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Triad-conditioning Transcranial Magnetic Stimulation in Parkinson's Disease

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ABSTRACT

Background: Transcranial magnetic stimulation (TMS) has been used to reveal excitability changes of the primary motor cortex (M1) in Parkinson's disease (PD). Abnormal rhythmic neural activities are considered to play pathophysiological roles in the motor symptoms of PD. The cortical responses to external rhythmic stimulation have not been studied in PD. We recently reported a new method of triad-conditioning TMS to detect the excitability changes after rhythmic conditioning stimuli, which induce facilitation by 40-Hz stimulation in healthy volunteers.
Objective: We applied a triad-conditioning TMS to PD patients to reveal the motor cortical response characteristics to rhythmic TMS.
Methods: The subjects included 13 PD patients and 14 healthy volunteers. Three conditioning stimuli over M1 at an intensity of 110% active motor threshold preceded the test TMS at various inter-stimulus intervals corresponding to 10–200 Hz.
Results: The triad-conditioning TMS at 40 Hz induced no MEP enhancement in PD patients in either the On or Off state, in contrast to the facilitation observed in the normal subjects. Triad-conditioning TMS at 20–33 Hz in the beta frequency elicited significant MEP suppression in PD patients. The amount of suppression at 20 Hz positively correlated with the UPDRS III score.
Conclusion: We observed abnormal M1 responses to rhythmic TMS in PD. The suppression induced by beta frequency stimulation and no facilitation by 40-Hz stimulation may be related to abnormal beta and gamma band activities within the cortical-basal ganglia network in PD patients. The motor cortical response to rhythmic TMS may be an additional method to detect physiological changes in humans.

Introduction

The pathophysiological changes in Parkinson's disease (PD) remain unclear. The motor symptoms have been explained by motor cortical excitability changes caused by abnormal modulation via the basal ganglia-thalamo-cortical loop [1]. Transcranial magnetic stimulation (TMS) has been used to reveal various excitability changes of the motor cortex in patients with PD [2]. Single pulse or paired pulse TMS has detected hyper-excitability or inhibition reduction of the primary motor cortex (M1) in PD. Shortening of the cortical silent period [3] or short intracortical inhibition (SICI) decrements [4] have been reported in PD. These findings remain controversial, and the hyper-excitability or reduced inhibitory circuit of M1 cannot entirely explain the physiological mechanisms of the motor symptoms.

Oscillatory neuronal rhythms have recently been considered to play an important role in the pathophysiology of PD. Exaggerated beta frequency synchronizations (approximately 20 Hz) in the basal

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ganglia are suggested to be related to the pathophysiological mechanism for Parkinson's motor symptoms [5]. EEG recordings showed a delayed beta activity desynchronization and an abnormal gamma frequency shift with visual-motor tasks in PD patients [6]. The degree of these abnormalities correlated with the severity of the akinetic symptoms [6,7]. Brown et al. [8] reported that muscle activities of approximately 40 Hz that are driven by the contralateral motor cortex (Piper rhythm) [9] were decreased in PD. These findings suggested that the motor cortical abnormal beta and gamma rhythms are important in the generation of motor symptoms in PD. To study the cortical oscillatory or rhythmic activities, we usually record the field potentials from the cortices and analyze the desynchronization or synchronization within a certain frequency range during a task or calculate the coherence between cortical and muscular activities. These conventional methods were used to study the physiological features of cortical spontaneous rhythms during a certain functional state.

We recently reported a triad-conditioning method to study the modulation of motor cortical excitability in response to the rhythmic stimulation of M1. We used three monophasic, subthreshold TMS pulses over M1 applied at a certain frequency as the external rhythmic conditioning stimuli. The cortical excitability was evaluated by the size of the motor evoked potentials (MEPs) to a succeeding test-TMS given at an identical interval after the triad-conditioning TMS (the triad-conditioning TMS pulses technique). The M1 responsiveness to the rhythmic stimulation may have some relationship with the intrinsic motor cortical rhythm, even though some other mechanisms may explain this responsiveness. Previously, we reported that in healthy volunteers the MEPs were enhanced only when the triad-conditioning TMS pulses are given at a frequency of 40 Hz [10]. We hypothesized that the MEP enhancement by 40 Hz conditioning stimuli reflects some motor cortical gamma rhythm. We also showed that the MEP-enhancing frequency shifted to 25 Hz in cortical myoclonus [11].

