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NEUROLOGY AND PRECLINICAL NEUROLOGICAL STUDIES - ORIGINAL ARTICLE

Altered N100-potential associates with working memory impairment in Parkinson's disease

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Abstract The diagnosis of cognitive impairment and dementia often occurring with Parkinson's disease (PD) is still based on the clinical picture and neuropsychological examination. Ancillary methods to detect cognitive decline in these patients are, therefore, needed. Alterations in the latencies and amplitudes of evoked response potential (ERP) components N100 and P200 have been described in PD. Due to limited number of studies their relation to cognitive deficits in PD remains obscure. The present study was designed to examine if alterations in the N100- and P200-potentials associate with neuropsychological impairment in PD. EEG-ERP was conducted to 18 PD patients and 24 healthy controls. The patients underwent a thorough neuropsychological evaluation. The controls were screened for cognitive impairment with Consortium to Establish Alzheimer's disease (CERAD)—testing and a normal result were required to be included in the study. The N100-latency was prolonged in the patients compared to the controls ($p = 0.05$). In the patients, the N100 latency correlated significantly with a visual working memory task ($p = 0.01$). Also N100 latency was prolonged and N100 amplitude habituation diminished in the patients achieving poorly in this task. We conclude that prolonged N100-latency and diminished amplitude habituation associate with visual working memory impairment in PD.

Keywords Evoked response potential · Cognition · Parkinson's disease

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Introduction

Parkinson's disease (PD) is a complex neurodegenerative disorder with motor, autonomous and cognitive symptoms. The motor symptoms dominate the clinical picture especially in the early stages of the disease. However, neuropsychological testing often reveals subtle cognitive changes typical of PD even at the early stages of the disease. Verbal and visual memory deficits, executive dysfunction, problems in language and attention are the most prevalent findings (Aarsland et al. 2008; Muslimovic et al. 2005; Pfeiffer et al. 2014; Uc et al. 2005) that in some patients deepen to the level of mild cognitive impairment (PD-MCI). As the disease progresses, the neuropsychological symptoms tend to advance and a substantial proportion of the patients with PD-MCI will develop Parkinson's disease dementia (PDD) during its course (Aarsland et al. 2003; Pigott et al. 2015; Riedel et al. 2008). Movement Disorder Society has recently published guidelines to diagnose both PD-MCI (Litvan et al. 2012) and PDD (Emre et al. 2007). According to the guidelines the diagnosis of PD-MCI and PDD are based on clinical and neuropsychological evaluation and ruling out other causes. As to date, there are no clinically applicable ancillary methods to establish PD-MCI or PDD. The situation is, therefore, different from the other common dementias, such as Alzheimer's disease and vascular dementia, where brain imaging findings are an essential

part of the diagnosis. New methods to examine cognition in PD are needed not only to diagnose dementia but also to identify at-risk patients to support the preservation of cognition and hopefully in the future offer medication to prevent future cognitive decline.

Electroencephalogram (EEG) with evoked response potentials (ERP) is a safe and non-invasive method in providing real-time information of the brain's response to sensory stimuli indicating not only stimulus detection but also ensuing conscious processing and orienting to novel stimuli. The ERPs have been examined in Parkinson's disease (Green et al. 1996; Hayashi et al. 1996; Hozumi et al. 2000; Katsarou et al. 2004), mild cognitive impairment (Bennys et al. 2011), Alzheimer's disease (Lai et al. 2010) and schizophrenia (Hasey and Kiang 2013) but there are no clinical applications in this field. In PD, the main focus of research has been on the late component P300, latency of which is usually prolonged in PD-MCI and PDD or the response may be absent altogether. P300 latency and amplitude have also been found to correlate to neuropsychological disturbances such as impaired executive function and verbal fluency indicating that alterations in P300 reflect frontal lobe dysfunction in PD (Chen et al. 2006; Tsuchiya et al. 2000).

