consisted of four magnetic pulses separated by interstimulus intervals (ISIs) of 5 or 50 ms for excitatory or inhibitory rTMS, respectively. One rTMS block consisted of 360 consecutive trains that took 30 min, and the intensity of rTMS was set at 90% AMT.

fMRI Scanning

MRI scanning was conducted using a 3T MRI scanner with a one-channel head coil (Signa HDxt 3.0T, GE Healthcare, Milwaukee, WI). T1-weighted structural images were obtained as the anatomical reference (resolution = 0.81 × 0.81 × 1.20 mm^3). fMRI was conducted using gradient echo echo-planar sequences (TR = 2.5 s, TE = 35 ms, flip angle = 90°, resolution = 4 × 4 × 4 mm^3, 32 slices). The first five functional images of each run were discarded to minimize the effects of transient magnetic saturation.

The localizer fMRI scans were conducted to identify the M1 for the right FDI. The fMRI scans consisted of two runs of 5 min, and the subjects were instructed to continuously tap their right or left index finger during blocks of 16 s, intervened by control blocks of resting for 16 s. The resting-state fMRI scans consisted of five runs of 5 min each, and the subjects were instructed to fix their gaze on a fixation point during the fMRI scans.

In the present procedure of rTMS stimulation, we determined the location of the target region (left M1) on the basis of MEP responses. On the other hand, in the following analysis of rTMS-induced effects on RSFC, we determined the location of the left M1 on the basis of the functional localizer scan. Although the discrepancy between these two estimations is a potential limitation, fairly good correspondence between the locations of the MEP-based M1 and the functional-localizer-based M1 has been demonstrated in prior literatures [Sparing et al., 2008].

Analysis of fMRI Data

The obtained localizer fMRI images were first realigned, slice-timing-corrected, normalized to the default template with interpolation to a 2 × 2 × 2 mm^3 space, and spatially smoothed (full width at half maximum = 10 mm, Gaussian filter) using SPM8 (http://www.fil.ion.ucl.ac.uk/spm/). In one subject, the preprocessed data were analyzed in a boxcar design. The event timings of two types of trials (tapping of the right/left index finger) were coded into a general linear model (GLM), together with run-specific effects and other events of no interest, using the canonical hemodynamic response function in SPM8. By calculating the contrast image defined as right > left, we determined the M1 in the left hemisphere for the right FDI.

The resting-state functional imaging data were analyzed using the following procedure, which is essentially the same as that used in the previous studies [Fair et al., 2007; Fox et al., 2005]. The images were realigned, slice-timing-corrected and normalized to the default template in SPM8. Although we compared BOLD signal magnitude in the whole brain between the baseline and post-rTMS sessions, we did not detect any consistent difference between them owing to a large variance derived from different sessions. The data were subjected to temporal band-pass filtering (0.01–0.1 Hz) using in-house-written Matlab scripts, and were spatially smoothed (FWHM = 8 mm). GLM was used to regress out nuisance signals that correlated with head motion, whole-brain signals, average ventricular signals, and average white matter signals.

We first conducted an exploratory search by estimating how rTMS changed the voxel-wise functional connectivity in the whole brain using the left M1 as a seed region (radius, 5 mm). The coordinates of the left M1 of each subject were determined on the basis of the results of the localizer task. Functional connectivity was calculated on the basis of Pearson's correlation coefficient, and was first transformed to t value as follows.

$$t\left(\frac{N-2}{BCF}\right) = r\sqrt{\frac{N-2}{BCF}(1-r^2)},$$

where BCF indicates the Bartlett correction factor, N is the number of fMRI images, and r denotes Pearson's correlation coefficient. On the basis of Bartlett's theory, we used BCF to take into account autocorrelation in the fMRI signals and to correct the degrees of freedom [van Dijk et al., 2010]. After that, we evaluated corresponding P values and then estimated corresponding z scores. Using the z scores, we estimated the difference between the functional connectivity z-map for excitatory/inhibitory rTMS and that for the baseline session for each subject as follows.

$$\Delta FC = z_{Post-rTMS} - z_{Pre-rTMS}$$

This difference was subjected to a second-level analysis using a one-sample t-test. Consequently, we obtained two whole-brain maps: a connectivity map for excitatory rTMS session > baseline session (Fig. 3B) and a connectivity map for inhibitory rTMS session > baseline session (Fig. 3C). Significant connectivity changes were evaluated by using a threshold of FDR-corrected $P < 0.05$.

We next conducted a region-of-interest analysis by estimating changes in interhemispheric RSFC between the stimulated region (i.e., the left M1) and the contra-lateral region (i.e., the right M1). The stimulated region was determined on the basis of the results of the functional localizer session (radius = 5 mm). The contralateral region was determined as a 5-mm-radius sphere around the corresponding voxel (i.e., when the center of the left M1 was $[X_1, Y_1, Z_1]$, the center of the contra-lateral region was determined to be $[-X_1, Y_1, Z_1]$). On the basis of the definitions of the regions, we estimated the amount of change in interhemispheric RSFC induced by excitatory and inhibitory rTMS.

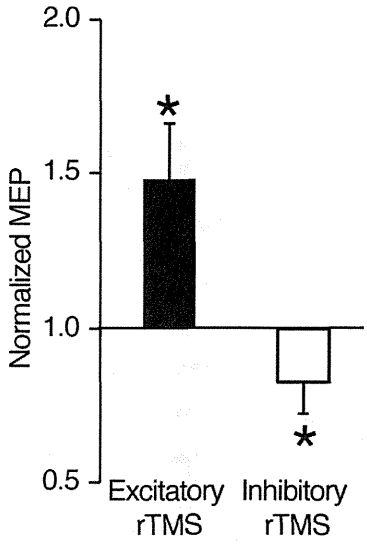

Figure 2.
Effects of rTMS on MEP. The Y axis shows the ratio of the post-rTMS MEP of the right FDI to the baseline MEP. In both excitatory and inhibitory rTMS, the expected changes in MEP were observed. Error bar: s.e.m. *: $P < 0.05$.

