Effects of Low-frequency Repetitive Transcranial Magnetic Stimulation in Parkinson's Disease

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Objective: The therapeutic effects of low-frequency repetitive transcranial magnetic stimulation (rTMS) were investigated in Parkinson's disease with cognitive dysfunction known as impaired set switching.
Methods: Six patients with Parkinson's disease exhibiting impaired performances on the Wisconsin card sorting test (WCST) were enrolled. Under electroencephalogram (EEG) monitoring, rTMS was performed using a concave circular coil once a week for three months. A 0.2-Hz rTMS was applied over the frontal region (Fz) at an intensity of 1.2 x the motor threshold of the abductor pollicis brevis (APB) for a total of 100 stimuli per session. The Trail Making Test part B (TMT-B), WCST, Wechsler Adult Intelligence Scale Revised (WAIS-R), Self-rating Depression Scale (SDS), Functional Independence Measure (FIM), and 20 m Walk time were evaluated before and after rTMS. Subjective symptoms and objective findings were also evaluated.
Results: Significant improvements in the TMT-B and WCST scores after rTMS were observed for all six patients. In addition, the subjective symptoms and objective findings also improved. The 20 m walk time decreased significantly in all four subjects after rTMS. The SDS scores improved in four of the five subjects, although the differences between the baseline and follow-up scores were not significant. No significant improvements in the WAIS-R, FIM scores were observed.
Conclusions: Low-frequency suprathreshold rTMS applied over bilateral prefrontal areas alleviated impaired set switching in Parkinson's disease. These results suggest that rTMS can affect the functional recovery of the frontostriatal circuit.

Key words: Parkinson's disease, repetitive transcranial magnetic stimulation, impaired set switching, prefrontal area, Wisconsin card sorting test

INTRODUCTION

Parkinson's disease is a chronic progressive neurodegenerative disease caused by abnormal degeneration and the detachment of dopaminergic neurons in the ventral tegmental area and substantia nigra pars compacta in the midbrain, with subsequent basal ganglion damage. It is characterized by four major motor system disorders (tremor, rigidity, akinesia and impaired postural reflex) and non-motor disorders (cognitive disorder and higher brain dysfunction). The main treatment are drug therapy and rehabilitation, but surgical therapies, such as stereotactic surgery including basal ganglion destruction and deep electric brain stimulation, have also been performed. While the effects of these surgical treatments require clarification, some studies have reported complications, such as brain edema and bleeding, as well as neurologic symptoms, such as hallucination, delusion, mood disorder and cognitive dysfunction [1, 2]. In Parkinson's disease accompanied by intractable depression, the therapeutic effects of electroconvulsive therapy have also been documented [3]. However, this is an invasive treatment conducted under general anesthesia. Therefore, noninvasive therapies that can be combined with drug therapy and rehabilitation are required.

In recent years, transcranial magnetic stimulation (TMS) has been closely examined as a possible noninvasive treatment. Ever since Barker *et al*. [4] performed single-session magnetic stimulation and recorded evoked potentials from hand muscles in 1985, this procedure has been widely used to assess motor function in the central nervous system.

After the development of repetitive transcranial magnetic stimulation (rTMS), the cortex can be repeatedly stimulated at a specific frequency and an adjustable intensity. Since Pascual-Leone *et al*. [5] first used rTMS in humans in 1991, it has been used for the treatment of various diseases. Pascual-Leone *et al*. [6] were the first to perform rTMS in Parkinson's disease, and Mally *et al*., Shimamoto *et al*. and Siebner *et al*. reported that rTMS was useful for reducing motor impairment [7, 8, 9]. On the other hand, Ghabra *et al*. and Boylan *et al*. reported that it was ineffective [10, 11]. As these studies used different parameters of magnetic stimulation and assessments, no definite conclusion regarding the effects of rTMS on the motor functions and activities of daily living (ADL) in Parkinson's disease has been made. Furthermore, some safety issues also remain.

