

Event-related potentials for response inhibition in Parkinson's disease

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Abstract

This study investigated inhibitory function in patients with Parkinson's disease (PD) by recording event-related brain potentials (ERPs) during a Go/NoGo task. Fourteen healthy volunteers and 13 patients with PD without dementia performed a cued continuous performance test that included Go and NoGo trials. The peak latency, amplitude, and topographic distributions of the ERPs to Go and NoGo stimuli were analyzed. Cognitive function was evaluated using the Wisconsin Card Sorting Test (WCST), Kana Pick-out Test, and Verbal Fluency Test (VFT). Performances in the WCST and VFT were significantly impaired in the PD group as compared with the control group. The PD group had significantly higher rates of omission and commission errors during the ERP task. The ERP study found no differences in the latency and amplitude of the Go-P3 between the two groups. By contrast, the NoGo-P3 latency was significantly longer in the PD group than in the control group. The amplitudes of the NoGo-P3 and NoGo-N2 were also significantly smaller in the PD group than in the control group. The NoGo-P3 latency was significantly correlated with the Kana Pick-out Test and VFT scores. The NoGo-P3 amplitude was significantly correlated with the WCST and VFT scores, as well as with the number of commission errors. There were no significant correlations between the cognitive function tests and either the Go-P3 or NoGo-N2 measures. The behavioral and ERP data suggest that there is selective impairment of inhibitory function in PD and that this deficit may be related to impaired inhibitory executive function in the frontal lobe.

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1. Introduction

Parkinson's disease (PD) is characterized by motor impairment, such as bradykinesia or rigidity, but clinical evidence suggests that PD patients develop deficits across many cognitive functions (Brown & Marsden, 1990; Charbonneau, Riopelle, & Beninger, 1996; Gotham, Brown, & Marsden, 1988). One of the focuses in the study of impaired cognitive functions in PD is the executive control system in the frontal lobe. For example, PD patients have impaired attentional set-shifting (Raskin, Borod, & Tweedy, 1992) and delayed-response tasks (Labutta, Miles, Sanes, & Hallett, 1994), which often result from frontal lobe pathology (Pascual-Leone & Hallett, 1994). In addition to attentional or working memory deficits, PD patients have difficulty inhibiting an ongoing reaction independent of general cogni-

tive impairments (Franz & Miller, 2002; Gauggel, Rieger, & Feghoeff, 2004). Studies using positron emission tomography (PET) (Buchsbaum et al., 1990), near-infrared spectroscopy (Fallgatter & Strik, 1997), and functional magnetic resonance imaging (fMRI) (Casey et al., 1997; Konishi, Nakajima, Uchida, Sekihara, & Miyashita, 1998) have shown that activation of the inferior frontal area is associated with the inhibition of motor responses. The anterior cingulate cortex is also an important locus within a distributed network for the inhibitory control of behaviors such as in the Stroop interference task (Bench et al., 1993; Cabeza & Nyberg, 2000; Carter, Mintun, Nichols, & Cohen, 1997; Taylor, Kornblum, Minoshima, Oliver, & Koeppe, 1994). Although recent neuroimaging studies have revealed the anatomical locus of cognitive inhibitory function in the normal population, the neural substrates for impaired inhibitory function in neuropsychiatric disorders including PD remain unclear.

Event-related brain potentials (ERPs) can reveal the time course of information processes with high temporal resolu-

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tion and have provided electrophysiological indices for cognitive functions in PD patients. Aotsuka, Weate, Drake, and Paulson (1996) studied conventional auditory P3 and contingent negative variation (CNV) in patients with PD and found longer latencies and smaller amplitudes of N2 and P3 in PD patients as compared with controls. They also demonstrated that the P3 latency was correlated with cognitive function, whereas the CNV amplitude was correlated with measures of motor disability. Their study suggests that extrastriatal dopaminergic systems modulate the N2 and P3 components associated with cognitive impairments. It has also been reported that P3 latency to novel stimuli was prolonged and the amplitude was reduced over the frontal site in PD patients (Tsuchiya, Yamaguchi, & Kobayashi, 2000). The prolonged latency and frontal amplitude reduction were correlated with poor performance in the Wisconsin Card Sorting Test. These reports suggest that dopamine deficiency in PD patients affects neurophysiological indices related to various aspects of frontal cognitive functions. In this study, we sought electrophysiological evidence for impaired inhibitory control in PD by using an ERP technique. We recorded ERPs in PD patients during a Go/NoGo task, which is a prevailing paradigm for investigating inhibition.