RESULTS

MEP Results

We confirmed the excitatory and inhibitory rTMS effects on MEP in the left M1 found in our previous investigations [Hamada et al., 2007, 2008]. We compared the MEPs recorded before the rTMS with average MEPs recorded immediately after and 60 min after the rTMS. Consequently, we found that excitatory rTMS induced a significant increase in normalized MEPs, and the inhibitory rTMS induced a significant decrease (excitatory rTMS, $t_{(5)} = 3.0$, $P < 0.05$; inhibitory rTMS, $t_{(5)} = 3.2$, $P < 0.05$ in two-tailed t tests; Fig. 2). These findings were consistent with those of our previous studies [Hamada et al., 2007, 2008], which confirms that the following fMRI results reflected the effects of excitatory/inhibitory rTMS.

RSFC Results

We conducted an exploratory search by estimating changes in RSFC at every voxel in the whole brain with the seed placed in the left M1, which was determined by the localizer fMRI scanning. After excitatory rTMS, functional connectivity with the left M1 significantly decreased in several regions including the right primary motor area and middle frontal gyrus (Fig. 3B, Table I). There were no brain regions that showed a significant increase in the RSFC with the left M1. In contrast, after inhibitory rTMS, functional connectivity significantly increased in brain regions including the left primary motor area, bilateral superior temporal gyrus, and left cerebellum (Fig. 3C, Table I). There were no brain regions showing a significant decrease in the RSFC with the left M1. Among these responsive regions shown in Figure 3B,C, significant bidirectional changes were observed at the contralateral M1 after both excitatory and inhibitory rTMSs. Note that Figure 3B,C show the subtraction between the functional connectivity maps of the pre-rTMS and post-rTMS sessions, and the local effects were not detected.

We then conducted a region-of-interest analysis by evaluating rTMS-induced changes in interhemispheric RSFC between the stimulated region and the coordinate-based contralateral region. The excitatory rTMS significantly decreased interhemispheric RSFC ($t_{(5)} = 13.0$, $P < 0.001$, Fig. 4A). In contrast, after the inhibitory rTMS, interhemispheric RSFC significantly increased ($t_{(5)} = 11.8$, $P < 0.001$, Fig. 4A), which is consistent with the findings of previous studies in which the effects of inhibitory rTMS on RSFC were investigated [Eldaief et al., 2011; Vercammen et al., 2010]. In addition, these effects were statistically significant even in a single-subject-level analysis (Table II): In the case of the excitatory rTMS, the least sensitive subject exhibited a significant decrease in interhemispheric RSFC as shown by a large z value ($|z| = 5.3$, $P < 10^{-6}$). In the case of the inhibitory rTMS, even the least sensitive subject also showed a significant increase in interhemispheric RSFC as shown by a large z value ($|z| = 6.1$, $P < 10^{-6}$). These results show that the inhibitory and excitatory rTMSs induced significant bidirectional changes in interhemispheric RSFC. These bidirectional changes were also observed even when we defined the contra-lateral right M1 on the basis of the localizer fMRI images ($P < 10^{-5}$). Indeed, exploratory functional connectivity analysis revealed that the right M1 defined on the basis of the functional localizer was located closely to the brain regions that showed the largest changes in RSFC with the left M1 in both single-level analysis and group-level analysis (Supporting Information Fig. 1).

Moreover, the magnitude of the changes in interhemispheric RSFC was significantly correlated with the magnitude of the changes in MEP in both of the excitatory and inhibitory rTMSs (excitatory rTMS: $r = -0.81$, $P = 0.04$, inhibitory rTMS: $r = -0.84$, $P = 0.03$, Fig. 4B). In contrast, the changes in RSFC showed neither significant correlation with the intensity of rTMS, baseline MEP amplitude, nor the intensity of the fMRI local activation. These significant correlations confirm that the observed changes in interhemispheric RSFC were induced by the rTMS. Furthermore, these bidirectional effects on RSFC were observed in rTMSs over the prefrontal and parietal association areas (Supporting Information Figs. 3 and 2, Supporting Information Table I).

DISCUSSION

In this study, using a QPS protocol, we found that excitatory rTMS over the M1 induced a decrease in interhemispheric RSFC, whereas inhibitory rTMS induced an increase in RSFC. This effect was consistently significant in

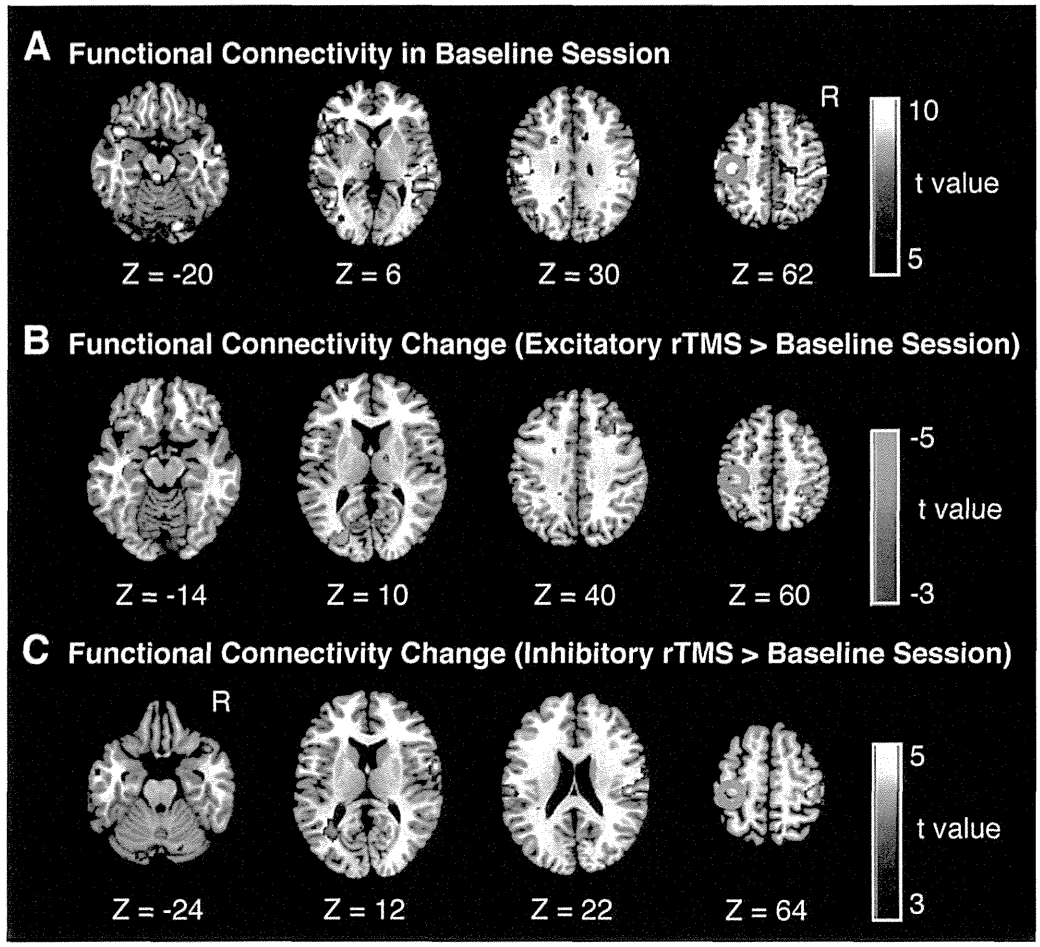

Figure 3.

