age of 55.2 (7.8) years, disease duration 14.4(4.6) years, and Hohen and Yahr stage 3 in the on phase and 4 in the off phase were examined. All patients experienced severe motor fluctuation, which was an indication of surgical treatment with DBS. Severe FOG had been observed, mainly during the off phase and also during the on phase. The patients exhibited no mental deterioration and no hallucination prior to the operation. The unified Parkinson's disease rating scale (UPDRS) was applied for scoring the parkinsonian symptoms before and after the operation.

2.2. Examination of electromyograms (EMGs) during DBS on and off

EMGs of the lower extremities during stepping were examined in DBS on and DBS off states in one patient treated with subthalamic DBS. EMG was recorded on four muscles of the legs. EMGs were examined, firstly in the DBS on state, and then in the DBS off state.

2.3. Disturbance of rhythm formation

The finger tapping test was performed on five normal subjects (mean age 59.8 years) and one parkinsonian patient with severe FOG. Subjects listened to sounds of 1, 2, 3, 4 and 5 Hz and were requested to follow the sound by tapping on the table with the index finger. During the examination, surface EMGs were recorded from the forearms. Normal subjects performed the test using only their left hand, whereas both hands of the patient were examined. The frequencies of flexor muscle activities were measured from the EMGs. The patient was examined before the DBS operation and during the DBS on state.

3. Results

3.1. Effects of subthalamic DBS

The average score of UPDRS, during the on phase and the off phase examined before and after the operation is shown in Fig. 1. The improvement of parkinsonian symptoms following subthalamic DBS is very clear and similar to those in several previous reports. There is no subscore of UPDRS to estimate FOG. The two subscores for gait and postural instability were markedly diminished and all eight patients exhibited improvements in motor fluctuations and FOG.

3.2. EMG examination during DBS on and off

The EMG results are shown in Fig. 2. EMGs in the upper part of the figure were recorded during DBS on
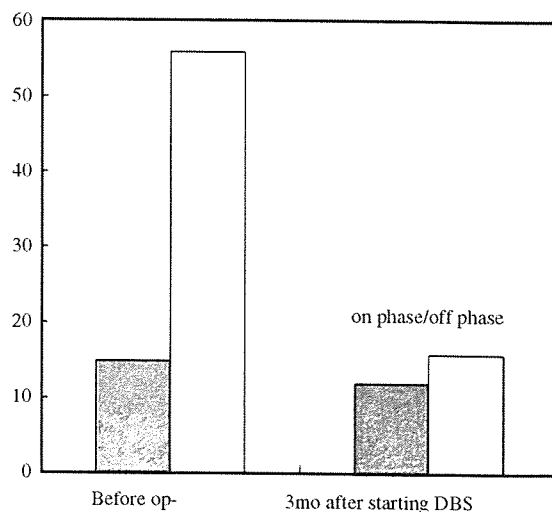

Fig. 1. Average motor score of UPDRS before and after DBS. The solid columns represent scores for the on phase and the open columns represent scores for the off phase.

and those in the lower part, during DBS off. During DBS on, the patient could step regularly, but the regularity was lost during DBS off. The regularity of stepping gradually slowed down and finally disappeared. However, the patient attempted to continue stepping.

3.3. Disturbance of rhythm formation

The results are shown in Fig. 3. Normal subjects could tap regularly, following the sounds. The patient could tap only following 1 Hz. The patient's tappings, following sounds of frequency higher than 2 Hz, were unsuccessful and the frequency of EMGs converged to 4 or 5 Hz. The patient was unable to maintain a synchronous response. During DBS on, the patient exhibited a slight change in the response to sounds.

4. Discussion

FOG is observed in many situations such as, hesitation at gait initiation upon reaching the destination, and at doorways or during turning while adjusting to circumstances [4]. FOG is not a phenomenon particular to PD, and is observed in other diseases such as multiple system atrophy, progressive supranuclear palsy, vascular Parkinsonism and drug-induced Parkinsonism.

Even in PD, FOG is observed in both the off and on phases. The relationship between L-dopa administration and freezing is considered complex. L-dopa administration both improves and worsens FOG. Alternatively, FOG observed in progressive supranuclear palsy has no response to L-dopa administration. It is conceivable that
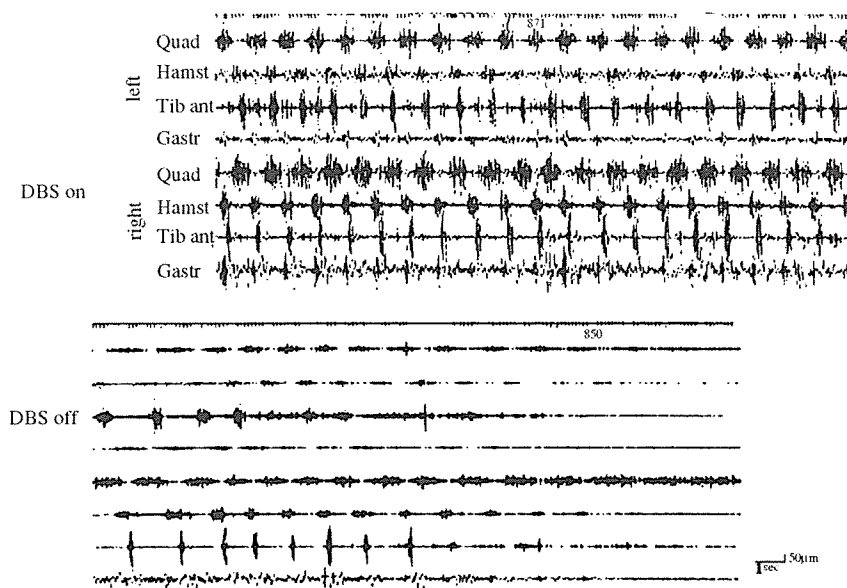
Fig. 2. EMGs during stepping. EMGs in the upper part were recorded during DBS on, and those in the lower part during DBS off.
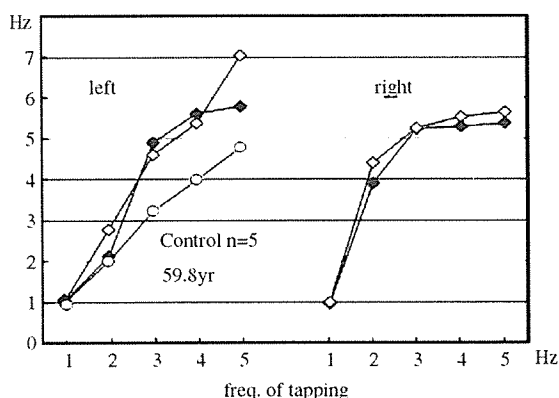

Fig. 3. Tapping test. The vertical axis shows the frequency of tapping performed by the subject and the horizontal axis shows the frequency of the sounds. The circles represent results for normal subjects, and the squares represent those for the patient. The open squares represent before DBS, and the solid squares represent after DBS.

the symptoms and mechanisms of FOG are complex and difficult problems to solve.