Two major ERP components have been investigated using Go/NoGo tasks. First, a negative potential within a latency range of 200–300 ms (N2 component) is generated in NoGo trials (Eimer, 1993; Fallgatter, Mueller, & Strik, 1999; Fallgatter & Strik, 1999; Jodo & Kayama, 1992). Falkenstein, Hoormann, and Hohnsbein (1999) reported that the NoGo-N2 was attenuated and delayed in subjects with high false alarm rates compared with subjects with low false alarm rates. Geczy, Czigler, and Balazs (1999) found that the N2 amplitude in response to NoGo stimuli increased after Go cues, which might be related to the increased effort of activating a response inhibition system and interrupting preparation for response execution. Pliszka, Liotti, and Woldorff (2000) also reported that normal children had a negative wave (N2) over the right inferior frontal cortex when response inhibition was required, whereas it was markedly reduced in children with attention-deficit/hyperactivity disorder. These findings suggest that NoGo-N2 reflects an inhibitory neuronal process. Second, a positive wave peaking between 300 and 600 ms (P3 component) is modulated in Go/NoGo conditions. The frontal P3 amplitude is larger in the NoGo than in the Go condition (Eimer, 1993; Kopp, Mattler, Goertz, & Rist, 1996). Topographically, the P3 in the Go condition is maximal at centroparietal sites, whereas the NoGo-P3 is maximal at frontocentral sites (Fallgatter et al., 1999; Fallgatter & Strik, 1999). A three-dimensional source localization analysis showed that P3-related neural activity occurred in the right frontal lobe during NoGo trials as compared with Go trials (Strik, Fallgatter, Brandeis, & Pascual-Marqui, 1998). Using a high-density EEG recording system, we have also demonstrated that NoGo-P3 source activity was located in the left lateral orbitofrontal area, whereas the main Go-P3 source activity was located in the parietal area (Bokura, Yamaguchi, &

Kobayashi, 2001). Therefore, we speculate that a Go/NoGo paradigm would be suitable for elucidating the physiological basis of the impaired inhibitory control in PD.

Several NoGo-ERP studies in PD have used a Go/NoGo paradigm (Pulvermuller et al., 1996; Iijima, Osawa, Ushijima, & Iwata, 1999). For example, Pulvermuller et al. (1996) found that the P3 amplitude was significantly reduced in PD patients after Go stimuli and was maximally attenuated after NoGo stimuli, as compared with controls. Their study suggests that an inhibitory component in executive function is selectively impaired in PD patients. However, it is not clear whether the electrophysiological measures actually reflect behavioral impairment related to inhibitory function in PD. Here, we investigated frontal lobe functions and Go/NoGo ERPs in patients with PD to test the hypothesis that PD patients show selective abnormalities in ERPs related to NoGo trials in comparison with controls and that these changes are correlated with impaired neuropsychological measures of inhibitory functions in PD. Our findings should extend knowledge of the neurophysiological basis for the inhibitory aspect of the behavioral deficits in PD.

2. Methods

2.1. Subjects

This study examined 13 patients with non-dementia PD (5 females and 8 males, age 71 ± 9.7 years (mean $\pm$ S.D.)), and 14 healthy volunteers as control subjects (7 females and 7 males, age 71 ± 6.5 years). None of the participants had a history of cerebral infarction, neurological disease (except PD), or psychiatric illness (such as depression). All of the subjects were right handed, and none were taking psychotropic drugs. The demographic data for the patients with PD are presented in Table 1. Cognitive functions were estimated using the revised version of the Hasegawa Dementia Scale (HDS-R), which is the most popular verbal intelligence scale for the elderly in Japan. The maximum score is 30 points, and the cut-off for dementia is 20 points. No patients had an HDS-R score of less than 20 points. The education level was the same in the PD and control groups (9.8 ± 2.4 years versus 10.1 ± 2.5 years). All the patients were receiving L-dopa therapy and were at clinical stage 2–4 using Hoehn & Yahr's classification (Hoehn & Yahr, 1967). All of the subjects gave informed consent, and the study was approved by the review board of our university.

2.2. Stimulus and experimental paradigm

Each subject was seated with the head on a chin-rest at 60 cm from a computer screen in an electrically shielded, dimly lit room. The experiment consisted of 500 stimuli. Nine single digits (1–9) were used as the stimuli, presented sequentially one at a time in a pseudo-random order. All the digits were presented for 500 ms, and the interstimulus in-

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