Changes in RSFC after rTMS of left M1. **A.** Statistical maps of functional connectivity with the left M1 in pre-rTMS sessions (i.e., baseline sessions). **B** and **C**. Changes in RSFC with the left M1 induced by excitatory rTMS (panel B) and inhibitory rTMS (panel C). The color scale shown on the right indicates statistical significance level. The blue circles indicate the approximate location of the left M1, which was determined by the functional localizer scan. These panels indicate the subtraction between the functional connectivity maps of the pre-rTMS and post-rTMS sessions; as a consequence, the local effects were eliminated. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

all the subjects. The effects were also observed in the prefrontal and parietal association areas, implying that the bidirectional effects of rTMS could be observed in brain areas other than the M1.

The effect of excitatory rTMS on RSFC is consistent with that found in previous studies in which rTMS-induced changes in functional connectivity were investigated by electroencephalography (EEG) [Fuggetta et al., 2008; Oliviero et al., 2003]. Those studies have demonstrated that excitatory rTMS decreases cortico-cortical coherence in the alpha band. Our present findings of the effect of inhibitory rTMS on RSFC is also consistent with those of a line of previous studies using EEG [Chen et al., 2003; Strens et al., 2002], positron emission tomography (PET) [Lee et al., 2003], and fMRI [Eldaief et al., 2011; Grefkes et al., 2010; Vercammen et al., 2010]. Previous EEG studies have shown that inhibitory rTMS increases coherence in both the resting state [Strens et al., 2002] and task period [Chen et al., 2003]. Among other PET studies [Horacek et al., 2007; Paus et al., 2001], a previous PET study has shown that inhibitory rTMS increases effective connectivity [Lee et al., 2003]. Prior fMRI studies using inhibitory rTMS have also observed increases in effective connectivity [Grefkes et al., 2010] and functional connectivity [Eldaief et al., 2011; Vercammen et al., 2010]. Another study has shown that rTMS induces the release of dopamine and

TABLE I. RSFC change induced by quadripulse rTMS

Anatomical label	MNI coordinates X	Y	Z	*t* value
Excitatory rTMS > baseline session				
Lt. middle frontal gyrus	−22	54	−14	−4.5
Lt. middle occipital gyrus	−24	−90	10	−4.8
Rt. middle frontal gyrus	28	20	40	−4.2
Rt. middle frontal gyrus	30	6	58	−4.3
Rt. precentral gyrus (M1)	34	−20	60	−4.4
Inhibitory rTMS > baseline session				
Lt. cerebellum	−14	−82	−22	3.9
Rt. superior temporal gyrus	40	14	−24	4.6
Rt. precentral gyrus	64	0	12	4.8
Lt. postcentral gyrus	−60	−20	20	4.7
Rt. inferior parietal lobule	50	−26	22	4.8
Rt. postcentral gyrus	64	−18	24	4.7
Rt. precentral gyrus (M1)	32	−30	64	4.9

MNI: montreal neurological institute. Anatomical labels are based on WFU pickatlas (http://fmri.wfubmc.edu/).

increases task-specific functional connectivity [van Schouwenburg et al., 2012]. Although one of the studies has demonstrated large effects of excitatory rTMS and relatively moderate effects of inhibitory rTMS [Eldaief et al., 2011], to the best of our knowledge, our present study is the first to clearly demonstrate the bidirectional effects of excitatory and inhibitory rTMSs on the same RSFCs.

This successful detection of the bidirectional effects is considered to rely on the long-lasting effects of QPS [Hamada et al., 2007, 2008; Hanajima et al., 2001; Shirota et al., 2010] and interhemispheric RSFC [Stark et al., 2008; Zuo et al., 2010]. The effects induced by conventional rTMS protocols [Eldaief et al., 2011] appear ~20 min after the stimulation and last up to 60 min after the stimulation [Siebner et al., 2003; Speer et al., 2000; Valero-Cabre et al., 2007]. In contrast, in the present protocol, the effect of QPS appears ~10 min after the stimulation and lasts for over 90 min after rTMS [Hamada et al., 2007, 2008]. In the current study, these long-lasting effects of QPS are considered to enable us to record a sufficient amount of stable fMRI data, which would be one of the major reasons we were able to detect the clear bidirectional effects.

The physiological basis of this rTMS-induced connectivity change remains unclear. A previous PET study examining online effects of rTMS has demonstrated that excitatory rTMS increases blood flow in the stimulated site immediately after the stimulation [Strafella et al., 2001]. In contrast, several previous MRI studies using arterial-spin labeling to evaluate the off-line effects of rTMS have implied that inhibitory rTMS subsequently induces a compensatory increase in blood flow into the stimulated region [Moisa et al., 2010; Orosz et al., 2012]. In addition, a previous study using near-infrared light to measure cortical activity has shown that the inhibitory-rTMS-induced activity change in the stimulated region is similar to that in the contra-lateral brain region [Parks et al., 2012]. On the basis of these reports, one possible physiological basis is that rTMS induces a compensatory reaction in the stimulated region and subsequently induces a similar reaction in the contra-lateral region, which should result in an increase in inter-hemispheric RSFC. Considering the strong correlation between rTMS-induced RSFC changes and MEP changes (Fig. 4B), we also speculate that the present findings indicate a causal relationship between rTMS-induced RSFC changes and MEP changes. That is, excitatory and inhibitory rTMSs might enhance and reduce inter-hemispheric inhibition from the contra-lateral brain regions, which subsequently decreases and increases activity in the