EMG observations have revealed that regularity of stepping disappeared when DBS was switched off. When switched on, the active DBS treatment on the sub-thalamic nucleus improves or maintains the rhythm of stepping. Disturbance of the rhythm formation could be one of the factors underlying the mechanism of freezing. Moreover, results from the finger-tapping test are too preliminary to discuss the effect of subthalamic DBS. It is necessary to examine the rhythm of the lower extremities. It is possible to elucidate some issues concerning the mechanisms of FOG by studying the

relationship between the function of the subthalamic nucleus and the rhythm formation disturbed in PD.

Kinesie paradoxale refers to the improvement of FOG due to external cues. In a reaction time study, an external cue as a warning signal makes the reaction time shorter. An explanation for this phenomenon is related to the change in attention or arousal caused by a warning signal [5]. The function of an external cue in FOG is similar to the function of the warning signal in the reaction time study. FOG is improved by a change in attention or arousal by an external cue. It is suggested that FOG is not only a motor phenomenon but also a phenomenon generated by the attention or arousal system. It is clear that further studies on the mechanism of FOG are necessary.

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Measurement of transcallosal inhibition in traumatic brain injury by transcranial magnetic stimulation

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Abstract
Primary objective: To study whether transcallosal inhibition (TCI) can evaluate the severity of traumatic brain injury (TBI).
Research design: Case-control study.
Methods and procedures: Twenty patients with a chronic TBI and 20 control subjects were studied. The following transcranial magnetic stimulation parameters were checked; resting motor threshold, central motor latency times, onset latency of TCI, duration of TCI, transcallosal conduction times and amount of TCI. The severity of TBI was evaluated using the Glasgow Coma Scale (GCS).
Main outcome and results: The amount of TCI was significantly lower in the patients than the control subjects ($p < 0.001$). The amount of TCI was highly correlated with the GCS ($r = 0.787$, $p < 0.001$).
Conclusion: An assessment of TCI was found to be a more sensitive and useful method for an evaluation of the severity of TBI.

Keywords: *Traumatic brain injury, transcranial magnetic stimulation, corpus callosum, diffuse axonal injury*

Introduction

The functional integrity of the corpus callosum (CC) that connects homologous motor cortices can be tested electrophysiologically in humans by transcranial magnetic stimulation (TMS) [1]. When TMS is performed during an ongoing tonic voluntary contraction, the activity of the muscles ipsilateral to the site of the cortical stimulation is temporarily suppressed. This transcallosal inhibition (TCI) is not detected in patients with CC lesions [2]; hence, a transcallosal route is presumed to account for it. In recent years, TCI has been found to be a useful diagnostic tool in patients with multiple sclerosis, corticobasal ganglionic degeneration and progressive supranuclear palsy [3–5].

CC lesions are commonly detected in patients with traumatic brain injury (TBI) [6–12].

The diffuse axonal injury (DAI) due to acceleration–deceleration and rotational forces is considered to be an important factor in the formation of a CC lesion [6–8, 10, 11]. A majority of the TBI survivors recover from coma and show remarkable progress toward regaining their pre-injury functional abilities. However, patients with TBI often have cognitive impairments, including attention, memory and executive function deficits [8, 13]. When attempting to correctly evaluate the severity of TBI, a method that requires little cooperation from the patient is desirable so that any cognitive impairment is excluded.

The hypothesis was that the TCI method could detect an abnormality of the CC in patients with TBI. The TCI method is simple and objective and requires little cooperation from the patient; hence, this method has the advantage of excluding

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Table I. Clinical characteristics of patients with traumatic brain injury.

Patient no.	Age	Sex	GCS on admission	Duration since injury (months)	Type of lesions
1	29	M	9	29	Diffuse
2	60	F	10	38	Focal
3	31	M	9	23	Combined
4	40	M	8	25	Diffuse
5	26	M	7	9	Diffuse
6	31	M	8	45	Diffuse
7	56	M	13	24	Focal
8	52	F	9	31	Combined
9	18	M	6	21	Diffuse
10	23	M	6	27	Combined
11	33	M	6	51	Combined
12	60	M	12	10	Focal
13	28	F	6	32	Diffuse
14	52	M	6	28	Combined
15	25	F	8	15	Combined
16	43	M	7	18	Combined
17	33	F	14	23	Diffuse
18	52	M	9	19	Combined
19	23	M	8	24	Diffuse
20	55	F	13	14	Diffuse

GCS, Glasgow Coma Scale; Diffuse, MRI findings detected the small punctiform parenchymal haemorrhages in the mesencephalon, corpus callosum, basal ganglia or periventricular; Focal, MRI findings detected the haemorrhagic brain contusions in the frontal and/or temporoparietal lobes; Combined, Both of diffuse and focal lesions.

any cognitive impairment when the severity of the TBI was evaluated. To the authors' knowledge, imaging was the only available technique that could evaluate the severity of DAI while the patient was alive [9, 12, 14]. Therefore, TCI may be a unique diagnostic tool for electrophysiologically evaluating the DAI by monitoring the CC lesions. The present investigation examined whether TCI could evaluate the severity of TBI that was indicated by the Glasgow Coma Scale (GCS) [15].

Methods

Patients and controls

Twenty patients with TBI (14 men and six women; aged, 18–60 years; mean age, 38.5 ± 13.9 years) were studied (Table I). The mean period after their TBI was 25.3 ± 10.7 months. The GCS scores that were obtained at the time of their first admission after accident were used to evaluate the severity of TBI (scale mean, 8.7 ± 2.5; range, 6–14). All the patients who were enrolled for the study fulfilled the following criteria: (1) aged from 18–60 years, (2) drugs that are known to influence the excitability of the central nervous system (for example, an anti-epileptic or psychoactive drug) had not been administered in the past month and (3) no concomitant cervical or upper limb injury

that could affect conduction along the peripheral nerves and spinal cord. The exclusion criteria for patients in this study were as follows: (1) the subjects, their guardians or legal representatives were unwilling to give consent for participation in the study and (2) the patient had a history of neurological disease.

Twenty normal subjects, who were matched for age and sex (15 men and five women, aged 20–56 years; mean age, 35.3 ± 11.2 years), participated as control subjects in the study. They did not have any history or clinical evidence of any neurological disease. Informed consent for the study was obtained from all the patients and control subjects. The protocol was approved by the local ethical committee of the Hokkaido University Graduate School of Medicine.

Magnetic stimulation and recording

Focal TMS to the motor cortex of each hemisphere was performed using a 70-mm figure-of-eight coil connected to a Magstim 200 stimulator (2-T version; Magstim Company, Dyfed, UK). The stimulation point for eliciting the maximal hand motor responses for each subject was determined. The current in the axis of the stimulation coil was directed anteroposteriorly (the induced current had the opposite orientation) because this direction is the

most effective for eliciting TCI [16]. The electro-myographic (EMG) responses were recorded bilaterally from the first dorsal interosseous muscle (FDI) using Ag–AgCl surface electrodes. The EMG signal was amplified, filtered and stored in a personal computer for off-line analysis (Neuropack; Nihon Koden, Tokyo, Japan).