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Table 1 Profiles of patients and summary of clinical findings during baseline period

Subject	1	2	3	4	5	6
Age (years)	64	66	71	69	62	69
Sex	F	M	M	F	F	M
H&Y	3	2	3	2	2	2
Disease duration (years)	7	8	11	6	2	9
MMSE	29	30	27	26	26	29
WAIS-R (TIQ)	103	101	101	100	72	100
(VIQ)	121	103	115	109	69	113
(PIQ)	79	98	86	90	79	85
WCST (CA)	2	4	0	4	2	0
(PEN)	7	0	10	2	4	19
(TE)	19	15	35	12	23	48
TMT-B	323.2	204.8	337.4	191.2	329.4	806.6
SDS	49	68	64	77.5	57.5	-
FIM (total)	68	122	114	90	126	120
(motor)	37	87	79	55	91	85
(cognitive)	31	35	35	35	35	35

The SDS was evaluated in 5 of the 6 subjects. H & Y: Hoehn and Yahr classification; WCST, Wisconsin card-sorting test (Keio version); CA, categories achieved; PEN, perseverative errors of Nelson; TE, total errors; TMT-B, trail-making test B; WAIS-R, Wechsler adult intelligence scale – revised; TIQ, total intelligence quotient; VIQ, verbal IQ; PIQ, performance IQ; SDS, self-rating depression scale of Zung; FIM, functional independence measure.

In most previous studies, rTMS was applied to a motor area. The functional failure of the frontostriatal circuit has been suggested to be the neural basis of cognitive dysfunction in Parkinson's disease; therefore, the stimulation of the frontal cortex might reasonably be expected to be effective in Parkinson's disease based on this neural basis and the observation that the application of rTMS to the prefrontal cortex can effectively alleviate depression. In fact, studies have reported that low-frequency repetitive magnetic stimulation over the dorsolateral prefrontal area is effective for improving depression in Parkinson's disease and cognitive task performance in patients with major depression [12, 13].

In the present study, the therapeutic effects of rTMS on cognitive dysfunction, particularly on impaired set switching, in Parkinson's disease were evaluated by simultaneously stimulating bilateral dorsolateral prefrontal areas using a concave circular coil over the frontal region (Fz).

MATERIALS AND METHODS

1. Subjects

Six patients (3 men and 3 women; between 64 and 71 years of age; mean age, 66.8 years) with Parkinson's disease referred to the Department of Rehabilitation Medicine, Tokai University Hospital, between June 2002 and March 2003 were enrolled. All the patients had displayed an impaired performance (≤ 4 categories achieved) on the Wisconsin card sorting test (WCST; Keio version) [14] and had a Mini Mental State [15, 16] score of ≥ 26 points (Table 1). None of the patients had a past history of cerebrovascular disorder, and all the patients had been diagnosed as Parkinson's disease by a neurologist. All the patients were receiving drug therapy, and their disease duration ranged from 2 to 11 years (Table 1). All the subjects gave their informed consent to participate in this research project, which was approved by the Ethics Committee of Tokai University School of Medicine.

2. Methods

(1) Repetitive transcranial magnetic stimulation (rTMS)

rTMS was delivered using a MagLite™ (Dantec, Skovlunde, Denmark) with a concave circulation coil (MMC-140; Dantec). The coil had a diameter of 140 mm, and the degree of change in the magnetic flux was highest at the central area adjacent to the coil surface, while the induced current was highest within a radius of 2 cm.

(2) Experiment procedure

Each subject was asked to sit in a reclining chair with their hip and knee joints at 90°. Using the International 10–20 method for electroencephalography (EEG), the Cz and Fz of the head were determined.

Disc surface electrodes were placed for motor evoked potential (MEP) recording on the right abductor pollicis brevis (APB) muscle according to the belly-tendon method to determine the optimal stimulation site and threshold for the motor cortex. The optimal stimulation site was determined by moving the coil around the left side of the scalp Cz until the maximum MEP response was achieved. The threshold was defined as the minimum stimulation intensity, required to elicit reproducible MEPs of at least 50 μV during at least four out of eight stimulations at the optimal stimulation site at rest.

Next, after attaching an EEG cap, the backrest was lowered to adjust the trunk angle to 45° in a resting sitting position. rTMS was delivered over the Fz at 1.2 times the motor threshold of the APB at 0.2 Hz for a total of 100 times once a week. The MEPs were also recorded during rTMS.