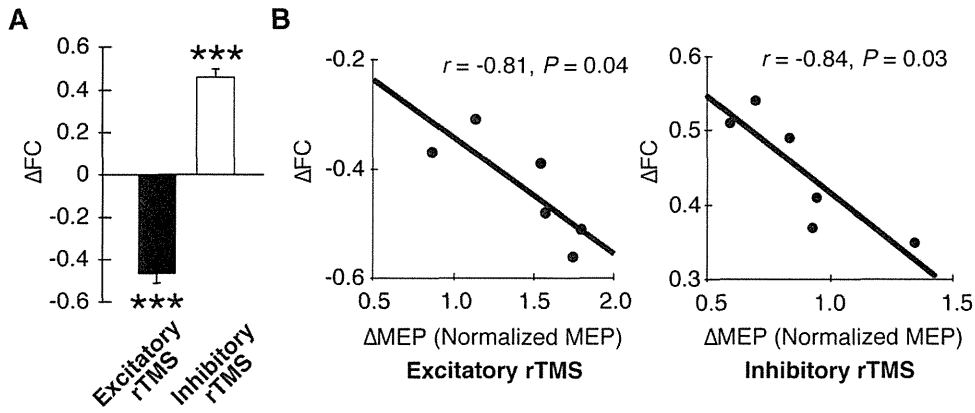

Figure 4.

Changes in inter-hemispheric RSFC. **A.** Group effects of rTMS. Excitatory and inhibitory rTMS induced significant decrease and increase in interhemispheric RSFC between the bilateral M1s. ***: $P < 0.001$ in one-sample *t* tests. Error bars: s.e.m. **B.** Correlation between effects of rTMS on MEP and RSFC. The magnitudes of the effects on inter-hemispheric RSFC were significantly correlated with the magnitude of the effects on MEP.

TABLE II. Statistical significance of interhemispheric RSFC change

	Excitatory rTMS					Inhibitory rTMS			
Subject	Pre-rTMS RSFC ($z_{pre\text{-}rTMS}$)	Post-rTMS RSFC ($z_{post\text{-}rTMS}$)	ΔFC	Z value	P value	Post-rTMS RSFC ($z_{ost\text{-}rTMS}$)	ΔFC	Z value	P value
S1	0.45	−0.03	−0.48	−8.3	$<1 \times 10^{-6}$	0.94	0.49	8.5	$<1 \times 10^{-6}$
S2	0.41	−0.1	−0.51	−8.8	$<1 \times 10^{-6}$	0.95	0.54	9.6	$<1 \times 10^{-6}$
S3	0.48	0.09	−0.39	−6.7	$<1 \times 10^{-6}$	0.89	0.41	7.1	$<1 \times 10^{-6}$
S4	0.42	−0.14	−0.56	−9.7	$<1 \times 10^{-6}$	0.93	0.51	8.8	$<1 \times 10^{-6}$
S5	0.52	0.15	−0.37	−6.4	$<1 \times 10^{-6}$	0.87	0.35	6.1	$<1 \times 10^{-6}$
S6	0.54	0.23	−0.31	−5.3	$<1 \times 10^{-6}$	0.91	0.37	6.4	$<1 \times 10^{-6}$

Z and *P* values were obtained by test of the difference in Pearson correlation coefficients. $\Delta FC = z_{post\text{-}rTMS} - z_{pre\text{-}rTMS}$.

stimulated regions and MEPs decrease and increase, respectively. Although these issues need further investigation, this study has raised a promising possibility that excitatory and inhibitory QPSs serve as powerful tools to modulate RSFC.

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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

brain in the posterior to anterior direction. To determine the motor hot spot for the first dorsal interosseous muscle in each subject, we changed the stimulation site in 1-cm steps antero-posteriorly and medio-laterally starting at a point 5 cm lateral to the vertex and determined the location at which the largest responses were elicited by stimulation of the identical intensity. This position was marked on the scalp using a red pen as a guide for repositioning the coil throughout the experiments. The outputs from four magnetic stimulators were connected with a special device (The Magstim Company Ltd., UK) that enabled us to deliver four monophasic pulses through the identical coil. We used three conditioning pulses and one test pulse. We determined the threshold for evoking EMG activities in the active target muscle (active motor threshold: AMT) when the subject maintained the target muscle at 5–10% of the maximum contraction. The stimulation intensity was changed in steps of 1% of the maximum stimulator output until we determined the lowest intensity that evoked a small response (ca. 200 μV) compared to the pre-stimulus background activity in one-half of the trials.

Triad-conditioning TMS

Three conditioning TMS pulses were set at 110% of the AMT. The test stimulus was set to elicit an MEP as large as 0.3 mV in the relaxed muscle when administered alone. The ISI of the four pulses was set at 5, 7, 8, 10, 15, 20, 25, 30, 40, 50, and 100 ms (corresponding to frequencies of 200, 143, 125, 100, 66, 50, 40, 33, 25, 20, and 10 Hz). We used a randomized conditioning test paradigm. In one session, several conditioned trials in which a test stimulus was preceded by triad conditioning pulses were intermixed randomly with control trials in which the test stimulus was given alone. The inter-trial interval was set at 10 s. Two blocks of trials were performed to investigate all the intervals. In the first block, the ISIs were 5, 7, 8, and 10 ms; in the second block, they were 15, 20, 25, 30, 40, 50, and 100 ms. Eight responses were collected and averaged for each ISI condition; 15 responses were collected for the control condition. For each subject, we calculated the ratio of the mean amplitude of the conditioned response to that of the control response (MEP ratio) at each ISI. The time course of the conditioning triad pulses effect was plotted with this ratio on the ordinate and the ISI on the abscissa.

Single-pulse-conditioning TMS study

We also obtained the time-courses of the single-pulse-conditioning TMS in 8 healthy volunteers and 8 PD patients to study whether the effects of triad conditioning TMS are the same as those of a single strong conditioning TMS. The intensity of the conditioning stimuli was set at 95% of the RMT. This intensity corresponded to approximately 150% of the AMT. We used a 95% RMT-conditioning stimulus in a single pulse conditioning experiment to confirm that no significant effects were evoked even using a strong conditioning stimulus because we had shown no significant effects when using a 110% AMT-conditioning stimulus in the single pulse conditioning pulse experiments in our previous paper (Hanajima et al., 2009). The intervals between the last conditioning pulse and the test stimulus pulse were set at the same as those in the triad conditioning TMS pulses.