The resting motor threshold (rMT) was defined as the lowest stimulator output that could produce motor evoked potentials (MEPs) with a peak-to-peak amplitude that was greater than 50 μV in at least five of 10 trials [17]. In a TCI session, each motor cortex was stimulated 20 times, with an intensity of 150% rMT, during unilateral maximal tonic contraction of the ipsilateral FDI. During each stimulation, the subjects maintained a sustained maximal tonic contraction of the FDI muscle, with visual and auditory feedback, for ∼2 seconds. To avoid central or peripheral fatigue during maximal tonic muscle contraction, the subjects rested for 3 minutes after a series of 10 stimuli. The stimuli at a frequency of 0.1 Hz were applied over the cortex. The peripheral latencies were obtained by magnetic stimulation of the cervical nerve roots using a 90-mm circular coil.

Response indices

The peak-to-peak amplitude of 10 averaged MEPs of the contralateral EMG obtained with an intensity of 120% rMT was determined. The central motor latency times (CMLTs) were calculated by subtracting the longest peripheral conduction time following magnetic stimulation of the cervical nerve roots from the onset latency of the cortically elicited contralateral EMG response.

The TCI parameters were evaluated by rectifying and averaging 20 EMG signals of the active FDI ipsilateral to the site of the cortex stimulation. The TCI was quantified by the period of relative EMG suppression after the stimulus, i.e. when the EMG activity dropped below the background activity. The onset latency of TCI was measured from the stimulus to where the EMG activity clearly fell below the mean amplitude of the EMG activity in the 100 ms before the stimulus. The duration of TCI was measured from its onset to where the EMG activity again reached the mean amplitude of the EMG activity before the stimulus. The transcallosal conduction times (TCTs) were determined by subtracting the onset latency of the corticospinally mediated contralateral responses from the onset latency of TCI in the same FDI. The area of suppressed EMG activity below the mean amplitude of the EMG activity before the stimulus was also averaged. The amount of TCI was then defined

as the percentage of this mean suppressed activity in the mean amplitude of the EMG activity before the stimulus [18]. That is to say, the more the EMG activity was suppressed the greater was the amount of TCI.

Statistical analysis

Any parameters of the MEPs (rMT, CMLTs, amplitude) and TCI (amount of TCI, duration of TCI, TCTs) of the patients that exceeded mean value ±2.5 SD (the pooled data across the left and right sides) of the control subjects were considered to be abnormal. The observed data (MEPs and TCI parameters) from the patients and the control subjects were compared by using a Mann-Whitney U-test. Any possible correlation between the amount of TCI and GCS was determined by using the Spearman rank correlation test.

Results

The data for the MEPs and the TCI parameters that were obtained for the control subjects and the patients are listed in Table II.

MEPs parameters

No difference was observed between the mean data of the control subjects and the patients for the rMT, CMLTs or amplitude (Table II). In addition, a significant difference was not observed in laterality in the MEPs parameters (rMT, CMLTs, and amplitude) for the control subjects and patients. An increased rMT was found in 15% (three of 20), a decreased amplitude in 15% (three of 20) and prolonged CMLTs in 20% (four of 20) of the patients with TBI on either or both sides.

TCI parameters

The amount of TCI was significantly lower in the patients than in the control subjects ($p < 0.001$). One patient (patient no. 13) did not display TCI on either side. Therefore, she was excluded from the TCI correlation study. In 70% of the patients (14 of 20) the amount of TCI was abnormal. However, when compared with the control subjects the latency onset of TCI, the duration of TCI and the TCTs of the patients with TBI were not significantly different. The typical TCI that were observed for the control subjects and patients are shown in Figure 1. The amount of TCI was significantly correlated with the GCS (Figure 2; $r = 0.787$, $p < 0.001$).

Table II. MEPs and TCI parameters.

Parameter	Control subjects, 40 hands		Patients with TBI, 40 hands	
	Mean ± SD	Normal range[a]	Mean ± SD	Abnormal hands/patients
Resting motor threshold (%)	44.1 ± 5.1	31.3–56.9	46.4 ± 8.2	4/3
Amplitude of MEPs (mV)	1.3 ± 0.4	0.3–2.3	1.1 ± 0.7	3/3
Central motor latency times (ms)	6.9 ± 0.6	5.4–8.5	7.2 ± 1.1	6/4
Onset latency of TCI (ms)	34.0 ± 2.6	27.5–40.5	35.1 ± 3.1[b]	4/3
Duration of TCI (ms)	26.2 ± 6.1	10.9–41.4	24.7 ± 7.6[b]	3/2
Transcallosal conduction times (ms)	12.5 ± 1.9	7.7–17.4	12.6 ± 2.2[b]	2/2
Amount of TCI (%)	54.1 ± 5.1	41.4–66.7	39.1 ± 10.3[b]*	22/14

[a] normal range = mean ± 2.5 SD.
[b] 38 hands (one patient had no TCI on both sides).
* $p < 0.001$ (compared with control subjects).
MEPs = motor evoked potentials; TCI = transcallosal inhibiton; TBI = traumatic brain injury.
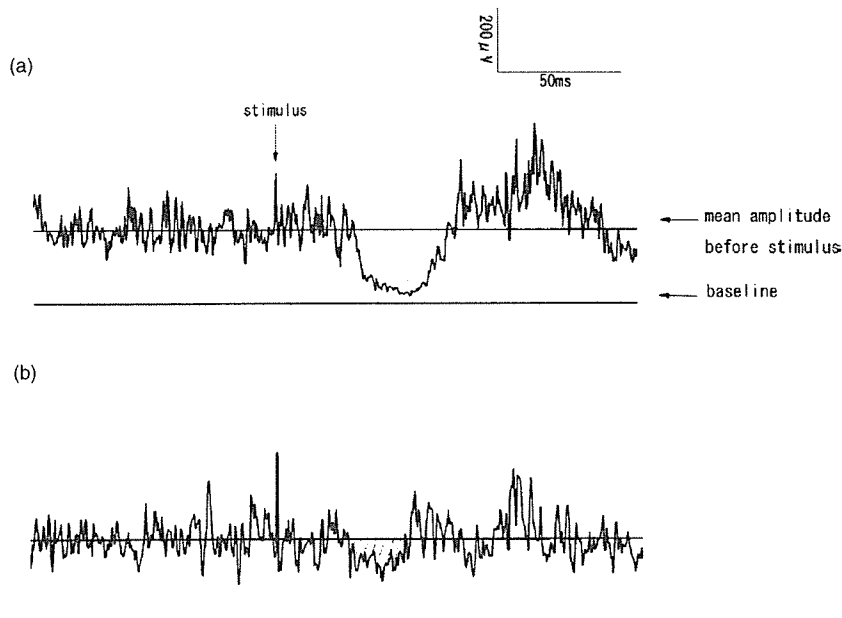

Figure 1. Examples of the TCI raw data. Each recording represents the average of 20 rectified electromyogram activities. (a) Typical TCI elicited from the first dorsal interosseous muscle (FDI) of control subject. An oblique line showed the area of TCI (The amount of TCI = 57.1%). (b) TCI elicited from FDI of patient with severe TBI. Note the amount of TCI was small (The amount of TCI = 24.9%, GCS = 7 points). TCI: transcallosal inhibition; TBI: traumatic brain injury; GCS: Glasgow coma scale.

