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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).

Subjects were instructed to push the response button as fast as possible when the white square turned red. After the response the red square turned white again until the next trial. The interval between the trials varied randomly between 2 and 6 s. Between the runs there was a break of 1 min.

The choice reaction time task (CRT) was presented in four runs of 40 trials. In each trial two whites squares (4 × 4 cm), one on the left side and one on the right side of the screen, were presented on a black background. When one of the two squares turned red the subject had to push the congruent response button, left or right. After the response the red square turned white again. The interval between the trials varied randomly between 2 and 6 s.

The visual stimuli were presented on a 16 in. computer screen. The responses were given on a standard five-options response box. The SRT and CRT were practised for 3 min prior to measurement during each visit, in order to prevent learning effects and to familiarise the subjects with the tasks.

2.3.2. CNV paradigm

The visual CNV paradigm consisted of a warning stimulus in the form of a big red dot (Ø 12 cm), followed by the imperative stimulus in the form of a big green dot (Ø 12 cm). A total of 36 trials were administered, the inter-stimulus interval (ISI) was 2 s and the inter-trial interval (ITI) varied between 5 and 10 s. The subjects were instructed to respond as fast as possible when the imperative stimulus appeared. The task was practised for three minutes prior to each recording session to prevent learning effects and to familiarise the subjects with the task. To prevent differences between the groups regarding practise intensity, the practise trails were similar for all subjects.

2.3.3. Oddball paradigm

A simple auditory two-tone discrimination or 'oddball' paradigm was used to elicit ERP responses. Thirty-two target tones (2000 Hz, 80 dB, 100 ms) were pseudo-randomly distributed within a stream of non-target tones (1000 Hz, 80 dB, 100 ms). A fixed inter-stimulus interval of 2 s was used. Target and non-target stimuli appeared with a probability of 15% and 85%, respectively. Subjects were requested to press a hand-held button when they detected a target stimulus. They were instructed to respond accurately without any emphasis on a speedy response in order to limit the possible contamination of the P300 with motor potentials. The task was practised for 3 min prior to each recording session to prevent learning effects and to familiarise the subjects with the task.

2.3.4. EEG acquisition

The EEG was recorded in a magnetically shielded and sound-attenuated room. The visual stimuli were presented on a flat LCD screen located outside the room. Subjects were able to see the screen through magnetically shielded glass. The auditory stimuli were presented from headphones placed on both ears. EEG was recorded on a commercially available EEG acquisition system (Nuamps®). Electrodes (Ag/AgCl) were positioned following the 10–20 system on a 32-channel electrode cap, using 19 electrodes (Medcat®). For the CNV recordings, a low-pass filter of 100 Hz and a high-pass filter of 0.01 Hz were applied. For the oddball paradigm a low-pass filter of 100 Hz and a high-pass filter of 0.1 Hz were applied. The sample frequency was 512 Hz and analogue-digital conversion was 20 bit. Electrode impedance was kept below 5 kΩ. A reference electrode was placed on the right ear lobe. To control for possible vertical eye movements, an electro-oculogram (EOG) electrode was placed 1 cm under the midline of the right eye. A ground electrode was placed on the forehead, at Fpz position. Neuroscan® 4.3 software was used for EEG recording and analyses.

2.4. ERP data analyses

2.4.1. CNV

The interval of 1 s prior to the imperative stimulus was analysed for CNV. Pre-processing procedures included ocular artefact reduction, low-pass filtering (0–30 Hz, 12 dB/oct), baseline correction and averaging of the data. The interval between 900 and 1000 ms after the warning stimulus was used for the baseline correction procedure. The peak amplitude of the epochs was calculated for each subject. The reaction times were calculated relative to onset of the imperative stimulus. Mean reaction times over the 36 trials were calculated; trials with reaction times faster than 60 ms and slower that 600 ms were omitted from analysis.

2.4.2. Oddball paradigm

The pre-processing steps of the oddball data included high-pass filtering (>1 Hz 12 dB/oct), ocular artefact reduction, low-pass filtering (<30 Hz, 12 dB/oct), baseline correction and averaging. Peak latencies were determined relative to the stimulus onset. The ERP epochs for the target and non-target tones were analysed separately. Amplitudes of the P300 and N200 were defined relative to a baseline period, 100 ms prior to stimulus onset. An automated peak-picking procedure was used to determine peak amplitudes and latencies. N200 was defined as the minimum point between 200 and 250 ms post-stimulus. The P300 was defined as the maximum point between 300 and 600 ms post-stimulus. There were no reaction times registered in the oddball paradigm.