Statistical analysis

Statistical analysis was performed using SPSS version 17.0 for Windows (SPSS Inc., Chicago, USA). To compare the time courses of the triad-conditioning TMS experiment between the healthy volunteers and the PD patients in the On and Off state, we used a two-factorial repeated measures analysis of variance (ANOVA) [group: PD On, PD Off and normal subjects and ISI: 5–100 ms]. The dependent variable was the size ratio of the MEPs (the ratio of the average size of the conditioned response to the average size of the control responses). When necessary, the Greenhouse–Geisser correction was used to correct for nonsphericity. Tukey's test was used for the multiple comparisons in the post hoc analyses; *P*-values less than 0.05 were considered significant. If there were a significant interaction between two factors, we made a planned comparison between the MEP size ratios among the groups with Tukey's test. Identical statistical analyses were performed for the single pulse conditioning experiments.

The data were reported as the mean ± standard error (SE), except when indicated otherwise.

To elucidate the correlation between the UPDRS and MEP size ratio, we performed linear regression analyses between the UPDRS part III and MEP size ratio at ISIs of 25 ms (40 Hz) for gamma rhythm or those at ISIs of 40 ms (25 Hz) and 50 ms (20 Hz) for the beta rhythm using SPSS version 17.0 for Windows. In this analysis, we used all the data obtained in the On and Off states because we wanted to know the relationship between the functional state at the experiment (UPDSR score) and the physiological parameter at that time (MEP size ratio) whether in the On or Off state. We also performed identical analysis for the patients in the On and Off state separately (not shown here) and obtained an identical tendency as that for all the data. This tendency did not reach statistical significance, probably because the range of the UPDRS at one state was too small to show a statistical significance. Based on these findings, we show the results of the entire data.

Results

Triad-conditioning TMS

The AMT was 40.5 ± 5.5% (maximum stimulation output: MSO) in the Off state and 41.2 ± 4.2% MSO in the On state. The RMT was 55.2 ± 6.9% MSO in the Off state and 59.2 ± 8.7% in the On state. There were no significant differences in the AMT and RMT between the Off and On states. Neither the AMT nor the RMT differed significantly between the de novo and long treated PD patients. Most of participants were able to maintain the target muscle in a relaxed state. In one patient, a resting tremor appeared intermittently during the experiments. We performed the data collection in this patient only when the resting tremor was not seen (1–2% of the stored data were rejected in the off-line analysis even in this patient).

Figure 1 shows the time-courses of the triad conditioning TMS in the healthy volunteers (squares), PD Off (triangles) and PD On (dots). Two-way repeated measures ANOVA revealed a significant effect of ISI and significant interaction between the two factors [ISI – $F(4.142, 153.25) = 25.908$, $P < 0.01$; Group – $F(2, 37) = 2.54$, $P > 0.05$; interaction of the two factors (ISI × Group – $F(8.284, 153.25) = 2.013$, $P < 0.05$)]. In the normal volunteers, the triad-conditioning stimulus produced facilitation at 7, 8, 10 and 25 ms (Tukey's test $P < 0.05$ for ISI = 7, 8, 10 and 25 ms). Because there was an interaction between the two factors, we compared the MEP size ratio between the Groups at each interval.

The post hoc analysis revealed significant differences among the Groups at 25 ms (40 Hz), 30 ms (33 Hz), 40 ms (25 Hz) and 50 ms (20 Hz). At 25 ms (40 Hz triad conditioning stimuli), 30 ms (33 Hz triad conditioning stimuli) and 40 ms (25 Hz triad conditioning stimuli), the MEP size ratio was significantly different between the healthy volunteers and PD Off ($P < 0.05$) and between the healthy volunteers and PD On ($P < 0.05$). It did not differ significantly between PD Off and PD On. At 50 ms (20 Hz triad conditioning

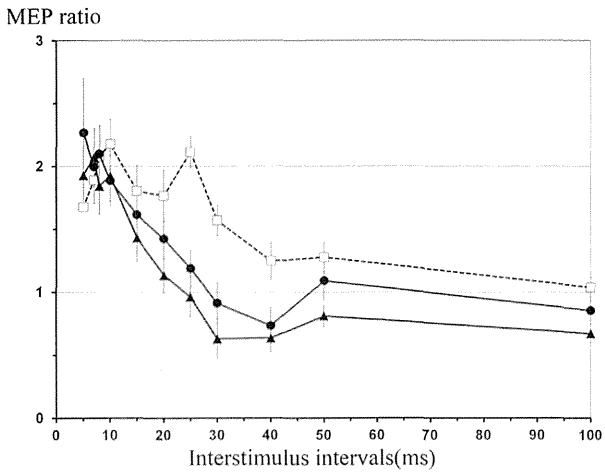

Figure 1. The time courses of the size ratio (mean + -SE) of the conditioned MEP to the control MEP for the triad-conditioning TMS in PD patients in the Off state (triangles), On state (dots) and healthy volunteers (squares). The ordinate shows the size ratio of the conditioned MEP to the control MEP; the abscissa is the ISI. There are significant interactions between the group and the ISI. Significant facilitation at 25 ms was evoked only in the healthy volunteers.

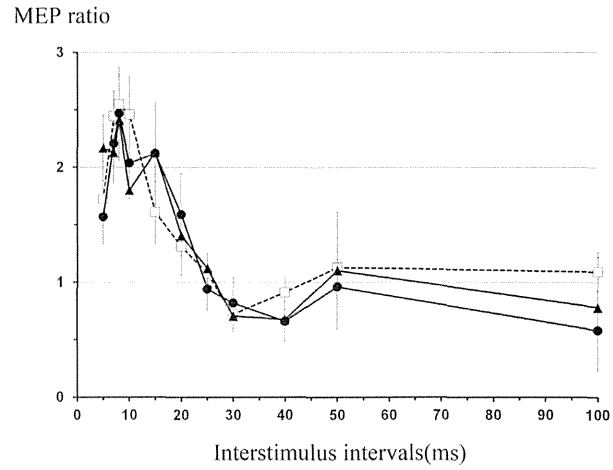

Figure 2. The time courses of the MEP ratio for the single-pulse-conditioning TMS experiment in the PD patients in the Off state (triangles), the On state (dots) and the healthy volunteers (squares). The ordinate and the abscissa are the same as in Fig. 1. There were no significant differences among them. The facilitations are evoked at the ISIs of 5–10 ms. The single-conditioning TMS evoked no inhibition at an ISI of 50 ms in any of the groups.

stimuli), the MEP size ratio was significantly different between the normal subjects and PD Off ($P < 0.05$). It was not significantly different between the healthy volunteers and PD On or PD On and PD Off. The MEP at 30 ms (33 Hz triad conditioning stimuli), 40 ms (25 Hz triad conditioning stimuli) or at 50 ms (20 Hz triad conditioning stimuli) in PD Off was significantly smaller than the control MEP ($P < 0.05$). At the other ISIs, the MEP size ration did not differ significantly between the groups.