Discussion

There was a significant difference between the control subjects and the patients with TBI for the amount of TCI, but not rMT, CMLTs or amplitude. This result suggested that the TCI method of evaluating CC was more sensitive for detecting abnormal findings in patients with TBI than the method of evaluating the excitability of the cortex and corticospinal tract function by TMS.

The GCS score has been reported to be strongly correlated with the severity of the TBI [19–21]. Therefore, the severity of TBI is usually described by the amount of impaired consciousness as defined by the GCS. Moreover, the GCS has a significant correlation with a CC lesion [6, 10]. TCI methods by TMS can evaluate the function of integrity of the CC connecting homologous motor cortices [1–5]. In this study, the amount of TCI was significantly correlated with the GCS. Based on these reports,
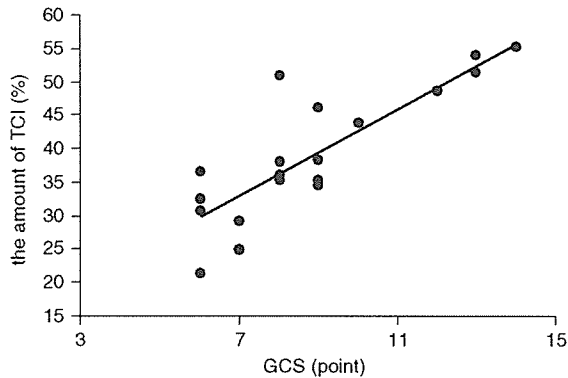
Figure 2. The amount of TCI had a significant correlation with GCS in 19 patients with TBI ($r = 0.787$, $p < 0.001$). TBI: traumatic brain injury; TCI: transcallosal inhibition; GCS: Glasgow coma scale.

it may be considered that the TCI method by TMS is useful for evaluating the severity of TBI by monitoring the CC function.

No significant difference in the MEPs parameters (rMT, CMLTs and amplitude) of the control subjects and patients was observed. The normal rMT and CMLTs in the patients with TBI may have indicated that they had only minimal or no loss of motor cortex excitability and conduction in the pyramidal tract. These results indicated that the abnormal findings in patients with TBI could not be easily detected by the well established method of determining the corticospinal tract function by using TMS. In contrast to these results, Chistyakov et al. [22, 23] have reported that patients with TBI had a higher rMT than the control subjects. However, this report had compared the more damaged side in TBI patients with that in control subjects [23]. In this investigation, the patients with TBI exhibited normal rMT and did not show significant laterality. Chistyakov et al., in a follow-up study, have also reported some improvement in the observed high rMT [22]. In fact, in this study, the period after the TBI was longer than the post-accident period of Chistyakov et al.'s study that reported the high rMT of patients with TBI. In addition, a severe brain injury that might preclude consciousness and voluntary movement did not invariably predicate an abnormal rMT and CMCT [24]. Based on these reports, the normal rMT observed in this study was not thought to be specific with regard to the studies that reported high rMT in patients with TBI. In addition, the TCI route is thought to be longer than rMT, CMLTs and amplitude because, in addition to the corticospinal tract, the TCI route included the commissural fibres via the CC. Therefore, the TCI method might detect the abnormal findings in patients with TBI more than the well established

method of evaluating corticospinal tract function by using TMS.

The patients with TBI often have cognitive impairments, including attention, memory and executive function deficits [8, 13]. A recent study reported that the area of the CC in patients with TBI correlated with the memory function [11]. Therefore, the TCI that can monitor the CC function might also be correlated with cognitive impairment in patients with TBI. In addition, the TCI as well as imaging is useful for accurately evaluating the patients with TBI because TCI is a simple method that requires little cooperation from the patient. Moreover, the CC lesion is considered to reflect the DAI [6–8, 10, 11]; therefore, TCI may be a diagnostic tool for electrophysiologically evaluating the DAI *in vivo* by monitoring the CC lesions. It has been recently considered that the diffusion MR tensor imaging may be able to detect the DAI [9, 14]; hence, some *in vivo* studies used the diffusion MR tensor imaging to detect the DAI [9, 12, 14]. Therefore, one must study the correlation between diffusion MR tensor imaging and the TCI to suggest the utility of TCI for evaluating the DAI in patients with TBI.

In conclusion, this study confirmed that the TCI was positively correlated with the severity of the TBI. Moreover, an assessment by TCI was found to be a more sensitive method for detecting abnormal findings in patients with TBI than the well-established method of evaluating corticospinal tract function by using TMS. This study is the first to report the evaluation of the severity of TBI by using a TCI method that tests the functional integrity of CC by using TMS.

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Motor learning of hands with auditory cue in patients with Parkinson's disease

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Summary. In the present research, changes in motor cortex function were observed in relation to repetitive, voluntary thumb movement (training) in patients with Parkinson's disease (PD) and normal control subjects. Changes in the direction of thumb movement due to motor evoked potential (MEP) by transcranial magnetic stimulation (TMS), after motor training with and without rhythmic sound, were measured using a strain gauge for 12 patients with PD and 9 normal control subjects. PD patients who experienced the freezing phenomena showed poor change in direction of TMS-induced movement after self-paced movement; however, marked change in direction of TMS-induced movement was observed after training with auditory cue. PD patients who had not experienced the freezing phenomena showed positive effects with the auditory cue, producing similar results as the normal control subjects. Two routes for voluntary movement are available in the nervous system. The decreased function of basal ganglia due to PD impaired the route from the basal ganglia to the supplementary motor cortex. These data suggest that the route from sensory input to cerebellum to premotor cortex could compensate for the decreased function of the route via the basal ganglia to the premotor cortex. Once change in the motor cortex occurred, such change persisted even after the interruption of training. These phenomena suggest that motor memory can be stored in the motor cortex.

Introduction

Patients with Parkinson's disease (PD) face difficulty in initiating and performing complex, sequential movements. PD patients frequently complain of slowness and early fatigue during movements associated with their motor disability. They show deficits in motor learning and in the acquisition of new skills, although the extent of the deficit remains unclear. Therefore, to elucidate the most effective motor learning interventions, it is important to generate basic insights into the learning capabilities of PD patients.

The involvement of the motor cortex in learning movements has recently attracted much attention. Transcranial magnetic stimulation (TMS) has proven to be a valuable and non-invasive tool for investigation of the central motor system (Barker et al., 1985;

Rothwell et al., 1991; Berardelli, 1991). Imaging studies using positron emission tomography (PET) have provided evidence that the motor cortex is more active during the process of motor learning (Grafton et al., 1992; Kawashima et al., 1994; Honda et al., 1998). Brain mapping using functional magnetic resonance imaging (fMRI) (Karni et al., 1995) and transcranial magnetic stimulation (Pascual-Leone et al., 1995) has also shown changes in the motor cortex during the acquisition of motor skills. Change in the motor cortex of healthy individuals during thumb movement exercise has been observed in studies similar to the present research. However, similarities between motor cortex function in healthy patients and in patients with PD are unknown. It appears that the same learning-related changes in the motor cortex of healthy individuals also occur in patients with PD. The present study used a metronome as an external auditory cue to determine whether external triggers are a factor in skill acquisition. As human cortical movement representation can undergo rapid plasticity (Classen et al., 1998), the aim of this study was to evaluate the differences in motor control reorganization between PD patients and

normal controls during thumb exercise with and without rhythmic sound as assessed by the directional change of TMS-induced thumb movements.