2.4.3. Statistical analysis

The primary endpoints in the current study were CNV amplitude, P300 amplitude and latency and reaction times. Statistical analysis was done with SPSS for Mac (version 16.0). Significance levels associated with the differences in ERP amplitude and latency between the AD, MCI and control groups were calculated for Fz, Cz and Pz using ANOVA. Post-hoc Bonferonni correction for multiple comparisons was used. For the ANOVA analysis, the mean ERP amplitude and latency over the two sessions were calculated for each subject and each electrode.

Reaction times were averaged for each subject and each session. ANOVA with post-hoc Bonferonni correction was used to calculate between group differences.

To examine test-retest reliability of the ERP, a paired samples *t*-test was used to evaluate potential differences between the two sessions for the Fz, Cz and Pz electrode. Furthermore, Pearson's correlation coefficient between the sessions was calculated at Fz, Cz and Pz. These analyses were done for each patient group separately. The same statistics were applied to evaluate the TRR of the reaction times. To evaluate the relation between the outcome measures and cognitive performance on ADAS-cog, Pearson's correlation coefficient between the outcome measures and ADAS-cog was calculated.

3. Results

3.1. Subjects' demographics

The fifteen AD patients had a mean age of 75.2 (SD 6.9) and a mean score on the mini mental state examination (MMSE) of 20.8 (SD 2.7, range 17–26). Eleven of the AD patients were male. The 20 MCI patients included had a mean age of 70.6 (SD 7.2) and a mean MMSE of 26.3 (SD 1.6, range 23–29). Twelve of the MCI patients were male. The 20 healthy control subjects included had a mean age of 69.5 (SD 6.1) and a mean MMSE of 29.3 (SD 0.8, range 28–30). Twelve of the healthy control subjects were male. There was no statistical difference in age between the groups ($F_{2,52} = 2.2$, $p = 0.14$).

3.2. Neuropsychological testing

Average ADAS-Cog scores were: 19.6 (SD: 5.9; *n* 15) in the AD group; 10.8 (SD: 4.5; *n* 20) in the MCI group; and 5.8 (SD: 2.6; *n* 20) in the control group. These scores showed a significant difference between the groups in the expected direction ($F_{2,52} = 84.8$, $p < 0.001$). Results from the NART showed that the mean estimated pre-morbid intelligence was 96.9 ($F_{2,52} = 2.3$, $p = 1.03$) and that it did not differ between the groups.

3.3. Test–retest reliability

The results from the TRR analysis are presented in Table 1. This table shows the values measured on Cz, which are comparable to the other midline electrodes.

The RS measured during the SRT, CRT and CNV task showed no significant difference between the test sessions. The correlation between the sessions for the RT measured during SRT was high for the AD group and moderate for the MCI and control group. The correlation between the sessions for the RT in the CRT was high to very high in all the patient groups.

The correlation between the sessions for the RT measured during CNV was high for the MCI and control group, but low for the AD group.

The CNV amplitude showed no significant difference between the sessions, and the correlation between the sessions was high in the MCI and control group but low in the AD group. In the oddball paradigm, the P300 showed a significant difference between the sessions for latency in the AD group. The correlation for P300 amplitude was high for all the groups. The P300 latency showed a moderate correlation between the sessions for the AD group and low correlation between the sessions for the MCI and control group. The N200 peak showed no differences between the sessions. The correlation was low except for the N200 amplitude in the AD group.

3.4. Group differences response speed tasks

The results of the RS tasks are presented in Table 2. In the SRT, ANOVA analysis showed significantly longer reaction times in AD compared to MCI and controls ($F_{2,52} = 7.5$, $p = 0.002$). Bonferonni post-hoc analysis showed that there was no significant difference between MCI and controls.

In the CRT, ANOVA analysis showed significantly longer reaction times in AD compared to MCI and controls ($F_{2,52} = 13.2$, $p < 0.000$). Bonferonni post-hoc analysis showed that there was no significant difference between MCI and controls.