Previous studies examining N100- and P200-potentials in PD are few and the results have been contradictory. The P200 response is considered to reflect conscious stimulus processing, which is often impaired or at least slowed in PD. Accordingly, the latency of P200 has been prolonged in some studies (Ebmeier et al. 1992; Hansch et al. 1982) but also normal results have been reported (Goodin and Aminoff 1987). Also the N100 latency has been reported normal in a number of studies concerning PD (Pekkonen et al. 1995; Vieregge et al. 1994). This is rather unexpected considering that the N100-potential most likely indicates stimulus detection and is, therefore, a measure of attention. It also associates with working memory by directing attention towards meaningful sensory information and blocking redundant stimuli (Lee et al. 2010). Sustaining attention and ignoring irrelevancies are often impaired in PD as well as is working memory. Considering these common cognitive deficits in PD as well as the cognitive processes that the P200- and N100 potentials are considered to measure, one would expect to find some association between P200- and N100 potentials and neuropsychological test performance.

In the present study, we conducted EEG with ERPs to 18 PD-patients and 24 healthy controls to investigate neurophysiological differences between the groups. We hypothesized that there would be alterations in the evoked response potentials in the patient group and that these alterations would reflect cognitive changes. Therefore, also a neuropsychological examination was done for patients.

Methods

14 PD-patients were recruited from a previously described population (Annanmaki et al. 2008). Due to dropouts in the primary sample, 4 additional consecutive PD-patients from the Neurological Outpatient Clinic of Jorvi Hospital of Helsinki University Central Hospital (HUCS) were invited to participate to the study. Inclusion criteria were idiopathic PD according to the UK Parkinson's disease Brain Bank Criteria(Hughes et al. 1992) and no clinical sign of Parkinson's disease dementia. Exclusion criteria were current use of medications affecting plasma uric levels other than levo-dopa. All the patients were examined by a neurologist to evaluate Unified Parkinson's disease Rating Scale (UPDRS) motor score, Hoehn&Yahr stage and Mini Mental State Examination (MMSE).

The controls were healthy volunteers from the hospital staff and their acquaintances with no sign of a neurological disease. Cognition was screened with Consortium to establish Alzheimer's disease (Cerad) -test series; a normal result was required to exclude mild cognitive impairment.

The demographic variables of the patients and controls are described in Table 1.

The study was approved by the Ethics Committee of Helsinki and Uusimaa Health District Area. All patients and controls signed a written informed consent.

Recording and quantification of electroencephalography

EEG recording and stimuli to induce ERP were done with a Cognitrace EEG/ERP-system version 3.3 (ANT Neuro, Enschede, The Netherlands, later abbreviated ANT). EEG was recorded with active shielded 64-channel Waveguard EEG caps with electrode layout following the international 10–10-system, electrode material Ag–AgCl (ANT) and with a DC-amplifier REFA-64 (ANT) using sampling frequency of 256 Hz. Cognitrace's amplifier uses inbuilt common average reference and it is constructed for direct current (DC) measurements and hence no high-pass filtering was applied. Impedances were made as low as possible. Timing of the different stimuli and responses were recorded together with the EEG.

Electro-oculogram (EOG) and electrocardiogram (ECG) were also recorded.

ERP-recording

During ERP-recording the patients were asked to follow a silent nature movie shown on a TV screen at a distance of 1.5 meters. Auditory stimuli were given through calibrated

Table 1 The demographic characteristics of the patients and controls as well as the latencies and amplitudes on the N100 and P200 potentials

	PD-patients ($n = 18$)	Controls ($n = 24$)
Age (range)	62 (42–71)	67 (60–79)
Gender, % of males	44%	33%
MMSE (range)	28 (23–30)	28 (28–30)
Duration of disease in years, mean (range)	6 (2–13)	
UPDRS, mean (range)	17 (1–51)	
Levo-Dopa usage	13	
Levo-Dopa dose, mean (range)	425 mg (250–875 mg)	
Dopamine agonist	12	
Selegiline	13	
N100 latency, mean (SD)	107.6 (23.2)*	95.1 (16.6)*
N100 amplitude, mean (SD)	−5.5 (2.0)	−5.3 (2.0)
P200 latency, mean (SD)	208.5 (30.7)	214.6 (21.5)
P200 amplitude, mean (SD)	5.3 (2.8)	4.3 (1.7)

* Mann–Whitney $p = 0.05$

headphones (Telephonics TDH-39P) and the patients were instructed not to pay attention to the tones.