Methods

Subjects

Twelve Parkinson's disease patients aged 52–77 years (65.1 ± 7.5 years, 8 males and 4 females) and nine normal age-matched volunteers aged 45–75 years (64.3 ± 8.5 years, 8 males and one female) with no history of neurological disorder participated in this study. The mental condition of Parkinson's patients was normal and in Hoehn and Yahr stages II or III. The freezing phenomena was assessed by the activities of daily living (ADL) section of the Unified Parkinson's Disease Rating Scale (UPDRS) and was considered to be present if the score was 1 or >1 on the 'freezing when walking' question. Parkinson's patients were divided in two groups according to presence or absence of the freezing phenomena. Type I patients (n = 7; 6 males and 1 female; mean age 68.1 ± 6.3 years) had experienced the freezing phenomena, while Type II patients (n = 5; 2 males and 3 females; mean age 61.0 ± 7.7 years) had not experienced the freezing phenomena. All subjects were right handed and provided informed written consent to participate in this study. Clinical characteristics and demographic data of the patients and normal volunteers are shown in Table 1. None of the patients displayed severe "on-off"

Table 1. Clinical and demographic data of Parkinson's disease patients and normal participants

Cases	Age (years)	M/F	Mentality	Frozen phenomenon	Hoehn & Yahr stage
1	77	M	N	+	3
2	75	M	N	+	3
3	62	F	N	+	3
4	64	M	N	+	3
5	64	M	N	+	3
6	72	M	N	+	3
7	63	M	N	+	2
8	70	F	N	−	2
9	52	M	N	−	3
10	54	F	N	−	2
11	66	F	N	−	2
12	63	M	N	−	2
Normal (n = 9)	45–75	8/1	N	−	−

M male; F female; N normal; + present; − absent

fluctuations and all were tested while they were in their "on"-stage.

Subjects were seated comfortably in a chair with their right forearm flexed at the elbow and positioned on the board of a strain gauge. In order to perform unidirectional thumb movement, the thumb was fixed to the strain gauge by a splint. The training movement was performed against a one dimensional rubber expander, which enabled the thumb to return passively to the starting point of movement. The strain gauge moved with TMS-evoked thumb movements either in extension or flexion. The thumb was fixed to the strain gauge plate during both exercise and TMS trials while the investigator continuously monitored the correct performance of thumb movement. This particular model is a modification from Classen et al., who used two accelerometers fixed to the thumb to record movement directions; one accelerometer measured abduction or adduction movements and the other measured flexion or extension movements. However, in the present study, a strain gauge was used to record the unidirectional flexion or extension movements of the thumb.

Stimulation and procedure

TMS was performed using a MagStim 200 (UK) connected to a figure-of-eight coil held with the handle pointed backwards and laterally at a 45° angle to the sagittal plane. The optimal coil position was defined as the scalp position at which small thumb movements in a constant direction (flexion) could be evoked. After marking the coil position on the scalp with a pen, a stimulation intensity of 120% of resting movement threshold was used. This intensity evoked consistent isolated thumb movements in all subjects. The movement threshold was defined as a displacement of the splint on the strain gauge ≥ 50 gm in three of five trials. Motor training, namely thumb movement exercise, was executed on the strain gauge, which was connected to a highly sensitive amplifier (WGA-710 A), which in turn was connected to an evoked-potential, electromyography measuring system (Neuropack Σ). The amplifier was zeroed while the thumb rested on the strain gauge to counteract the weight of the thumb. Minimum movement of the thumb, either TMS-evoked or self-induced, accelerated the amplifier marker +.01 for flexion, which in turn showed a downward deflection of movement trace, and −.01 for extension, which show an upward deflection of movement trace on the monitor. Movement signals were recorded by Neuropack Σ using 50 Hz and .01 Hz as high and low cut filters, respectively. A baseline (pre-training) TMS-evoked thumb movement in a specific direction (flexion) was established during rest. Subjects were asked to voluntarily extend their thumb slowly and continuously for 15 minutes without external sound (self-paced) in the

opposite direction of the baseline movement (flexion) at a rate of 60 movements per minute. Five-minute intervals of TMS-evoked movement were recorded to examine changes in the direction of thumb movement. After the first 15 minutes of training, subjects were allowed to rest for another 15 minutes. Every additional 5 minutes, TMS-evoked movement was recorded to examine whether the change of direction returned to the baseline (pre-training). During the TMS study, subjects were required to suspend thumb extension exercise for 15 seconds for three stimulation trials. In the first sitting, TMS-evoked movement of direction was recorded during the 15-minute thumb extension exercise without cue followed by 15 minutes rest. In the next session (not in the same day), the technique was repeated and TMS-evoked movement of direction after the 15 minutes thumb extension exercise was recorded with a metronome beat of 1 Hz as an auditory cue, followed by 15 minutes rest.

Change of direction in TMS-induced movement indicates motor reorganization. In addition, changes in amplitude from the baseline of TMS-induced movement with sound (metronome-paced) and without sound (self-paced) were compared across the three groups of normal participants, freezing PD patients, and non-freezing PD patients (normal, freezing, non-freezing groups, respectively) to evaluate the effect of sensory cues on motor reorganization.

TMS-induced movement
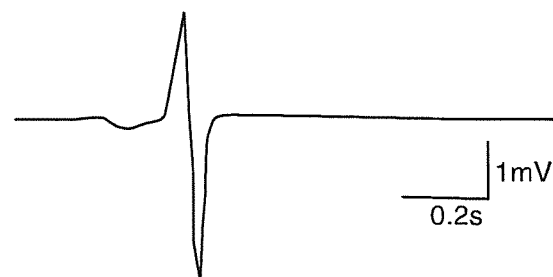

TMS-induced MEP

Fig. 1. Upper trace of thumb movement on strain gauge induced by transcranial magnetic stimulation (TMS) and lower trace of motor evoked potential by TMS recorded by electrode from thenar eminence of right thumb

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TMS-induced movement differs from motor evoked potentials (MEP). MEP is the electrical activity of muscles evoked from cortical motor neuron stimulation and is recorded by electrodes. In contrast, TMS-induced movement is recorded by the displacement of a strain gauge following pressure from contracted muscles evoked by cortical stimulation (Fig. 1).