The reaction times measured in the CNV paradigm showed a significant difference between the groups ($F_{2,52} = 4.17$, $p = 0.02$). The RT was highest for the AD group and lowest for the control group. Bonferonni post-hoc analysis showed that there was only a significant difference between the AD and control group in this respect.

Table 2
Event related potential amplitude and latency and reaction time. All measures from Cz electrode except P300 (Pz).

Component group	Amplitude (μV)	Latency (ms)
CNV (ns)		
AD	−3.8 ± 2.7	N.A.
MCI	−4.1 ± 4.2	N.A.
Control	−3.5 ± 2.6	N.A.
P300[a,b]		
AD	4.8 ± 2.0	433.6 ± 51.5
MCI	7.0 ± 3.5	422.9 ± 34.7
Control	8.4 ± 3.1	395.1 ± 30.7
N200 (ns)		
AD	−3.9 ± 5.3	257.3 ± 32.5
MCI	−3.2 ± 3.7	253.1 ± 29.3
Control	−3.7 ± 3.4	247.1 ± 27.8
Reaction time (CNV)[c]		
AD		342.1 ± 66.9 (ms)
MCI		302.5 ± 54.2 (ms)
Control		287.4 ± 59.2 (ms)
Reaction time (SRT)[c]		464.31 ± 192.6 (ms)
AD		355.79 ± 81.2 (ms)
MCI		
Control		305.47 ± 45.0 (ms)
Reaction time (CRT)[c]		645.71 ± 210.5 (ms)
AD		459.95 ± 87.9 (ms)
MCI		
Control		411.22 ± 56.7 (ms)

N.A.: not applicable and ns: No significant between group differences.
[a] Significant difference between the groups in amplitude in targets ($p < 0.05$).
[b] Significant difference between the groups in latency in targets ($p < 0.05$).
[c] Significant difference in RT between the groups ($p < 0.05$).

3.5. Group differences CNV paradigm

The results of the ERP analysis for the CNV paradigm are presented in Table 2. The analysis showed that the task provoked a CNV complex in all subjects. There were, however, no statistical differences between the AD, MCI and control group for the amplitude of the CNV complex ($F_{2,52} = 0.06$, $p = 0.94$), as can be seen in Table 2. The average number of 'clean' EEG trails that could be included in the analysis were; AD: 24, MCI: 26, controls 29. The number of trails was significantly lower for the AD group compared to the MCI and control group ($F_{2,52} = 3.7$, $p = .036$).

3.6. Group differences oddball paradigm

The results of the ERP analysis for the oddball paradigm are presented in Table 2. Figs. 1 and 2 show the mean amplitudes and latencies of P300 over Fz, Cz and Pz. The P300 showed a significant

Table 1
Test retest reliability of outcome measures. A paired samples *t*-test was performed per group to examine differences between the sessions. Pearson's R reflects the correlation between the sessions.

	Alzheimer's disease (*N* = 15)				Mild cognitive impairment (*N* = 20)				Control group (*N* = 20)			
	Mean s1	Mean s2	Sig. *p*	Pearson's *R*	Mean s1	Mean s2	Sig. *p*	Pearson's *R*	Mean s1	Mean s2	Sig. *p*	Pearson's *R*
RT SRT (ms)	474.0	456.2	0.73	0.82*	363.2	343.6	0.49	0.38	307.5	314.2	0.48	0.48
RT CRT (ms)	597.5	616.8	0.78	0.81*	455.3	458.9	0.78	0.90*	410.8	415.1	0.75	0.71*
RT CNV (ms)	342.0	367.6	0.41	0.24	321.8	350.6	.06	0.87*	289.2	278.1	0.39	0.69*
N200 amplitude (μV)	−4.1	−4.4	0.65	.94*	−2.9	−3.1	0.89	0.42	−4.2	−3.6	0.56	0.32
Latency (ms)	262.0	255.3	0.51	0.48	261.1	255.3	0.44	0.48*	239.6	249.2	0.26	0.49*
P300 amplitude (μV)	5.2	4.2	0.30	0.65*	6.1	6.5	0.26	0.77*	7.7	8.2	0.66	0.72*
Latency (ms)	416.0	427.6	0.04	0.73*	416.1	403.5	0.39	0.42	393.6	397.2	0.51	0.57*
CNV amplitude (μV)	−4.8	−3.7	0.49	−0.19	−2.9	−3.7	0.22	0.67*	−3.7	−3.7	0.99	0.63*

* $p < 0.05$.