The auditory ERPs were stimulated with pairs of tones with an inter stimulus interval (ISI) of 0.5 s. The responses to first and second tones of pairs with 0.5 s ISI were analyzed. ERP responses for 40 pairs of stimuli were averaged. The interval between pairs of stimuli were 12 s. The duration of the sound stimuli was 60.8 ms with rise and fall times of 11 ms each, leaving about 40 ms of steady plateau. Frequency of the stimuli was 1000 Hz and sound pressure level 60 dB above the hearing threshold, measured before the ERP recording and with the same tones as in the paradigm.

EEG-ERP analysis

The recordings were analyzed off-line using ASA software version 4.8.0 (ANT). Only channels of the international 10-20 system (Fp1, Fp2, F7, F3, Fz, F4, F8, T3, C3, Cz, C4, T4, T5, P3, Pz, P4, T6, O1 and O2) were considered in the analysis. All data was first inspected visually and the channels with excessive artifacts were removed prior to further analysis.

Pre-processing and analysis of the recordings were done with ASA-software version 4.6.2.0 (ANT). EEG was filtered with a bandpass of 0.3–30 Hz (12 dB/octave roll-off). Blink artefacts were removed by an algorithm based on spatial filtering (Ille et al. 2002). The manually selected prototypes of blinks per recording numbered at least ten. After artefact correction, the data were re-referenced to average reference and digitally filtered (high-pass 0.5 Hz, low-pass 30 Hz, 24 dB/octave). Remaining artefacts were excluded with amplitude criterion of ±75 μV before calculating the averaged waveforms.

The continuous EEG data was transformed off-line to 600 ms epochs, starting 100 ms before the onset of each stimulus. Finally, the averaged waveforms were baseline corrected by the 100 ms preceding the stimulus as the baseline. The amplitude and latency of N100 (Cz) and P200 (Cz) elicited by the auditory stimuli were measured with respect to the highest negativity in a 60-170 ms post stimulus time interval and the highest positivity in a 100–260 ms interval, respectively. The results of the automated peak detection were verified manually and corrections performed when necessary. Habituation of the N100 was calculated as the difference between the amplitudes elicited by the first and second tones of a pair with 0.5 ms ISI.

Neuropsychological examination

Finnish translations of both traditional neuropsychological tests and computerized tasks were applied.

Depression was assessed with a 21-item version of the Beck Depression Inventory (BDI-II). General knowledge was assessed with the information and similarities subtests of the Wechsler Adult Intelligence Scale Revised (WAIS-R).

Visuospatial and visuoconstructive functions were assessed with the block design and picture completion subtests of the WAIS-R. The digit span and digit symbol subtests of the WAIS-R were used to assess working memory. Verbal learning and memory were assessed with the logical memory subtest of the Wechsler Memory Scale-Revised (WMS-R) and the word list subtest of the Wechsler Memory Scale-Third Edition (WMS-III). Visual memory was assessed with the visual reproduction subtest of the WMS-R. Verbal fluency was assessed with two tests;

at first the subject was asked to list as many animals in a minute as he/she could and then words that begin with the letter K.

Executive function was assessed with two traditional neuropsychological tests as well as computerized tasks. Of the traditional tests, Trail making and Rule shift cards tests from Behavioral Assessment of the Dysexecutive syndrome (BADS) were used. Computerized tasks included seven tasks from the Cognispeed© for Windows 1.0 software (Revonsuo and Portin 1995). Reaction times were measured with simple-, two-choice- and ten-choice-tasks. Subtraction-, statement verification- and Stroop-type tasks were used to assess controlled cognitive processing and attention. Stroop effect was measured using two separate colour-word naming tests. First the subjects were asked to read colour names written in concordant colour (e.g., blue written in blue) to measure facilitation and then in discordant colour (e.g., red written in blue) to measure interference. Vigilance task was used to measure sustaining attention. This is a monotonous task lasting 15 min during which letters appear on the screen. Among them are two target letters occurring at random in a relatively slow rate.

Statistics

The statistical analysis was carried out using IBM SPSS Statistics 20 software. Due to the small sample size and non-normal distribution of some of the data, only non-parametric tests were applied. Kruskal–Wallis Test for Several Independent samples was used to analyze overall variance in the neuropsychological performance. The N100 latency median, P200 latency median and N100 amplitude habituation median were used as a grouping variable in the respective analysis. Mann–Whitney test was used to compare the mean latencies and amplitudes of N100 and P200 potentials and Spearman rank to measure correlation between the neurophysiological and neuropsychological parameters.