Results

Effect of pre- and post-training thumb movement exercise: Data concerning TMS-evoked change in direction of movement is shown

in Fig. 2. Figure 2A shows the downward pre-exercise movement direction caused by flexion of the thumb during TMS at the representative cortical motor area defined by pre-exercise movement. Following thumb extensions at a rate of 1 Hz without external sound (self-paced), TMS-induced movement direction changed to the direction of exercise during TMS at the same representative cortical motor area and at the same intensity. Before exercise, the strain faced the downward direction, but after 5 minutes of exercise, the
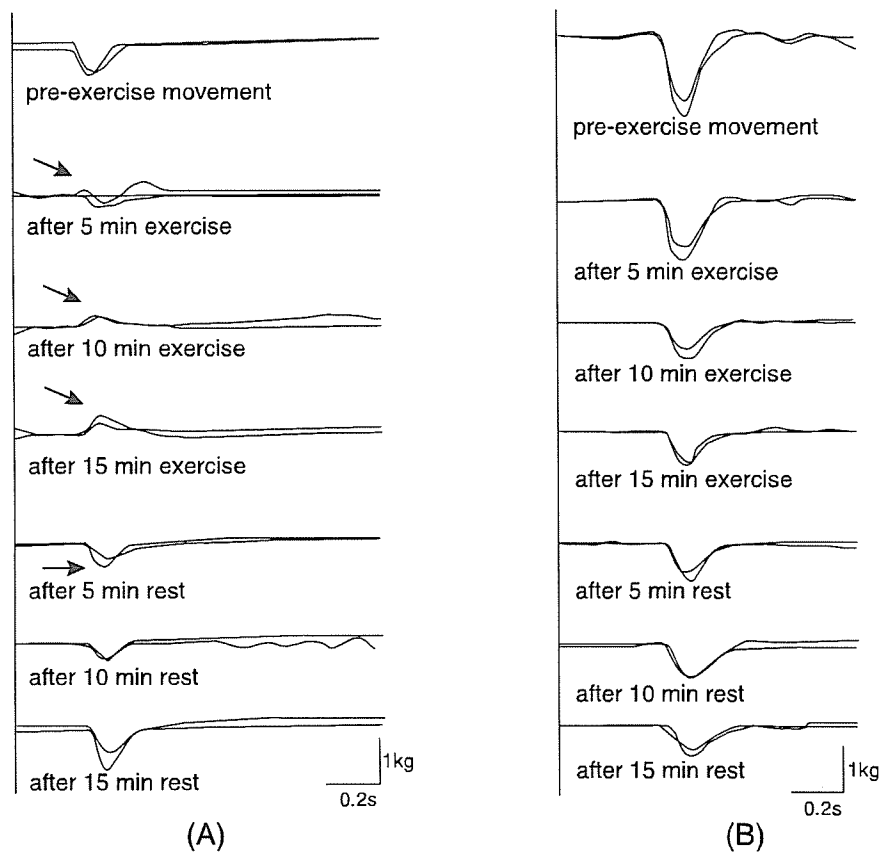

Fig. 2. Example of TMS-induced movement during 15 minutes exercise and 15 minutes rest from two normal representative controls during self-paced exercise. Pre-exercise movement direction derived from TMS-induced thumb flexion movement. After exercise in the opposite direction (extension) of the thumb, the direction of TMS-induced thumb movement changed from the pre-exercise direction to the exercised direction (A). The changes appeared after 5 minutes of exercise (arrow head). After 5 minutes of rest the direction of movement began to return to its original or pre-exercise position (4th arrow head). TMS trials were given at 5-minute intervals. B Representative data from one control (two responses are superimposed), indicating a decrease in amplitude rather than no change in the TMS-induced movement direction after 15 minutes thumb extension exercise

direction of strain began to move toward the direction of exercise. At rest, the movement returned to the original, pre-exercise direction. This pattern was observed in 5 of 9 controls

Fig. 3. Example of TMS-induced movement during 15 minutes exercise without cue and 15 minutes rest from one representative freezing PD patient. The change of direction was initiated after 5 minutes of training (arrow head), note that the change in direction of TMS-evoked movement after thumb exercise for 15 minutes remained as a memory trace for 5 minutes after cessation of the exercise and the change occurred to the pre-exercise direction after 10 minutes of rest (5th arrow head)

and in 9 of 12 PD patients (5 freezing PD patients and 4 non-freezing PD patients) during both self-paced and metronome-paced thumb exercise. Figure 3 shows that the directional change of TMS-evoked movement after 15 minutes of thumb extensions in PD patients remained as a memory trace 5 minutes after stopping the exercise. Three control subjects and one freezing PD patient who did not produce a directional change in the TMS-induced movement demonstrated a slight reduction in amplitude (Fig. 2B).

Following self-paced thumb training, one freezing PD patient did not show a change in TMS-induced movement direction; however, the movement direction did change to the metronome-paced rhythm after 10 minutes of exercise (Fig. 4A). One control subject and one non-freezing PD patient showed a change to the practice direction after 15 minutes of thumb exercise (Fig. 4B) and were excluded from the statistical analyses.

Effect of sensory cue on motor learning: The influence of auditory cue was examined by measuring the peak amplitude of strain in all subjects who demonstrated a change in the amplitude of TMS-evoked movement every 5 minutes during 15 minutes of continuous exercise. These measurements were compared between the self-paced and metronome-paced training of each group. Mean difference values between the baseline amplitude (pre-exercise) and the amplitude following the three pulses of TMS are plotted in Table 2.

Mean strain amplitude of the three groups (normal, non-freezing and freezing) were compared between the self-paced and metronome-paced rhythms at three time points by analysis of variance (ANOVA), and post hoc comparisons with Bonferroni corrections were applied. The level of significance was set at $p < 0.05$.