Over a period of about 3 months, rTMS was performed for a total of 1200 stimulations. The period was divided into three in relation to the therapeutic

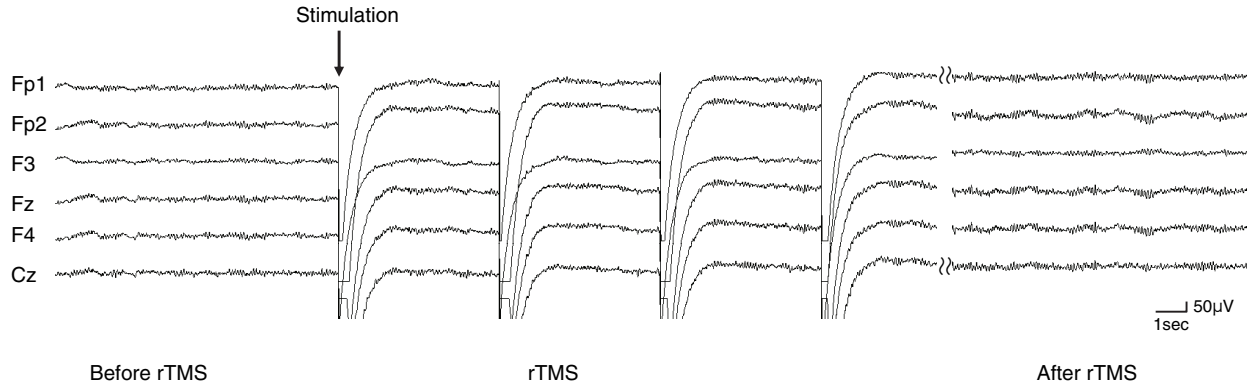

Fig. 1 EEG before, during and after rTMS.
The brain waves were primarily within a range of 8 – 10 Hz. Even after stimulation of the Fz region, no abnormal waves were observed at any of the monitoring sites (Fp1, Fp2, F3, Fz, F4, and Cz).

schedule: the baseline period (about 1–2 months before the rTMS period), the rTMS period (about 3 months), and the follow-up period (about 1–2 months after the rTMS period). Over the period, no changes were made in drug therapy and rehabilitation. During the baseline and follow-up periods, we performed the neuropsychological tests described below and evaluated the patients' activities of daily living. During the follow-up period, these tests and evaluations were performed, starting one week after the end of the rTMS period.

(3) EEG

EEG was monitored and recorded with the patient's eyes open during and for 30s before and after rTMS. According to the International 10–20 method, electrodes were placed at Fpz, Fp1, Fp2, F3, Fz, F4 and Cz. A signal processor (DP1100; NEC Medical Systems, Tokyo, Japan) was used for waveform reading, and Hyper Wave (Kissei Comtec, Tokyo, Japan) with a bandpass of 0.5–30 Hz was used to record the wave.

(4) Neuropsychological tests, assessment of ADL, Unified Parkinson's Disease Rating Scale (UPDRS), and 20 m walk

With regard to the neuropsychological tests, each of the six subjects were asked to perform the trail-making test part B (TMT-B), the Wisconsin card-sorting test (WCST; Keio version), and the WAIS-R. The self-rating depression scale (SDS) [17] was assessed in five of the six subjects. With the TMT-B, the task execution time(s) was measured using a stopwatch.

With regard to the assessment of ADL, the functional independence measure (FIM) was evaluated in all six subjects. The Japanese version of the Unified Parkinson's Disease Rating Scale (UPDRS) [18] was also used to evaluate the severity of the disease. In these subjects, no diurnal variations were observed and the assessments were made during the "on" time. In four of the six subjects, a 20 m walk test was administered: the length of time required for each subject to walk 20 m down a flat linear corridor at their own pace was measured.

The TMT-B and 20 m walk test are measured five times during the baseline and the follow-up period and then averaged for analysis. The other tests are evaluated once during the second week of the baseline and the follow-up period.

Changes in subjective symptoms and objective findings were also assessed. During the follow-up period, each subject and his family were asked once a week about changes in subjective symptoms and objective findings in daily life. Physical therapists were also interviewed regarding the conditions of the patients.

(5) Statistical analysis

The neuropsychological tests, assessments of activity of daily living, UPDRS, and 20 m walk test between the baseline period and the follow-up period were compared. SPSS[C] was used for the statistical analysis, and the Wilcoxon signed rank test was used, with a level of significance set at $p < 0.05$.