Identical analyses performed separately for the de novo PD and long-treated PD patients showed similar results (not shown). The lack of significant differences between the two groups may be because of the small number of subjects in each group. We here show the results from all the patients as a whole.

Single-pulse-conditioning TMS

Figure 2 shows the time courses for the single pulse conditioning experiment for PD Off, PD On and the normal volunteers. The two-way repeated measures ANOVA revealed a significant effect of the ISI, but the group had no significant effects and there was no interaction between the two factors [ISI – F (4.054, 85.191) = 19.9, $P < 0.01$; Group – F (1, 21) = 1.13, $P > 0.05$; interaction of the two factors (ISI × Group – F (8.113, 85.191) = 0.665, $P > 0.05$)]. The post hoc analysis revealed significant facilitation at ISI 5, 7, 8 and 10 ms (Tukey's test $P < 0.05$).

Correlation between UPDRS III score and MEP size ratios

Figure 3 shows the scatter plots depicting the correlation between the UPDRS part III score and the MEP size ratio of the triad conditioning TMS at ISI of 25, 30, 40 and 50 ms. The correlation coefficients between the UPDRS and the MEP ratio at the ISIs of 25 ms (40 Hz), 30 ms (approximately 33 Hz) or 40 ms (20 Hz) were 0.134, −0.161, −0.361, respectively ($P > 0.05$). There was no correlation between the UPDRS part III and the MEP size ratio at 25 ms (40 Hz), 30 ms (approximately 33 Hz) or 40 ms (20 Hz). On the other hand, the UPDRS had a significantly negative correlation with the MEP size ratio at 50 ms (20 Hz) ($P < 0.05$, correlation coefficient was −0.486).

Discussion

The triad-conditioning TMS experiments showed a lack of normally evoked MEP enhancement at 25 ms at either the On or Off states in PD. In addition, the MEP size ratios by triad-conditioning TMS at 30, 40 and 50 ms were significantly smaller in PD than those in healthy volunteers. The MEP ratio at 50 ms showed a significant negative correlation with UPDRS part III, namely the degree of MEP suppression related with UPDRS part III score positively. We first demonstrated abnormal cortical responsiveness to rhythmic TMS in PD.

Cortical modulation by a triad-conditioning TMS

The triad-conditioning TMS induced facilitation when the four TMS pulses were given every 7–10 ms or 25 ms in healthy volunteers [10]. The facilitation at 7–10 ms should be the same as ICF originally reported by Kujirai et al. [15] because it was also elicited by a single pulse-conditioning stimulus. The facilitation at 25 ms can represent enhanced motor cortical responsiveness to rhythmic external stimuli because single pulse conditioning did not elicit this facilitation and the facilitation could be induced only by 40 Hz rhythmic stimulation [10]. We hypothesized that the facilitation at 25 ms in the triad-conditioning TMS might reflect an intrinsic 40 Hz rhythm of M1. We previously applied this method to patients with cortical myoclonus [11]. It revealed no MEP enhancement at 25 ms interval but significant MEP enhancement at an interval of 40 ms, corresponding to 25 Hz, which is consistent with cortical beta rhythmic enhancement of approximately 20 Hz previously reported in cortical myoclonus [16,17]. Based on these arguments, the present lack of facilitation at 25 ms and the suppression at 30–50 ms in the triad conditioning TMS may reflect motor cortical changes in PD.

Through the networks of the basal ganglia and the motor cortex, the cortical activities may be affected by input from the basal ganglia with abnormal rhythm [18–20] and also entrain the abnormal rhythm of the basal ganglia [21]. The external rhythmic stimulation over the motor cortex can interact with the intrinsic rhythmic activities generated in the motor cortex-basal ganglia network. The changes in responsiveness to certain rhythmic TMS stimuli shown here could reflect the abnormal rhythmic activities