Here, we applied this triad-conditioning TMS method to patients with PD to study the motor cortical responsiveness to rhythmic external stimulation, specifically focusing on the previously reported 40 Hz and beta range frequencies.

Methods

Subjects

Thirteen patients with idiopathic PD [7 men and 6 women, 58.9 ± 7.4 (Mean ± SD) years of age] according to the United Kingdom Parkinson's Disease Society Brain Bank clinical diagnostic criteria [12] and 14 healthy volunteers (8 men and 6 women, 51.4 ± 13.7 years of old) participated in this study (Table 1). All the PD patients were studied twice at On (approximately 2 h after intake of anti-Parkinsonian medication) and Off states of medication, which were separated by 1–2 months. Eight of the patients had received no medical treatment (de novo PD) at the first study. The first study was done in the Off state in these patients. We studied them in the On state on the next appointment day after they had started the medication and shown marked improvement of their symptoms. The order of the studies was fixed in these eight patients. In patients already treated with some anti-Parkinson's disease drugs, the On and Off state (more than 12 h after the intake of anti-Parkinsonian medication) studies were performed in random order (PD1 ~ 5). The daily L-dopa equivalent dose was calculated based on the theoretical equivalence to L-dopa as follows: L-dopa dose + L-dopa dose × 1/3 if on entacapone + bromocriptine (mg) × 10 + cabergoline or pramipexole (mg) × 67 + ropinirole (mg) × 20 + pergolide (mg) × 100 [13,14].

Table 1
Clinical features of the studied patients.

	Gender	Age	UDRS		LEDD (mg)	Disease duration (years)
			Off	On		
de novo PD1	M	47	4	2	100.5	2
de novo PD2	W	51	12	3.5	100.5	4
de novo PD3	M	58	13	5	260	2
de novo PD4	W	62	22	14	80	1
de novo PD5	M	63	11	5	200	3
de novo PD6	M	64	11	7	100.5	1
de novo PD7	M	64	10	6	300.5	1
de novo PD8	W	67	19	8	167	0.5
PD1	M	47	47	26	784	11
PD2	W	51	29	15	687.5	14
PD3	M	60	23	9	775	11
PD 4	W	65	24	13	450.5	12
PD 5	W	67	12	8	981	5

UPDRS III, Unified Parkinson's disease Rating Scale motor scores (part III); LEDD (mg), levodopa equivalent daily dose.

The mean ± SD Unified Parkinson's Disease Rating Scale (UPDRS) motor scores (Part III) were 18.2 ± 11.2 in the Off state and 9.3 ± 6.4 in the On state. None of the healthy volunteers had histories of neurological disorders or seizure episodes. Written informed consent to participate in this study was obtained from all the subjects. The experiments were performed according to the Declaration of Helsinki; the procedures were approved by the Ethics Committee of the University of Tokyo. No side effects were noted in any individuals.

Electromyogram (EMG) recordings

Subjects sat in a comfortable reclining chair during the experiments. We studied the more affected side in the patients and the right hand in the healthy volunteers. A surface electromyogram (EMG) was recorded from the first dorsal interosseous muscle using Ag–AgCl surface cup electrodes of 9-mm-diameter. The active electrode was placed over the muscle belly and the reference electrode over the metacarpophalangeal joint of the index finger. The responses were amplified (Biotop; GE Marquette Medical Systems Japan Inc., Japan) through filters set at 100 Hz–3 kHz, digitized at a sampling rate of 20 kHz and stored on a computer (TMS bistim tester; Medical Try System, Japan) that performs a randomized conditioning test paradigm and off-line averaging. Because muscular relaxation was important in this experiment, the EMG activities were monitored at high gain with an oscilloscope during the experiments. The subjects kept the first dorsal interosseous muscle relaxed throughout the experiments, which was monitored by EMG activity on the oscilloscope. When we noticed EMG activities during monitoring, we stopped the trials and waited for the appropriate recording time without any EMG activities and restarted the session. Even with this precaution, unintentional EMGs were associated with the data for the analysis in a few occasion. The trials in which EMG activity appeared during the data collection period were not used in the off-line analysis (1–2% or less of the stored trials). Such off-line rejection trials were present in approximately 1–2% of all the stored trials in the normal subjects.

Transcranial magnetic stimulation (TMS)

Magstim 200^2 magnetic stimulators (The Magstim Company Ltd., UK) were used. We placed a figure-8-shaped coil (7-cm external diameter at each wing; The Magstim Company Ltd., UK) over the primary hand motor area (M1) contralateral to the target muscle. The coil was placed in orientations to induce currents in the