RESULTS

(1) EEG and MEP

Fig. 1 shows a representative EEG pattern during magnetic stimulation. No abnormalities were observed during the 30-s periods of EEG monitoring before and after stimulation. During the stimulation period, the EEG mostly showed approximately 8-Hz α-waves at rest; no abnormalities were seen in any of the subjects. None of the subjects showed abnormal waveforms during the 30s periods of EEG monitoring before and after stimulation.

The MEPs from the right abductor pollicis brevis monitored and recorded during magnetic stimulation were less than 50 μV in all the subjects.

(2) Changes in neuropsychological tests, assessments of ADL, UPDRS, and 20 m walk

During the baseline period, the average TMT-B execution time was 365.4 seconds, which was longer than the average time for healthy people in their 60s [19] (Table 2). The WAIS-R TIQ was ≥ 100 points in five of the six subjects, and although the results were comparable to the average for healthy adults, differences of more than 15 points in the WAIS-R between verbal and performance IQ were seen in four of the six patients (Table 2).

When comparing the baseline and follow-up periods, no significant changes were found in the WAIS-R subscales or in any of the FIM motor or cognitive scores (Table 2). The SDS scores improved in four of the five subjects, although the differences between the baseline and follow-up scores were not significant.

Table 2 WCST, TMT-B, WAIS-R, SDS and FIM scores before and after rTMS

Test	Before	After rTMS
WCST (CA)	2 ± 1.8	5.8 ± 0.4 *
(PEN)	7.0 ± 6.9	0.7 ± 1.0 *
(TE)	25.3 ± 13.7	10 ± 2.1 *
TMT-B	365.4 ± 225.7	207.7 ± 84.6 *
WAIS-R (TIQ)	96.2 ± 11.9	99.3 ± 14.4
(VIQ)	104.8 ± 19.0	108.3 ± 18.0
(PIQ)	86.2 ± 7.2	88.7 ± 11.2
SDS	63.2 ± 10.8	56.1 ± 16.1
FIM (total)	106.7 ± 22.9	106.2 ± 21.3
(motor)	72.3 ± 21.6	71.3 ± 21.0
(cognitive)	34.3 ± 1.6	34.8 ± 0.4

*P < 0.05; value indicates results of Wilcoxon signed-rank test (n = 6). Values represent means ± SD. Trail-making test B scores represent time in seconds required to complete test. WCST, Wisconsin card-sorting test (Keio version); CA, categories achieved; PEN, perseverative errors of Nelson; TE, total errors; TMT-B, trail-making test B; WAIS-R, Wechsler adult intelligence scale – revised; TIQ, total intelligence quotient; VIQ, verbal IQ; PIQ, performance IQ; SDS, self-rating depression scale of Zung; FIM, functional independence measure

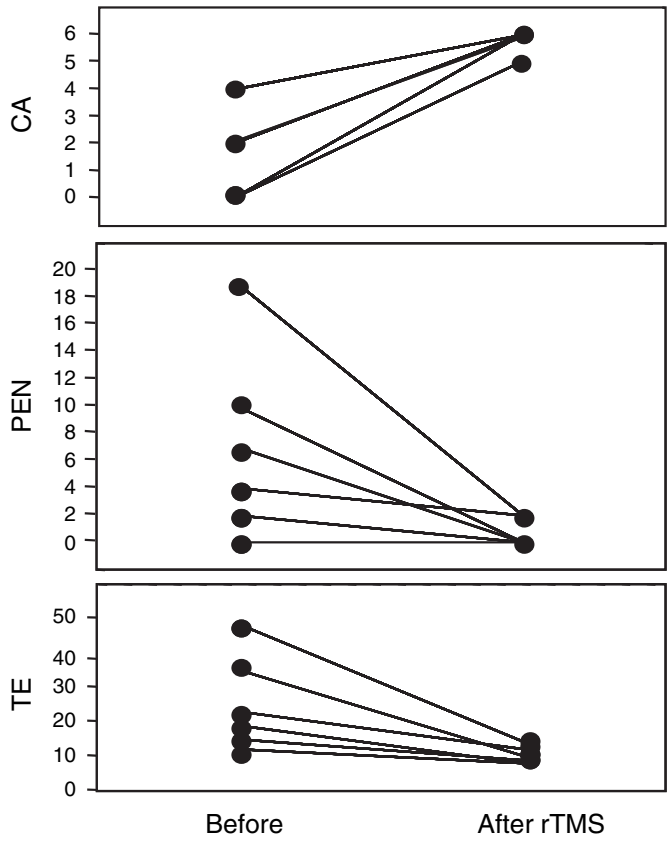

Fig. 2 Changes in the categories achieved (CA), perseverative errors of Nelson (PEN) and total errors (TE), as assessed using the WCST before and after three months of rTMS.
After three months of rTMS, the CA increased and the PEN and TE decreased in all the subjects ($p < 0.05$). CA: Number of categories in which six consecutive correct responses were achieved. PEN: Number of categories where wrong responses were given before and after rTMS. TE:Total number of errors.

