Katzman, & Peck, 1980) higher than three and/or a history of substance abuse and/or other serious system diseases (e.g. malignancy, uncontrolled hypertension and neuropathy or seizure disorders).

All AD and MCI patients were recruited at the Memory Clinic of University Hospital Maastricht and were judged competent to give consent by their treating physicians. All participants gave written informed consent prior to the study; in the case of AD patients a family member also signed the consent form. The local Medical Ethics Committee of the University Hospital Maastricht approved the study.

2.2. Experimental procedure

All subjects took part in two identical recording sessions, temporally spaced apart by one week. On both occasions the cognitive subscale of the Alzheimer's disease assessment scale (ADAS-cog) (Rosen et al., 1984; Verhey et al., 2004) was assessed prior to EEG acquisition. The Dutch version of the National Adult Reading Test (NART) (Schmand, Bakker, Saan, & Louman, 1991) was performed to estimate pre-morbid intelligence. A simple reaction time task (SRT) and a choice reaction time task (CRT) was performed to measure reaction time speed. After the assessment of NART, ADAS-cog and the response speed tasks, there was a break of 30 min in which the participants could rest while the EEG cap was attached. The CNV and P300 EEG data were acquired in the first 15 min of the EEG test session to prevent effects of fatigue on the results. The two electrophysiological outcome measures i.e. CNV and P300 were part of a larger study, which further included: three gamma band paradigms, 40 Hz steady state response and a visual checkerboard task. The order of the administration of the tasks was similar for each patient and on both test sessions.

2.3. Behavioural paradigms

2.3.1. Simple and choice reaction time tasks

The simple reaction time task (SRT) was presented in four runs of 40 trials each. In each trial of the SRT a white square (4×4 cm) on black background was followed by a red square (4×4 cm).