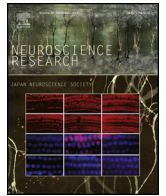




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Parkinson's disease patients showed delayed awareness of motor intention

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ABSTRACT

Although dopamine plays an important role for motor control and modulates the frontal function via basal ganglia-thalamo-cortical loop, it is not known whether dopamine can affect the awareness of motor intention or not. To test this hypothesis, we applied Libet's clock paradigm to Parkinson's disease (PD) patients. Thirteen PD patients and 13 age-matched, healthy controls took part in the experiment which consisted of three judgment paradigms: W, M and S judgment. In W and M judgments, subjects were asked to press the key at self-willed timing. In W judgment, subjects reported the location of the clock's hand when they became aware of the intention (W-time). In M judgment, subjects reported the time when they became aware of the actual movement (M-time). In S judgment, subjects reported the time of the electrical stimulation given to their hand (S-time). W-time was significantly shorter in PD patients than in healthy control subjects while M-time and S-time were not different between the two groups. Delayed awareness of motor intention but not of action in PD patients might be related to dopamine depletion in those patients.

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1. Introduction

In everyday life, we experience “free will” when we act voluntarily with prior decision and intention to perform a certain action. However, in the light of recent progress in human neuroscience this apparent link between the intention and action is not as straightforward as it appears. Significant temporal gap between them and the possible existence of subconscious or automatic intention urged some investigators to cast serious doubts on the concept of “free will” (Libet et al., 1982).

Libet's classic experiment using a rotating clock (Libet et al., 1983) revealed that the awareness of the intention to move occurs 200 ms before the actual action and that the electroencephalographic activity precedes this intention by 300 ms. Neurophysiologic studies consistently showed that the implicit

motor preparation measured by cortical slow potentials or change in neural oscillations can start more than 1 s earlier than the movement onset (Kornhuber and Deecke, 1965; Shibasaki, 2012; Shibasaki and Hallett, 2006). Moreover, one recent functional MRI study reported the time delay of 10 s or more between the subconscious brain activation and actual overt movement (Soon et al., 2008). As for the brain representation of intention, human neuroimaging and lesion studies implicated the medial frontal areas (pre-SMA/SMA proper) and prefrontal-parietal networks for relevant cortical regions (Cunnington et al., 2002; Lau et al., 2004; Nachev et al., 2005; Sirigu et al., 2004; Soon et al., 2008).

Although the functional importance of the motor loop of the basal ganglia-thalamo-cortical network for controlling volitional movements has been suggested (Alexander et al., 1986; Rouiller et al., 1994; Sakai et al., 1999; Schell and Strick, 1984; Wiesendanger and Wiesendanger, 1985) and dopamine plays an essential role in motor control as well as motivation and modulates the prefrontal and frontal function via basal ganglia thalamo-cortical loop (Tinaz et al., 2010; Zgaljardic et al., 2003), behavioral studies in patients with dopamine depletion investigating the timing of motor intention have never been conducted.

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Striatal dopamine depletion due to degeneration of the nigrostriatal dopaminergic neuron causes motor disturbance of Parkinson's disease (PD), where the self-willed movement initiation without external cues is most severely disrupted. To test whether the perceived times of actions and intentions are abnormal in PD patients without medication, we applied Libet's clock paradigm (Libet et al., 1983) to patients and age-matched controls.

Since previous studies showed the deficits of timing discrimination in PD patients (Artieda et al., 1992; Fiorio et al., 2007), the use of Libet's task in those patients has some methodological limitations. Thus, we used the control condition of the somatosensory timing detection task to account for this disturbance in timing perception.

2. Subjects and methods

2.1. Subjects

Participants consisted of 13 patients with PD (5 males, 8 females) and 13 healthy adults (6 males, 7 females) whose ages were matched (PD group: 67.4 ± 7.1 years old, healthy group: 70.2 ± 2.2 years old).

Patients with PD were diagnosed according to the UK Parkinson's Disease Society Brain Bank criteria (Hughes et al., 1992). They were mildly impaired (Hoehn and Yahr 1: 4 patients, 2: 5 patients, 3: 4 patients). Unified Parkinson's Disease Rating Scale (UPDRS) part 3 for off period was 16.6 ± 7.2 . The mean levodopa equivalence (LDE) of their medication was 174 ± 177 mg (Tomlinson et al., 2010). All patients with PD who were prescribed with levodopa/carbidopa or dopamine agonists showed responsive to the drugs (UPDRS part 3 of medicated patients: on 14.7 ± 5.2 , off 18.3 ± 6.0). Following the previous study (Dagher et al., 2001), patients were instructed to stop medication for PD at least 12 h before the experiment. None of the subjects had a history of neurological, psychiatric or addictive disorders other than PD according to self-report. None of the subjects showed the dementia according to the Mini-Mental State Examination (MMSE > 27) and Frontal Assessment Battery (FAB > 16).