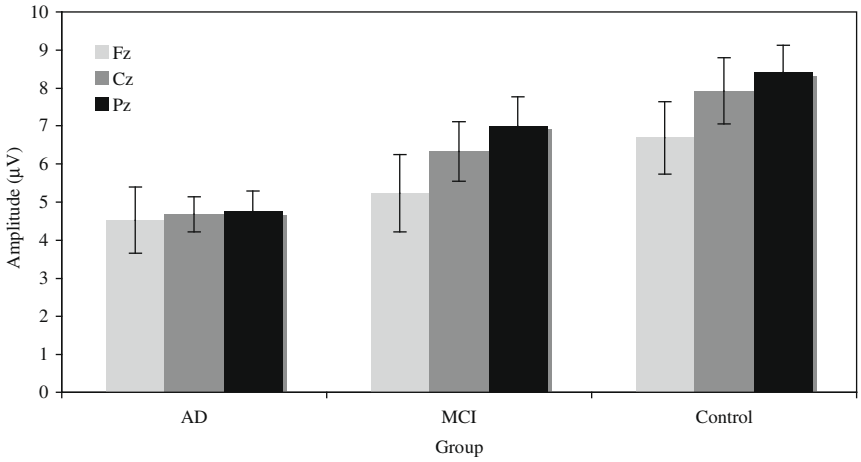

Fig. 1. P300 amplitudes for Fz, Cz and Pz. Differences are significant ($p < 0.05$) for Cz and Pz between the AD and control group.

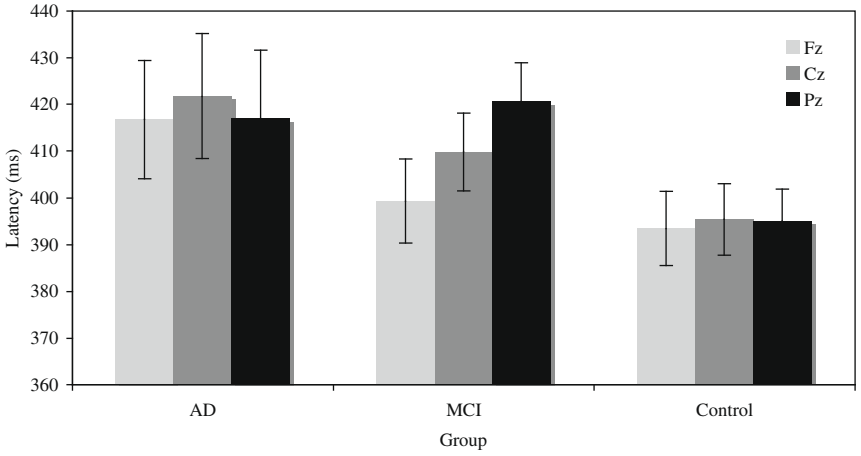

Fig. 2. P300 latency for Fz, Cz and Pz. Differences are significant ($p < 0.05$) for Fz and Cz between the AD and control group and for Pz between the MCI and control group.

difference between the groups for amplitude at Cz ($F_{2,52} = 4.0$, $p = 0.025$), and Pz ($F_{2,52} = 5.94$, $p = 0.005$). Post-hoc Bonferonni showed that the amplitudes at Cz and Pz separated the AD group from the control group. The P300 latency was significantly longer for the AD and MCI group compared to the control group ($F_{2,52} = 4.77$, $p = 0.013$). Post-hoc Bonferonni showed that Fz and Cz separated the AD and control groups. The Pz electrode separated the MCI and control group. There was no significant difference in latency between the AD and MCI group. The N200 component was analysed to ensure that P300 differences are not related to amplitude and latency differences in the N200 component. The N200 showed no significant differences between the groups on amplitude ($F_{2,52} = 1.72$, $p = 0.189$) and on latency ($F_{2,52} = 1.54$, $p = 0.223$). The average number of 'clean' trails that could be used for the analysis of the P300 and N200 components was; AD: 25, MCI: 27, controls: 28. There was no significant difference in the number of 'clean' trails between the groups ($F_{2,52} = 2.1$, $p = 0.132$).