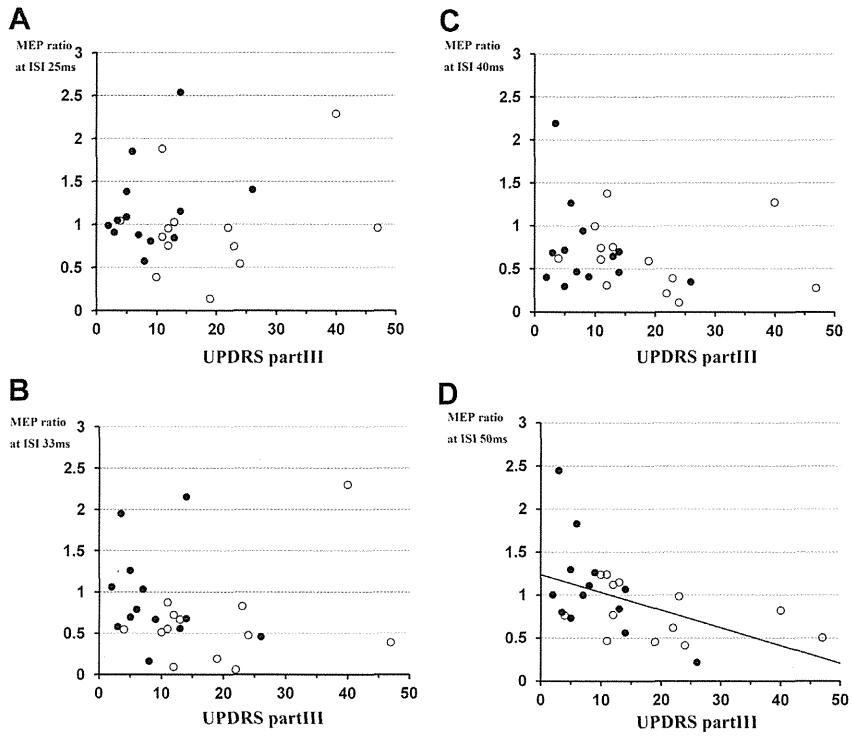

Figure 3. The correlations between UPDRS and the MEP size ratio at the ISIs of 25 ms (40 Hz) (A), 30 ms (approximately 33 Hz) (B), and 40 ms (25 Hz) (C) and at the ISIs of 50 ms (20 Hz) (D). The circles represent the Off medication state, and the dots represent the On state. The correlation between UPDRS and the MEP ratio at 25 ms (40 Hz) for the gamma rhythm was not significant (correlation coefficient was 0.134, $P > 0.05$) (A). The correlation was not significant at 30 ms (approximately 33 Hz) (the correlation coefficient was −0.161, $P > 0.05$) (B) or at 40 ms (25 Hz) (the correlation coefficient was −0.361, $P > 0.05$) (C). The UPDRS significantly correlated with the MEP size ratio at 50 ms (20 Hz) for the beta rhythm (correlation coefficient was −0.486, $P < 0.05$) (D).

in the motor cortex-basal ganglia network in PD even though other mechanisms may explain the present abnormal responsiveness to rhythmic stimulation. Another interpretation for the facilitation at an ISI of 25 ms is that a new intracortical facilitation was induced by rhythmic stimulation, which has no relation to some intrinsic cortical rhythm. In that case, there are facilitatory mechanisms elicited by external rhythmic stimulation in the cortex.

Lack of facilitation by 40 Hz triad-conditioning TMS

The changes in response characteristics to 40 Hz TMS may be related to changes in 40 Hz activities including gamma frequency of M1 in PD. In PD, abnormal gamma frequency activities in field potential have been demonstrated, in addition to abnormal beta activities [5,7]. In healthy volunteers, the beta rhythm inhibition and gamma activity bursts were recorded at some movement initiation [22]. In PD, gamma activity reduction associated with beta activity enhancement is considered to produce akinesia in PD [5,7]. The 40 Hz rhythm known as piper rhythm was reported to be reduced in PD [8]. The cortico-muscular coherence revealed a loss of the piper rhythm (40 Hz) in PD [8,9]. The thalamo-cortical connection is thought to generate cortical 40 Hz rhythm [23] and GPi over-activities in PD might diminish the 40 Hz oscillation in the cortex [9]. The loss of facilitation by 40 Hz triad-conditioning TMS may reflect the lack of piper rhythm in PD. Because we did not record EEG activities in our TMS experiments, our results did not directly show cortical rhythms or activities. This indirect interpretation may be one of the candidates to explain our results. Some other mechanisms may explain the present results. Regardless of the underlying mechanisms, the lack of facilitation by 40 Hz rhythmic stimulation in PD is a conspicuous finding suggesting abnormal rhythmic activities.

Beta range triad-conditioning TMS

We showed that the MEP size ratios at frequencies of 20, 25 and 33 Hz (i.e., corresponding to ISIs of 30, 40 and 50 ms) were suppressed in PD comparing with that in healthy volunteers. It did not differ significantly between in PD On and PD Off. The UPDRS part III had a negative correlation with the size ratio at 50 ms. It suggests that the amount of suppression may relate to motor symptoms in PD: the more suppression, the severe the symptoms. The cortical response to beta range rhythmic TMS could represent one of characteristic physiological features of cortical excitability changes in PD. In PD, enhanced beta oscillation of approximately 20 Hz has been recorded in the basal ganglia and the motor cortex [2]. The changes in responsiveness to beta rhythm TMS stimuli shown here could reflect the abnormal beta activities in the motor cortex-basal ganglia network in PD. The enhanced beta rhythm in the field potential recorded within the basal ganglia has been suggested to have some relation with hypo-kinetic symptoms in PD [5]. The suppression observed in the triad conditioning TMS at 50 ms also correlated with motor symptoms in PD. It may support some relation of the motor cortical suppression and the enhanced beta rhythm in PD. The lack of EEG or field potential recording is here again a limitation of our experiments. Because of this lack, we cannot definitely conclude that the triad conditioning TMS experiment tackles the intrinsic cortical rhythms. However, this is one of the plausible explanations for the result.

There is another methodological limitation of the present experiments. We monitored the EMG activities during the TMS experiments, but we did not perform a quantitative EMG analysis at

the baseline, and we may not detect small differences in the background EMGs between the normal subjects and the PD patients. We cannot completely exclude the possibility that the results might be partly affected by the baseline EMG activity differences, which is another limitation of our study.

We showed new physiological features of the motor cortical excitability in PD using the non-invasive rhythmic TMS stimulation experiment (triad-conditioned TMS).

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Movement Disorders

RESEARCH ARTICLE

CLINICAL PRACTICE

Official Japanese Version of the International Parkinson and Movement Disorder Society–Unified Parkinson's Disease Rating Scale: Validation Against the Original English Version

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Abstract: The International Parkinson and Movement Disorder Society (MDS)-sponsored revision of the Unified Parkinson's Disease Rating Scale (MDS-UPDRS) has been developed and is now available in English. Part of the overall program includes the establishment of official non-English translations of the MDS-UPDRS. We present the process for completing the official Japanese translation of the MDS-UPDRS with clinimetric testing results. In this trial, the MDS-UPDRS was translated into Japanese, underwent cognitive pretesting, and the translation was modified after taking the results into account. The final translation was approved as the Official Working Draft of the MDS-UPDRS Japanese version and tested in 365 native-Japanese–speaking patients with PD. Confirmatory analyses were used to determine whether the factor structure for the English-language MDS-UPDRS could be confirmed in data collected using the Official Working Draft of the Japanese translation. As a secondary analysis, we used exploratory factor analyses to examine the underlying factor structure without the constraint of a prespecified factor organization. Confirmatory factor analysis revealed that Comparative Fit Index for all parts of the MDS-UPDRS exceeded the minimal standard of 0.90, relative to the English version, and therefore the Japanese translation met the prespecified criterion to be designated, called an official MDS translation. Secondary analyses revealed some differences between the English-language MDS-UPDRS and the Japanese translation; however, these differences were considered to be within an acceptable range. The Japanese version of the MDS-UPDRS met the criterion as an Official MDS Translation and is now available for use (www.movementdisorders.org).