All subjects were right-handed and their handedness scores were between 0.8 and 1, which were assessed by the Edinburgh scale (Oldfield, 1971). The affected side for patients with PD was right for 11 patients and left for 2 patients. All participants provided written informed consent according to the study protocol approved by the Kyoto University Graduate School and Faculty of Medicine Ethics Committee.

2.2. Task paradigm

Following the previous study (Libet et al., 1983), subjects sat in front of a computer (DELL Latitude D810, USA) screen (about 50 cm from the screen) with their right thumb on a keyboard. We used Matlab6.5 for programming. A clock (the diameter 3.5 cm) with marks placed at every 5 from 0 to 55 appeared in the center of the screen (Fig. 1). At the beginning of each trial, the clock's hand started to move clockwise from 0 and it completed a round in 2560 ms. Subjects were asked to report the timing with the precision of 6 degrees (42.7 ms).

The experiment consisted of 3 judgment paradigms: W, M and S judgment. Subjects were instructed to remember the image of the clock at every judgment task and report the location of the clock's hand after each trial.

In W and M judgments, subjects were asked to press the key by their right thumb at his/her will any time after the clock's hand completed the first round. They were instructed not to plan the timing to push the button in advance and not to pay attention to the timing for a key press. After pressing the key, the clock hand

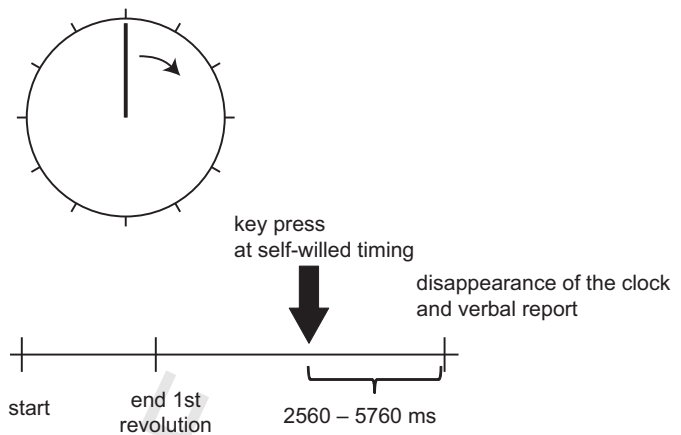


Fig. 1. Time course of the task. At the beginning, the clock appeared and the hand started to move clockwise from 0. The hand completed a round in 2560 ms. In W and M judgments, subjects were asked to press the key by their right thumb at self-willed timing after the clock's hand completed the first round. Subjects were instructed not to plan the timing to push the button in advance and not to pay attention to the timing for a key press. After pressing the key, the clock hand continued to rotate for another 2560–5760 ms and then disappeared.

continued to rotate for another 2560–5760 ms and then disappeared. In W judgment, subjects were required to report the location of the clock's hand when they became aware of the intention and to push the button (W-time). In M judgment, subjects were instructed to pay attention to the onset of their finger movement and report the location of the clock's hand when they became aware of the actual movement of their finger (M-time). For each judgment, the time of the actual button press was subtracted from the time when the subjects reported as M judgment or W judgment.

A negative value indicates that subject's estimation preceded the actual button press; a positive value indicates that the estimation occurred after the real button press.

To evaluate each subject's ability to estimate time correctly, subjects performed S judgment. In S judgment, a pair of electrodes was put over the back of the right hand with the distance of 2–3 cm and an electrical stimulation was given. The electrical stimulation was performed by Digitimer constant current stimulation model DS7A (Digitimer Ltd., England). The pulse duration of the stimulus was 200 μ s. The stimulus intensity was just over the sensory threshold. The electrical stimulation was given at random after the clock's hand made a revolution (we measured the two point discrimination of the back of the right hand for each subject in advance. No subject showed the abnormality). Subjects were instructed to report the location of the clock's hand when they felt the electrical stimulation (S-time).

To monitor the electromyogram (EMG), a pair of silver electrodes placed over the right abductor pollicis brevis muscle using tendon-belly method. The EMGs were amplified and filtered (band-pass, 5–2000 Hz), and digitized at a sampling rate of 10 kHz using the Neuroscan system (Neuroscan Co., Herndon, VA, USA) and stored for offline analysis. The timing of the button press was simultaneously recorded by the Neuroscan system.

2.3. Task procedure

One session of each judgment consisted of 25 trials. Subjects performed two sessions for W and M judgment and one session for S judgment. For W, M and S judgment tasks, the order of testing conditions was counterbalanced between WMSMW and MWSWM. The S judgment task was performed at the middle of the experiment.

Five trials for the first W and M judgment were discarded. Subjects practiced 5 to 15 trials of S judgment in advance to adjust

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