The number of achieved WCST categories increased significantly ($p < 0.05$). In addition, the numbers of perseverative errors of Nelson and the total errors decreased significantly ($p < 0.05$) (Table 2 and Fig. 2).

The TMT-B execution time did not change significantly during the base line period, but significantly decreased after rTMS ($p < 0.05$) (Table 2 and Fig. 3) and maintained during the follow-up period. The 20m walk time did not change significantly during the base line period, but decreased significantly in all four subjects after rTMS and maintained during follow-up period. (Fig. 4). The decrease in the 20-m walk time was particularly marked in Subject 3.

With regard to the UPDRS, no changes were found in part I (mentation, behavior and mood), but improvements were seen in part II (activities of daily living) and part III (motor exam). In motor exam, there were some improvements in tremor at rest in legs, rigidity in legs, posture and body bradykinesia. No improvements were seen in tremor at rest in arm, rigidity in arm and rapid alternating movements in arm (Table 3).

(3) Changes in subjective symptoms and objective findings

During the follow-up period, changes in subjective symptoms and objective findings in daily life were reported by the subjects, their families, and the therapists. These changes included "faster reactions",

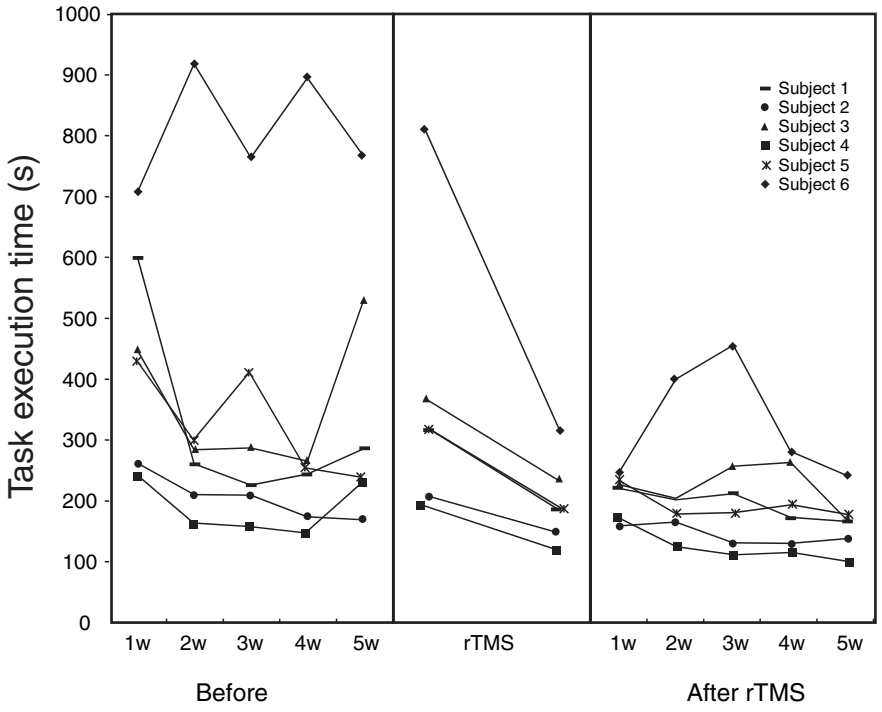

Fig. 3 Changes in TMT-B execution time during the baseline,before rTMS and during follow up period, after rTMS. The straight lines in the central column represent the difference in the task execution times measured pre-rTMS (mean of five measurements) and post-rTMS (mean of five measurements) in individual subjects.
For all the subjects, the task execution time was significantly shorter after three months of rTMS ($p < 0.05$).