3.7. Speed of response execution

An aspect that was not captured with the response speed task or ERP is the speed of response execution. As a post-hoc analysis we subtracted P300 latency from the reaction time in the CRT to capture this aspect. This analysis showed that this motor component takes significantly longer in the AD group compared to MCI and control groups ($F_{2,52} = 7.86$, $p = 0.001$).

3.8. Correlation between reaction time and CNV and P300

The correlation between RS and the CNV was analysed and showed no significant correlation between these measures, as can be seen in Table 3.

The correlation between the RS measured in the CRT and P300 amplitude showed only a significant negative correlation at Fz, Cz

Table 3
Correlations between the RT and ERP's.

	Pearson's *R*	Sig. *p*
CNV amplitude		
Fz	0.14	0.367
Cz	0.24	0.113
Pz	−0.19	0.212
P300 amplitude		
Fz	−0.38	0.011*
Cz	−0.39	0.009*
Pz	−0.42	0.004*
P300 latency		
Fz	0.30	0.047*
Cz	0.24	0.235
Pz	0.14	0.875

The RT in the CNV is measured during the CNV paradigm.
The P300 is correlated to the RT in the CRT.
* $p < 0.05$.

Table 4
Correlation between the outcome measures and ADAS-cog score.

	Pearson's *R*	Sig. *p*
SRT	0.41	0.005*
CRT	0.72	0.000*
RT (CNV)	0.37	0.015*
CNV amplitude		
Fz	−0.27	0.067
Cz	−0.33	0.025*
Pz	−0.37	0.010*
P300 amplitude		
Fz	−0.13	0.351
Cz	−0.29	0.032*
Pz	−0.44	0.001*
P300 latency		
Fz	0.21	0.131
Cz	0.22	0.110
Pz	0.27	0.047*

The correlation coefficient is reflected by Pearson's *R*.
* $p < 0.05$.

and Pz. The P300 latency showed a significant correlation at Fz only, as can be seen in Table 3.

3.9. Correlation with ADAS-cog

The correlations between ADAS-cog and the outcome measures of the current study are presented in Table 4. The RS measured in the SRT and CNV tasks show a moderate correlation with the ADAS-cog score. The RS measured during the CRT showed a high correlation with ADAS-cog.

The CNV amplitude showed a moderate negative but significant correlation at the Cz and Pz electrodes with ADAS-cog. The P300 amplitude showed a moderate but significant correlation with ADAS-cog on Cz and Pz. The P300 latency showed a significant correlation with ADAS-cog only at Pz.

4. Discussion

The main result of the current study is that RS as measured with SRT and CRT is slower in AD patients than in MCI and controls. Furthermore, group differences in RS are associated with differences in the P300 amplitude and latency.

The most prominent difference between the groups was increased RT in AD in the CRT, a finding congruent with earlier studies (Gordon & Carson, 1990; Levinoff et al., 2005). There was no difference between MCI and controls on RT in any of the RS tasks, which is in contrast with Levinoff et al. (2005). The patient groups in Levinoff's study and the current one are comparable with regard to the age, MMSE and years of education. However, the RS in the MCI and control group in Levinoff's study were markedly slower than in the current study, which might be explained by more extensive practise of the participants in the current study. The SRT and CRT further showed a satisfying TRR, a result comparable to an earlier study (Simpson, Wesnes, & Wilcock, 1991). Therefore we can conclude that RS tasks can reliably be used in the case of an older, cognitively impaired, population.

The P300 amplitude was reduced, and the latency increased in AD, which is in agreement with previous findings (Golob & Starr, 2000; Goodin & Aminoff, 1992; Polich & Corey-Bloom, 2005; Polich et al., 1990). Although decreased P300 amplitude and increased P300 latency are consistent findings in AD, some studies did not find differences in amplitude, latency or both (Duffy et al., 1984; Polich and Pitzer, 1999; Verleger et al., 1992). The TRR of the findings was satisfactory and in the same order of magnitude as reported earlier (Polich & Herbst, 2000). More importantly, the changes in P300 amplitude and latency were associated with changes in RS as measured by CRT. The correlation between P300 amplitude and latency and RS were analysed for the CRT only, as both the CRT and the oddball task require stimulus characterisation (ie left/right the CRT and target/non-target in the oddball paradigm). The other RS tasks; SRT and CNV did require such stimulus classifications.