Scores were found to be higher in metronome-paced training than self-paced training in all three groups (Table 2). Additionally, the main effect of both self-paced [F (2, 15),
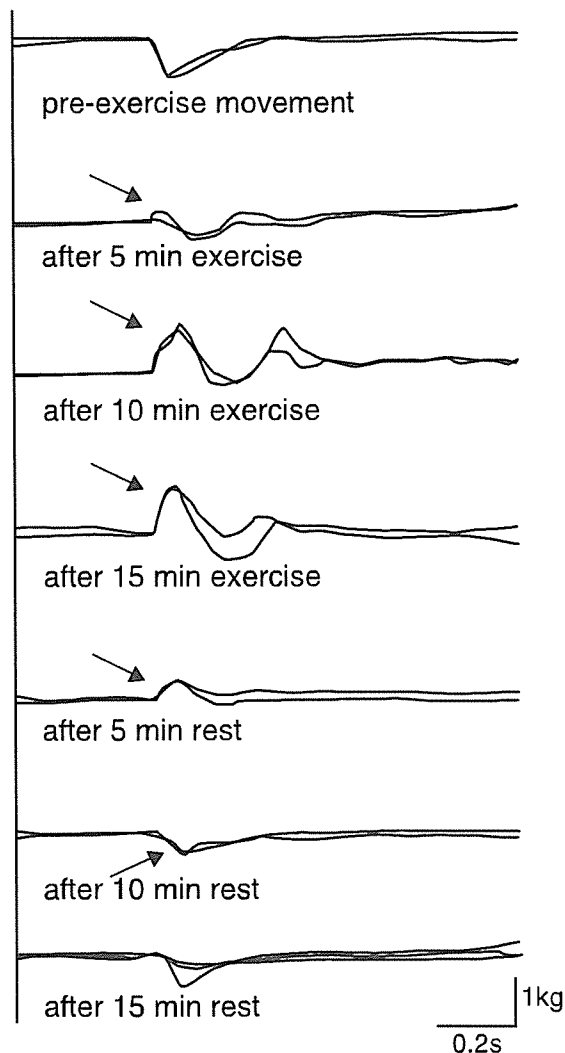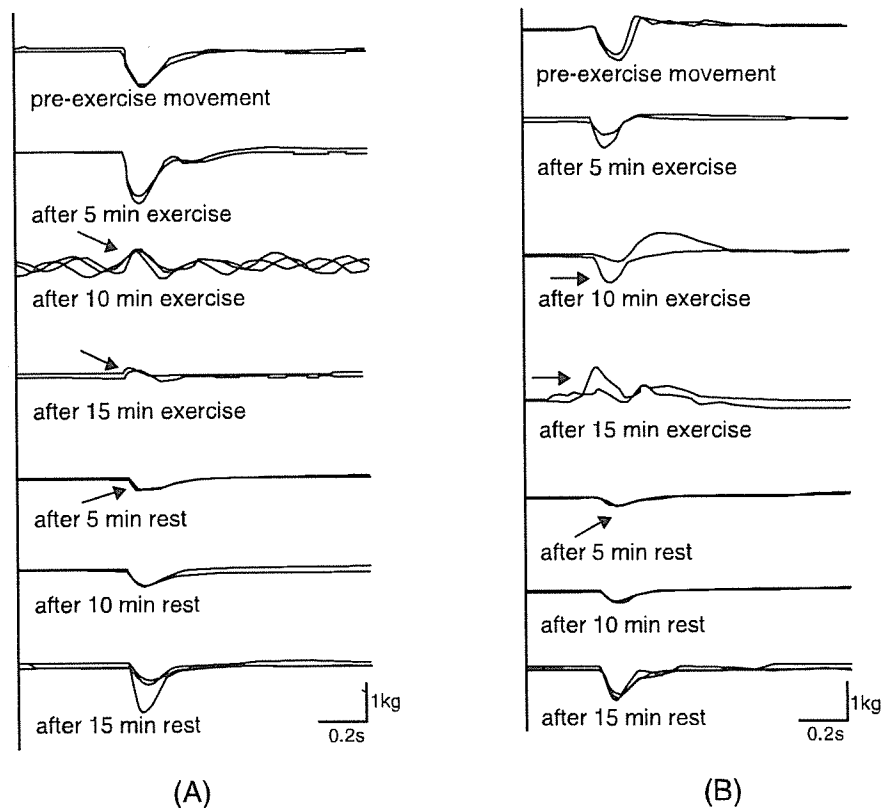
Fig. 4. Change in TMS-induced movement direction initiated after 10 minutes (arrow head) of thumb extension exercise with auditory cue in a freezing PD patient (**A**) (the wave in the trace is due to tremor) while the direction changed after 15 minutes of exercise with auditory cue in a normal participant (**B**)

p = .000] and metronome-paced [F (2, 15), p = .006] rhythm were seen after 5 minutes of exercise in each group. Post hoc comparison revealed that non-freezing and freezing PD patients showed significantly (p = .000 in both non-freezing and freezing groups) reduced amplitude compared to normal participants at self-paced rhythm, and also at metronome-paced rhythm but at a reduced level of significance (p = .027 in non-freezing group, p = .012 in freezing group). After 10 minutes of exercise, an increase in strain scores were observed, but no significant main effect was observed for both cue and non-cue rhythm. After 15 minutes of exercise, a significant main effect was observed in non-cue rhythm [F (2, 15), p = .048]. Post hoc com-

parison revealed that freezing PD patients showed a near significant (p = .059) effect compared to normal participants, whereas during metronome-paced exercise, the effect was not significant (p = .534) compared to normal participants.

Kinematical traces during thumb exercise (Fig. 5) with rhythmic sound and without rhythmic sound clearly indicate the effect of auditory cue on motor training. The wave without sound is irregular and not parallel, indicating a deficit in the execution of simultaneous and sequential movements. Conversely, waves recorded with rhythmic sound are regular, parallel to the baseline and flat for a short period. Rhythmic movements resulted from the external stimuli, which suggest that

Table 2. Comparison of TMS-induced movement amplitude of strain (gm) at self-paced and metronome-paced rhythms between time intervals in groups

	5-minute exercise		10-minute exercise		15-minute exercise	
	Self-paced	Metronome-paced	Self-paced	Metronome-paced	Self-paced	Metronome-paced
Normal (n = 8)	192 ± 15.7	197.5 ± 20	186 ± 29.8	199 ± 64.1	220.1 ± 45.9	238 ± 47.4
Non-freezing (n = 4)	125 ± 4.5[a]	141 ± 28.2[b]	144 ± 46.7	172.5 ± 6.4	175.5 ± 6.6	186.2 ± 8.5
Freezing (n = 6)	112.5 ± 10.7[c]	141.3 ± 42.4[d]	156 ± 12.2	159 ± 39.5	160.8 ± 48.1[e]	209.1 ± 36.2

[a,b,c,d,e] Significantly different from normal participants (p = .000, p = .027, p = .000, p = .012 and p = .048 respectively)

Parkinson's subjects are able to use sensory cues to overcome difficulties in initiation or continuation of movement.

Discussion

Improved motor learning with auditory cue was observed in the normal participants, freezing PD patients, and non-freezing PD patients. However, the main finding of the present research is that after 15 minutes of exercise with non-cue rhythm, the difference in TMS-evoked movement amplitude was marked in freezing patients when compared to normal participants, whereas after exercise with auditory cue, the TMS-evoked movement amplitude increased in freezing PD patients and showed no significant difference compared to normal participants. After 15 minutes of exercise, the increase in TMS-evoked movements from self-paced to metronome-paced in normal participants, non-freezing and freezing PD patients were 10.8%, 10.6% and 13.0%, respectively. This indicates that the motor learning of non-freezing PD patients is similar to that of normal participants.

Observation of change in movement direction required 5 minutes of thumb extension exercise for most subjects (14 of 21 subjects). For 2 subjects, 10 or 15 minutes of continuous training was required to initiate a change in TMS-evoked movement. Four subjects (3 normal participants and one PD patient) did not produce a directional change in TMS-induced movement but a trend of reduced amplitude was seen in those subjects, likely due to the training duration of 15 minutes. We expect that an increased duration of exercise would have resulted in a change in movement direction.