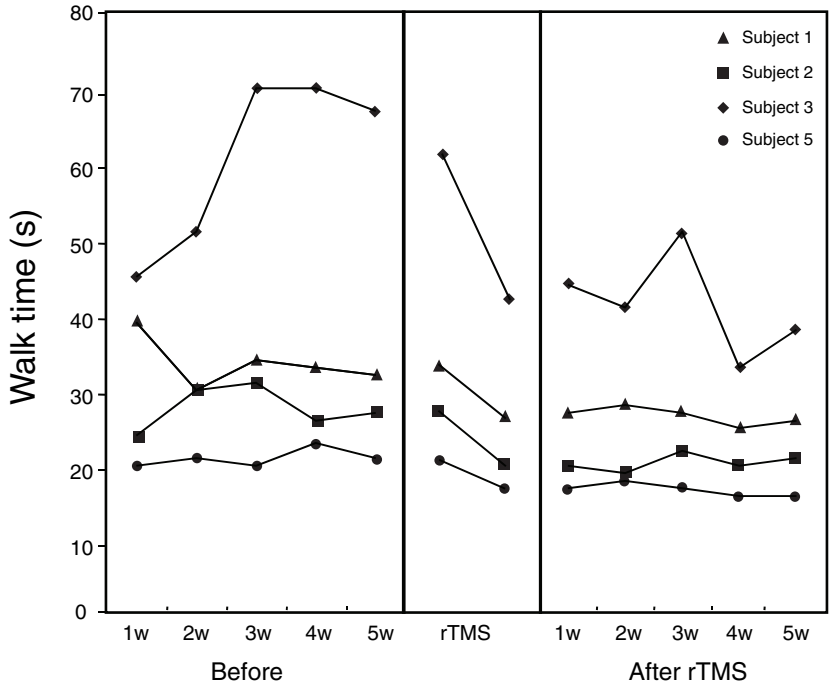

Fig. 4 Changes in 20 m walk time during the baseline,before rTMS and during follow up period, after rTMS. The straight lines in the central column represent the difference in the 20-m walk time measured pre-rTMS (mean of five measurements) and post-rTMS (mean of five measurements) in individual subjects.
In four subjects, the 20 m walk time was measured once a week for a total of five times on different days and the results were averaged. In all four subjects, the walk time after rTMS was significantly shorter.

Table 3 UPDRS before and after rTMS

Subject	1	2	3	4	5	6
rTMS	B / A	B / A	B / A	B / A	B / A	B / A
UPDRS						
(Mentation,Behavior,Mood total)	1 / 1	2 / 0	2 / 1	2 / 2	2 / 0	1 / 1
(ADL total)	21/18	9 / 7	9 / 7	13/10	10/ 5	10/ 8
Freezing When Walking	2 / 1	1 / 1	2 / 1	1 / 1	1 / 0	1 / 1
Walking	2 / 1	1 / 0	2 / 1	1 / 1	1 / 0	1 / 1
(Motor total)	35/31	14/11	29/24	28/25	18/12	19/11
Tremor at Res						
(LUE)	2 / 2	1 / 1	1 / 1	1 / 1	0 / 0	2 / 2
(RUE)	2 / 2	2 / 2	1 / 1	1 / 1	2 / 2	0 / 0
(LLE)	1 / 1	1 / 1	0 / 0	1 / 1	0 / 0	1 / 1
(RLE)	1 / 1	1 / 1	0 / 0	1 / 1	2 / 1	0 / 0
Rigidity						
(LUE)	1 / 1	0 / 0	1 / 1	1 / 1	1 / 1	0 / 0
(RUE)	1 / 1	0 / 0	1 / 1	1 / 1	1 / 1	0 / 0
(LLE)	1 / 1	1 / 1	2 / 1	1 / 1	1 / 1	1 / 0
(RLE)	1 / 1	1 / 1	2 / 1	1 / 1	1 / 1	0 / 0
Rapid Alternating Movement						
(pronate and supinate hands)						
(Left)	1 / 1	0 / 0	1 / 1	1 / 1	0 / 0	1 / 1
(Right)	1 / 1	0 / 0	1 / 1	1 / 1	1 / 1	0 / 0
Posture	2 / 1	2 / 1	3 / 2	1 / 1	0 / 0	2 / 1
Gait	2 / 1	1 / 0	2 / 1	1 / 1	1 / 0	1 / 0
Body Bradykinesia/Hypokinesia	2 / 1	1 / 1	2 / 1	2 / 1	1 / 1	0 / 0

B / A, before / after; UPDRS, Unified Parkinson's Disease Rating Scale; LUE, Left Upper Extremity; RUE, Right Upper Extremity; LLE, Left Lower Extremity; RLE, Right Lower Extremity

"better body movement and smoother standing-up and movement", "more active", "more cheerful", and "more expressive". An increase in the amount of conversation, an increase in mutual understanding characteristics within daily living, and an improvement in responses to visitors were also noted, compared to the baseline period. Additionally, changes such as better hand usage while eating and better sleep were also observed.