High amplitudes and short latencies of the P300 were associated with faster responses. This relation has been shown in healthy subjects (Dimoska et al., 2006; Holm, Ranta-aho, Sallinen, Karjalainen, & Muller, 2006) and an MCI population, but not in AD (Williams et al., 1991). The P300 amplitude is sensitive to the amount of attention that is allocated for the detection of a stimulus. In undemanding tasks, such as the oddball paradigm, processing resources are focussed on detecting the deviant stimulus, resulting in higher P300 amplitude. When task demands increase, for example by more types of stimuli to attend to, the processing resources are allocated to more different types of stimuli, resulting in lower P300 amplitude and a longer latency (Polich, 2007). The general state of arousal also affects the P300 amplitude as passive processing of stimuli generally produce smaller P300 amplitudes than active stimulus processing (Polich, 2007). The decreased P300 amplitude in AD during the oddball task, suggests that the amount of attentional resources that are focussed on the detection of the deviant stimulus is lower. The increased P300 latency further suggests that the processes involved in evaluating and categorising the stimulus is less efficient in AD (Bashore, Osman, & Heffley, 1989). The current results provide support for the hypothesis that reduced access to attentional resources and impaired stimulus classification are relevant in explaining longer reaction times in AD.

The CNV amplitude showed no difference between the groups, which is in contrast with earlier studies (Golob & Starr, 2000; Zappoli et al., 1987). Furthermore, was there no significant correlation between the CNV amplitude and RS measured during CNV, while this would have been expected based on earlier studies (Brunia & Vingerhoets, 1980; Brunia & Vingerhoets, 1981; Haagh & Brunia, 1985). Since the length of the inter-stimulus interval affects the CNV amplitude (Van der Lubbe, Los, Jaskowski, & Verleger, 2004), the lack of a difference between the groups in the current study might be related to the short inter-stimulus interval (ISI) (i.e. 2 s) used. In an earlier pilot study we found that an ISI of 4 s was too long for the AD patients (data not published). Furthermore, the TRR of the CNV in the AD group was low. Despite extensive practise during each visit prior to the measurement, some patients especially in the AD group were not able to perform the CNV paradigm properly, resulting in a significantly smaller number of viable trials and less reliability. Another explanation might be that the low TRR is related to the relatively long time lag compared to other ERP (e.a. 2 s) between the warning stimulus and the CNV peak. This long time interval might induce more variance and noise, especially in the AD group. The methodological issues together with the low TRR make it impossible to conclude whether anticipatory behaviour as defined by CNV, has an effect on the slowed RS in AD.

The present study further showed that there was a significant difference between the groups in the speed of response execution. These results suggest that impaired response execution contributes to the slowed RS in AD. The finding that the motor component of response execution is slowed in AD is in agreement with previous work (Bellgrove et al., 1997; Camarda et al., 2007).

The correlation between ADAS-cog and the other measures in this study was highest for the CRT. Although the ADAS-cog does not specifically measure speed, attentional or executive processes, it is plausible that the performance of these processes have an effect on the overall performance on ADAS-cog. This probably

explains the high correlation between CRT and ADAS-cog performance. The CNV amplitude showed no significant correlation with ADAS-cog, which is not surprising since it did not separate the patient groups. The P300 amplitude and latency showed a moderate correlation with ADAS-cog, which was comparable with a previous report of the correlation between P300 and MMSE (Bennys, Portet, Touchon, & Rondouin, 2007).

A weakness of the current study was its cross-sectional design that did not allow us to evaluate the sensitivity of the measures for changes in longitudinal studies. Another weakness is that all subjects were recruited in a University tertiary reference centre. Therefore the results may not be applicable to the general AD and MCI population. A strong aspect of the study was that patients were accurately diagnosed in accordance with standardised research criteria. Another strong aspect was that none of the subjects used psychoactive or cholinesterase inhibiting drugs that could have biased the results. Furthermore, the TRR design provided insight in the reproducibility of the endpoints.

The current study showed that especially the stimulus evaluation and the response execution component are impaired in AD. The results furthermore show that RS measures are reproducible and sensitive in detecting differences in AD compared to MCI and controls. Altogether, the current study suggests that RS measures on a behavioural and psycho-physiological level deserve more attention as a possible marker for the diagnosis and to assess changes in AD.

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