Results

The PD-patient's and controls clinical and demographic characteristics as well as the latencies and amplitudes of N100 and P200 are described in Table 1. Three patients did not attend to the neuropsychological evaluation leaving 15 patients for the respective analysis. The patients and controls were age matched apart from one outlier in the patient group (a 43 year old woman). The statistical analysis was repeated after the exclusion of the outlier and the results did not change significantly.

The N100 latency was prolonged in the patients compared to the controls with borderline significance (Mann–Whitney, $p = 0.05$). There were no other significant differences in the N100 and P200 latencies or amplitudes between the two groups. Figure 1 shows the ERP grand averages for the patients and controls. The habituation of the N100-amplitude was more pronounced in the controls compared to the patients, though this finding did not reach statistical significance.

In the Kruskal–Wallis test the performance in several neuropsychological tests varied according to N100 latency and amplitude habituation but there was no variance with respect to the P200 latency. The results of the Kruskal–Wallis test are displayed in Table 2. The neuropsychological tests with statistically significant variance were chosen for further statistical analysis.

In the patient group, the N100 latency showed a significant negative correlation with the delayed visual reproduction of the WMS-R (Spearman rank $R = -0.62$, $p = 0.010$) and a trend towards negative correlation with the immediate recall of the word list of the WMS-III (Spearman rank $R = -0.53$, $p = 0.056$). Habituation of the N100-amplitude correlated with delayed visual reproduction (Spearman rank $R = 0.57$, $p = 0.026$). The patients were divided into two groups according to the median of the delayed visual reproduction result. The patients with above median result had shorter N100 latencies and stronger habituation as shown in Table 3.

There was no correlation between the N100 latency or habituation and age, disease duration from the diagnosis, UPDRS-motor score and daily levo-dopa dose in the patients.

Discussion

In the present study the N100 latency was prolonged in PD-patients compared to healthy controls. This finding is in accordance with previous studies by Jiang et al. (2000) and Raudino et al. (1997). The latter also performed neuropsychological testing but did not find an association between cognition and the N100-potential. Interestingly, the N100 latency has been reported normal in a previous study concerning amnestic MCI and Alzheimer's disease (Lai et al. 2010) suggesting that prolonged latency of the N100 might aid in differentiating PD-related cognitive decline from these other common neurocognitive disorders.

The association of the N100 latency and amplitude habituation with a visual working memory task is interesting considering that problems in visuospatial abilities and working memory are common even in the early stages of PD (Aarsland et al. 2008; Kandiah et al. 2009; Muslimovic et al. 2005; Uc et al. 2005). Although at this stage the neuropathological changes of PD are confined to brain stem and basal ganglia (Braak et al. 2003), the ensuing

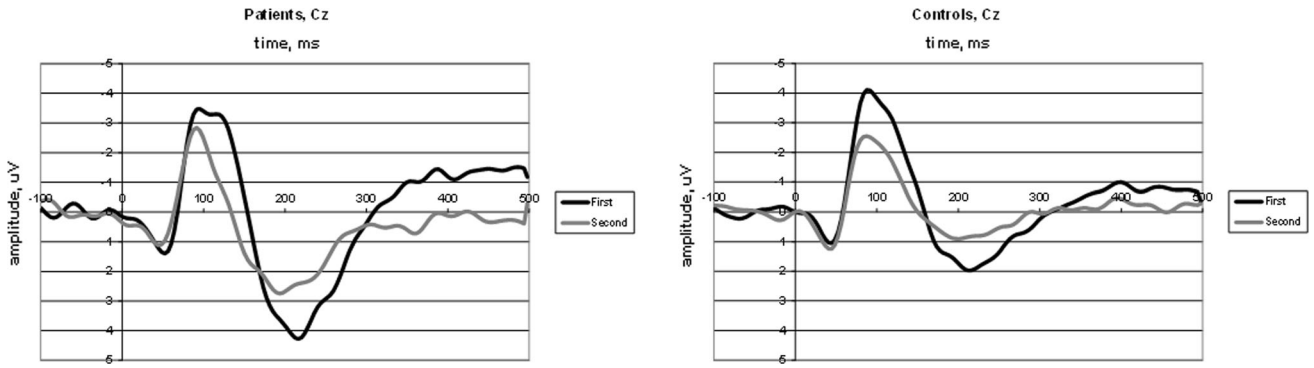

Fig. 1 Auditory event-related potentials in response to the first (*black*) and second (*gray*) tone of a pair of tones (ISI 0.5s) measured at the central (Cz) electrode location