DISCUSSION

(1) EEG

In the present study, continuous monitoring did not reveal any EEG abnormalities. While high-frequency rTMS has been reported to induce convulsions in healthy subject, low-frequency rTMS does not affect the EEG pattern [20, 21]. However, slow waves have been induced by low-frequency rTMS over the right prefrontal area [22]. Therefore, when performing magnetic stimulation for long periods of time, changes in EEG monitoring must be carefully observed [23, 24, 25] to confirm the safety of this procedure. No safety problems were noted in the present study.

(2) Changes in neuropsychological tests, assessments of ADL, UPDRS, and 20 m walk

Cognitive dysfunction occurs in Parkinson's disease at an early stage, and similarities between these patients and those with frontal lobe dysfunction have been emphasized [26, 27]. In particular, forms of cognitive dysfunction, such as reduced planning and problem solving, impaired set switching, impaired spatial working memory and visual cognitive dysfunction, have recently been reported. Furthermore, Laplane *et al.* [28] reported that the prefrontal area and basal ganglia play important roles in executive function. Cools *et al.* [29] reported that cognition and motor shifting aptitudes (ability to switch sets) are reduced in patients with Parkinson's diseases. Consequently, the core symptom for the cognitive dysfunction associated with Parkinson's disease appears to be executive dysfunction. Therefore, the present study utilized the WCST, which mainly examines concept and set switching and reaction flexibility, and the TMT-B, which is an attention-switching task. The long TMT-B execution times observed during the baseline period of this study may be one characteristic of the executive dysfunction associated with Parkinson's disease.

In addition, many subjects had discrepancies between performance and verbal tasks on the WAIS-R. In general, the total IQ in Parkinson's disease is normal, but the performance IQ is lower than the verbal IQ [30]. The results of this study also supported this finding. The WAIS-R is an intellectual function test that assesses posterior brain function [14]. By evaluating the WAIS-R, we were able to assess both anterior and posterior brain function.

In this study, the application of a low-frequency suprathreshold rTMS over bilateral dorsolateral prefrontal areas in Parkinson's disease improved not only executive function, but also motor function, subjective symptoms and objective findings. Although no significant changes in the WAIS-R scores before and after stimulation were found, the TMT-B execution time decreased and the scores in the WCST categories improved. These results suggest that rTMS specifically improves prefrontal function, one aspect of executive function.

In TMT-B, we have to consider the effect of improvement of motor function on TMT-B execution time. However we found some improvements in scores about trunk and legs in UPDRS exam, not in arms and hands. Therefore the improvement in TMT-B must be derived from the improved executive function, not from motor function.

When evaluating cognitive task performances, the effects of learning on the task performances must be also considered; nevertheless, the impact of the learning effects on the improvements observed in this study was thought to be small because the second assessment was performed three months later.

The SDS scores improved in four of the five patients, although the differences between the baseline and follow-up scores were not significant; these findings suggest that rTMS may be effective for alleviating depression and mood disorders in Parkinson's disease. The application of rTMS over the left prefrontal area has been reported to improve intractable depression; although no significant changes in verbal, memory or intellectual function tests were reported, the TMT-B execution time decreased [31]. In healthy subjects, rTMS over the right prefrontal area also improved set switching, while rTMS over the left prefrontal area improved the Stroop test reaction time [32, 33]. Thus, as one aspect of executive function is improved and depression is alleviated, a relation between rTMS and neurological functions performed in the prefrontal area is indicated.

In recent years, studies have documented the long-term effects of low-frequency rTMS in several continuous sessions on different days, rather than single-session rTMS [34, 35, 36]. Shimamoto *et al.* [8] used a large circular coil to perform low-frequency rTMS over a broad area including the left and right motor, premotor and supplementary motor areas for a period of two months, and observed some improvements in the UPDRS. Mally *et al.* [37] also reported the long-term effects of rTMS. In the present study, improvements were observed after performing 100 stimulations per week for 3 months. In this manner, periodic stimulation over several months appeared to facilitate the reconstruction of the central nervous system, thus favorably impacting the cognitive function in Parkinson's disease.