A period of 15 minutes exercise was chosen to maintain equal time duration and to avoid considerable fatigue in all subjects. After beginning the thumb extension exercise, a slight trend of whole upper limb movement during extension exercise was observed in some PD patients. However, in spite of this
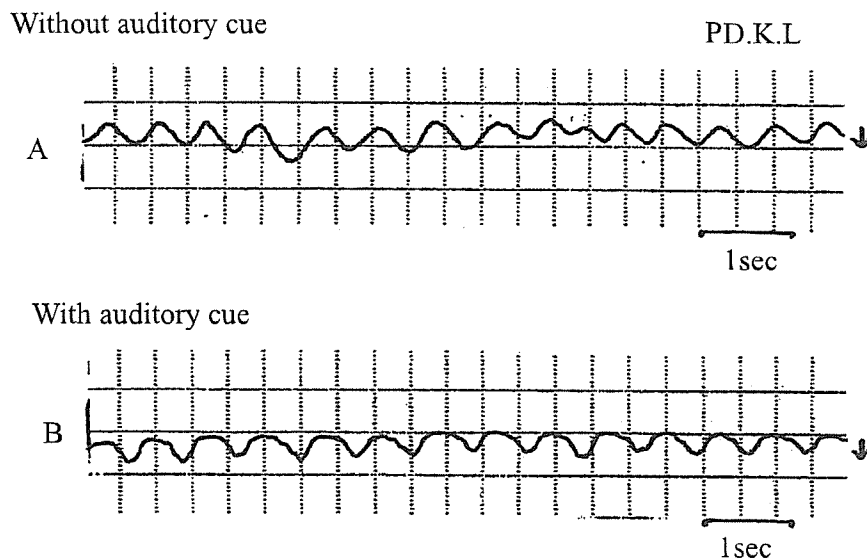
Without auditory cue

PD.K.L

A

1 sec

With auditory cue

B

1 sec

Fig. 5. Strain gauge recordings during motor training. Kinematically the shape of the wave during exercise with auditory cue (B) is smooth, regular, rhythmic and flat, in comparison to the wave of exercise without sound (A)

limitation, and in accordance with other studies (Classen et al., 1998; Karin et al., 2000), short training of a unidirectional thumb movement was found to exert a change in TMS-evoked movement direction, thus suggesting a transient change in the representing cortical area. This type of change, either morphological or functional, has been described as brain plasticity. Evidence of motor cortex reorganization has also been observed in subjects with chronic neurological disorders including cerebral tumor, amyotrophic lateral sclerosis (Seitz et al., 1995), after hemispherectomy (Cohen et al., 1991), after anastomosis of the musculocutaneous nerve and intercostals nerves following cervical root avulsion (Mano et al., 1995), and after limb amputation (Brasil-Neto et al., 1993). The findings of the present study further support the notion that the primary motor cortex can be reorganized by motor practice even in a single training period (Muellbacher et al., 2001). As a result of voluntary activation, a shift in the cortical motor map for the hand muscles was demonstrated in healthy subjects under the physiological condition (Wilson

et al., 1993). The results of the present study of thumb training showed similar abilities of healthy subjects and Parkinson's disease patients to represent encoded kinematic details of the practiced movement (Classen et al., 1998). Cortical reorganization, as observed in the present study, is likely due to functional synaptic mechanisms of corticocortical connections, which include the removal of local inhibition and changes in synaptic efficacy (Karin et al., 2000).

Plasticity has been clearly demonstrated using TMS in humans during motor learning, and in response to brain injury. To enhance plasticity so as to recover damaged brain function, several techniques have been used for rehabilitation. In addition to neuromuscular electrical stimulation, sensory stimulation, robot-enhanced training, and administration of pharmacological agents such as amphetamine, constraint-induced movement therapy plays a vital role in enhancing plasticity for skill acquisition even in intact humans (athletes) and in the rehabilitation of individuals with brain damage (Butefisch et al., 1995). Neural plasticity is associated with

the acquisition of motor skills (Cohen et al., 2002). These experiments have also shown that Parkinson's disease patients are able to change their performance as a result of practice, and that performance improves when supported by external stimuli. Studies of patients with Parkinson's disease and even in patients with normal pressure hydrocephalus indicated that rhythmic auditory stimulation, visual cue on gait velocity, cadence, and stride length were attributed to improvements in performance (Macintosh et al., 1997; Stolze et al., 2001). However, the present study focused on differences in peak amplitude between self-paced and metronome-paced TMS-induced movements following simple thumb training.

The freezing phenomena and starting hesitation play a vital role in the development of bradykinesia and gait disorder in Parkinson's disease patients. These phenomena may be improved in some patients by the use of motor and sensory "tricks" (Stern et al., 1980; Wolfson et al., 1995), such as alteration of body weight, taking longer strides, and walking sideways. Useful auditory and verbal stimuli include marching like a soldier to commands, walking to music or listening to a metronome ticking (David et al., 2002). Visual stimuli include stepping over objects such as another person's foot or the handle of a walking stick, and imagining colored lines on the floor to step over. In the present study we used the rhythmic sound of a metronome as an auditory stimulus in order to improve motor performance, which enhanced the motor reorganization by acquisition of skills.

Several mechanisms may explain the improved motor performances from an external cue. One previous study stated that different neural mechanisms mediate self-generated (internally triggered) and reaction-time (externally triggered) movements (Horak et al., 1996). As there are two routes in voluntary movement in the nervous system, the decreased function of basal ganglia due

to PD impaired the route from the basal ganglia to the supplementary motor cortex. It is suggested that the route of the external circuit (i.e. external sensory stimulus, to cerebellum, via premotor cortex to primary motor cortex to voluntary muscle contraction) could compensate for the decreased function of the route of the internal circuit (i.e. limbic system to basal ganglia, via supplementary motor cortex to primary motor cortex to voluntary muscle contraction) (Marsden and Obeso, 1994). In the case of insufficient substantia nigra function in PD patients, the external auditory cue was effective in facilitating the performance of strain gauge motor training in the present research. As in previous studies, once the change in TMS-evoked movement direction occurred, it persisted even after the cessation of training (Fig. 3) suggesting that motor memory could be stored in the primary motor cortex or in the premotor cortex (Mano et al., 2003).

The kinesiological traces during exercise with and without rhythmic sound clearly showed the effect of rhythmic sound in producing a smooth motor cue for PD patients. The set of waves recorded during exercise without sound are irregular, not parallel to the baseline, and decline sharply during simultaneous and sequential execution of movements. Conversely, with feedback (rhythmic sound) the cue is regular, parallel to the baseline and flat for a short period. Rhythmic movements resulted from the external stimuli that aid in overcoming deficiencies. The rhythmic sound induced rhythmic and forceful movements of the thumb and enabled skilled motor learning that subsequently increased the peak amplitude of TMS-induced movements. Since neuroanatomical evidence suggests a direct connection between Broca's area and the supplementary motor area, the present study indicates that for Parkinsonian patients who have experienced the freezing phenomena, repetitive and rhythmic sound activated the motor area and facilitated the maintenance of the motor set or motor plan

that aids the acquisition of motor skills (Albani et al., 2001). We conclude that the process of motor reorganization in patients with Parkinson's disease does not differ from that of normal subjects. In addition, rhythmic sounds may be an effective rehabilitation tool for improving gait disorder (Dibble et al., 2004) and motor performance in PD patients who experience the freezing phenomena.

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