Table 2 The results of the Kruskal–Wallis analysis of variance

Neuropsychological test	Grouping variable N100 Latency median	Grouping variable N100 amplitude habituation median
Verbal fluency (animals)		
Verbal fluency (letter K)		
Rule shift cards		
Word list A (immediate)	$p = 0.03$	$p = 0.04$
Word list B		
Word list A (delayed)		$p = 0.03$
Logical story	$p = 0.05$	
Visual reproduction (immediate)		
Visual reproduction (delayed)	$p = 0.003$	$p = 0.02$
Digit span		
Similarities		
Picture completion		
Block design	$p = 0.05$	$p = 0.01$
Trail making A		
Trail making B		
Simple reaction time		
Two-choice reaction time		
Ten-choice reaction time		
Subtraction		
Statement verification		
Stroop		
Stroop (interference)		
Vigilance		

Table 3 The difference between the N100 latency and amplitude habituation in the patient groups defined by the performance in the delayed visual reproduction test

	Delayed visual reproduction above median ($n = 7$)	Delayed visual reproduction below median ($n = 8$)	Mann–Whitney
N100 Latency, mean (SD)	95.5 (11.6)	131.7 (21.9)	$p = 0.07$
N100 Amplitude habituation, mean (SD)	−1.7 (1.8)	−3.4 (1.6)	$p = 0.04$

dopaminergic defect disturbs connections between striatum and frontal cortex. This frontostriatal dysfunction leads to early cognitive alterations such as poor attention and diminished working memory capacity (Jokinen et al. 2013; Lewis et al. 2003). Attention and working memory capacity are closely interconnected as previous studies indicate that working memory is under attentional control that is mediated by basal ganglia (Fielding et al. 2006; Lee et al. 2010; McNab and Klingberg 2008). The memory problems in PD may, therefore, partly be due to poor ability to filter out irrelevant information from taking space in easily overloading working memory. The N100 evoked response potential is considered a measure of focusing attention, demanding also suppression of irrelevant stimuli. The patients' difficulty in focusing attention would, therefore, explain the close connection of prolonged N100 latency and poor amplitude habituation with the visual working memory task. This hypothesis is in conjunction with previous work presented by Lijffijt et al. (2009), Brumback et al. (2004) and Soininen et al. (1995), who found N100 response to be associated with visual working memory and working memory span. The studied subjects were healthy volunteers from a community sample as there are no studies including PD-patients. These previous studies increase our knowledge of the N100 potential as a measure of attention and working memory although the number of subjects in the studies has been rather low. Also our results must be interpreted with caution considering the small sample size. Larger studies are needed to corroborate our findings and also to better control for possible confounding factors such as medication and mood.

Why haven't the previous studies found consistently prolonged N100 latency or altered N100 habituation in PD? All previous studies, as well as ours, include only a small number of patients with a large spectrum of age, duration of disease and disease severity. The statistical power to detect subtle differences in these patient samples has been rather low. Also methodological differences in EEG-ERP recordings and signal averaging may explain the inconsistent findings.

The treatment of cognitive decline remains an enigma. There is some evidence that life style factors such as exercising and social activity, as well as optimal treatment of vascular risk factors may help to preserve cognition in neurodegenerative diseases such as PD (Ngandu et al. 2015). Exercise has also been found to cause augmentation of the N100 amplitude in healthy elderly adults (Chang et al. 2013) and our findings further supports regular exercise as a part of PD treatment regimen.

The obvious limitation of our study is the small sample size, with many PD-patients not participating because of the laborious protocol.

We conclude that prolonged N100 latency and poor amplitude habituation have interesting associations with visual working memory in PD. Ours study adds to knowledge of the mechanisms of working memory impairment in PD and corroborates previous findings that link attention and working memory capacity. As to date there is too little information to judge if a clinical application of ERP-measurement would be useful in the diagnosis of cognitive decline and dementia in PD.

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Compliance with ethical standards

Conflict of interest We declare that we have no conflict of interest.

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