While improvements were observed in ADL and the motor scores of the UPDRS, no improvements in the cognition-related scores were seen. The UPDRS has many motor function-related items, but few items for psychological and cognitive function involving impaired memory, orientation and mood. Hence, the UPDRS is suitable for assessing rTMS targeting the motor area, but not as suitable for assessing executive dysfunction, such as impaired set switching.

In four subjects, the 20 m walk time significantly decreased. The decrease in the 20-m walk time was particularly marked in Subject 3. In this subject, assessment using UPDRS revealed alleviation of rigidity of both lower extremities, suggesting that rTMS was effective against rigidity, as reflected by the marked decrease of the 20-m walk time.

In Parkinson's disease, the cortical silent period (CSP) is reportedly shortened [9, 38], indicating a disturbed inhibitory mechanism in the motor cortex. On the other hand, low-frequency low-intensity rTMS suppresses the motor cortex, and high-frequency high-intensity rTMS excites the motor cortex [39, 40]. It has also been documented that not only the site of stimulation, but also related areas away from the site of stimulation are excited [41]. Gerschlager *et al.* [42] performed subthreshold 1-Hz rTMS for a total of 1500 times each in the prefrontal cortex, premotor cortex, motor cortex and parietal cortex to suppress the site of stimulation, depressing the MEP amplitude. Significant suppression was observed with premotor stimulation, and suppression, albeit not significant, was seen with prefrontal stimulation. In the present study, the MEP amplitude during rTMS was less than 50 μV. In other words, the intensity might be subthreshold for the motor cortex. Thus, this suprathreshold low-frequency stimulation over the prefrontal area served as a subthreshold low-frequency stimulation over the supplementary motor and motor cortexes. While no significant differences were found, the results indicate that gait function also improves after rTMS. Because the motor cortex might be suppressed, so that gait function can be improved by rTMS.

In UPDRS, we found some improvements in motor exam, especially in in tremor at rest in legs, rigidity in legs, posture and body bradykinesia as mentioned above. These results might be due to the same reason we mentioned in 20 m walk time. rTMS might be subthreshold low-frequency stimulation over the supplementary motor and motor cortexes as mentioned above. Therefore rTMS improved motor function of trunk and legs in Parkinson disease, so that the gait function might improve.

The improvements in the executive function test suggest improvements in the subjective symptoms and objective findings. These results indicate that delays in the start of movements within ADL in Parkinson's disease, such as a lack of smoothness in conversations, a slowness of movements, and frozen gait, are closely correlated with executive dysfunction.

In the present study, low-frequency suprathreshold stimulation over the prefrontal area was effective for executive function and ADL, allowing functional failure in the frontostriatal circuit to recover [43, 44]. Delong, Alexander and others [45, 46, 47 and 48] have described five circuits in mammals (motor circuit, ocular movement circuit, dorsolateral prefrontal circuit, lateral fronto-orbital circuit and anterior cingulate gyrus circuit); they reported that a closed circuit was formed through communications with certain areas of the cerebral cortex and basal ganglia. Three circuits, in addition to the motor and ocular movement circuits, were then combined as the cognition loop (prefrontal circuit and limbic circuit). Hence, rTMS over the bilateral dorsolateral prefrontal area may trans-synaptically affect the frontostriatal circuit, particularly the prefrontal circuit.

In this study, the bilateral dorsolateral prefrontal areas in Parkinson's disease were simultaneously stimulated with a low-frequency suprathreshold stimulation. Cognitive tests suitable for evaluating the prefrontal area were used to assess the effects of stimulation. In addition, the use of a circular concave coil enabled

relatively localized sites to be stimulated, with EEG monitoring for the safety.

In the future, the long-term therapeutic effects of rTMS, particularly with regard to the frequency, stimulation intensity and rTMS coil-type, need to be investigated. Low-frequency suprathreshold rTMS in Parkinson's disease improved cognitive function and symptoms related to the prefrontal area. Hence, when combined with drug therapy and rehabilitation, rTMS appears to be useful for maintaining and improving function. Further developments related to the application of rTMS in Parkinson's disease are expected.

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