The UPDRS has been widely used since the 1980s as a standard clinical rating scale for Parkinson's disease (PD).[1,2] However, increasing evidence indicates that several symptoms frequently experienced by PD patients that affect their quality of life, such as sleep problems, sensory disturbance, urinary problems, constipation, and fatigue, are not adequately evaluated in the original

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Relevant disclosures and conflicts of interest are listed at the end of this article.

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UPDRS.[3] In 2001, the International Parkinson and Movement Disorder Society (MDS) sponsored a critique of the UPDRS and subsequently developed a new version of the scale, termed the MDS-sponsored UPDRS revision. This new version, the MDS-UPDRS, was intended to be less ambiguous than its predecessor as well as to incorporate a number of clinically pertinent PD-related problems poorly captured in the original version.[4] In 2008, the MDS-UPDRS successfully passed clinimetric testing with high internal consistency and reliable factor structures for each part of the scale.[4] The new MDS-UPDRS comprises four parts: Part I evaluates nonmotor experiences of daily living, Part II evaluates motor experiences of daily living, Part III evaluates motor function, and Part IV evaluates motor fluctuations and dyskinesia.

After publication of the MDS-UPDRS, the MDS set forth a specific program to designate successful translations of non-English-language versions as official MDS translations. For this purpose, the MDS has set a strict protocol and criteria for testing. Currently, several official translations (Italian,[5] Spanish,[6] French, Estonian, German, and Slovakian) have already been established, and several other language programs are in progress. Herein, we present the scale translation and clinimetric testing results of the Japanese version of the MDS-UPDRS.

Patients and Methods

Translation of the MDS-UPDRS

The MDS-UPDRS was translated into Japanese by a team of natural Japanese speakers fluent in English who belong to the Department of Neurology of Wakayama Medical University in Japan, led by Kondo. The resultant Japanese translation was further reviewed by a team led by Mizuno from the Movement Disorder Society of Japan to establish the original Japanese translation of the MDS-UPDRS. The translation was then back-translated by a team of colleagues fluent in English and Japanese who had not been involved in the original forward translation. The back-translation was reviewed by the administrative team in charge of the overall translation program (Stebbins, Goetz, LaPelle, and Tilley).

Cognitive Pretesting

Cognitive pretesting is a qualitative approach to assess instrument completion in terms of task difficulty for examiner and respondent as well as respondent interest, attention span, discomfort, and comprehension.[7] Where there were observed differences between the back-translated Japanese and English versions, items were selected for cognitive pretesting, along with questions that had been identified during cognitive pretesting of the English version. Cognitive pretesting was performed on the following sections: Part I Hallucinations and Psychosis; Features of Dopamine Dysregulation Syndrome; and Urinary Problems; Part II Freezing; Part III Postural Stability; and Rest Tremor Amplitude; Part IV Time Spent with Dyskinesia; and Functional Impact of Dyskinesia. Three experienced Japanese movement disorder specialists not involved in the original translation performed cognitive pretesting. Based on the results of the initial cognitive pretesting, additional round(s) of translation, back-translation, and cognitive pretesting could be required. After taking the cognitive pretesting results into account, the final Japanese translation was obtained.

Testing of the Japanese Version of the MDS-UPDRS

A total of 30 experienced Japanese movement disorder specialists were recruited as members of the MDS-UPDRS Japanese version validation team led by Kashihara (members are listed in the Appendix) to examine native-Japanese–speaking PD patients who had provided informed consent. The sample size for the translation study was based on the need for 5 participants per questionnaire item in order to perform the statistical analysis.[8] There are 65 items on the MDS-UPDRS: Thus, a sample of at least 325 was required. Any participants with missing values within a part were excluded from the analysis of that part only. Hence, the sample size could vary by part. The investigators obtained approval to collect the data in accord with relevant institutional ethics policies regarding human subjects. Anonymized patient data were transferred to the analysis team by a secure website. The protocol for validation of the MDS-UPDRS Japanese version was approved by the ethics committees of each institute. Informed consent was obtained from all participants before the study.

Data Analysis

Factor Analysis

M-plus (version 6.11)[9] was used to perform confirmatory and exploratory factor analyses (EFA), because the variables are categorical. We used a weighted least squares with mean- and variance-adjusted weighted least square (WLSMV) approach to factor estimation that minimizes the sum of squared differences between observed and estimated correlation matrices not counting diagonal elements. To assist in interpretation of the factors, we used an orthogonal CF-varimax rotation that constrains the factors to be uncorrelated. These methods were chosen to follow those used in the original examination of the English MDS-UPDRS.[4]

Primary Analysis

We conducted a confirmatory factor analysis (CFA)[10] as the primary analysis of the Japanese data to determine whether the factor structure for the English-language MDS-UPDRS[4] could be confirmed in data collected by using the Japanese translation. This was the primary question of interest. The CFA was conducted separately for the MDS-UPDRS Parts I to IV, with the Japanese data constrained to fall into the factors defined in the English-language data.[4] We evaluated the CFA results based on the comparative fit index (CFI). According to

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protocol, to establish a successful translation and earn the designation of "official MDS-UPDRS translation," the CFI for each part (I–IV) of the translated instrument must be 0.90 or greater, relative to the English-language version.[4] Root mean square error of approximation (RMSEA) was also calculated as another test of model fit. RMSEA values <0.05 were considered to be a good fit, and RMSEA values of 0.1 or more were considered to be a poor fit. WLSMV estimators were used to confirm a model fit.

Secondary Analysis

As a secondary analysis, we conducted an exploratory factor analysis[11] for Parts I to IV of the Japanese version of the MDS-UPDRS to explore the underlying factor structure without the constraints of a prespecified factor structure. We used a Scree plot to choose the number of factors to retain for each part. The subjective Scree test[12] is scatter plot of eigenvalues plotted against their ranks with respect to magnitude to extract as many factors as there are eigenvalues that fall before the last large drop (i.e., an "elbow" shape) in the plot. Once the factors were chosen, an item was retained in a factor if the factor loading for the item was 0.40 or greater.

The default estimator for factor analysis in M-plus is unweighted least squares (ULS). When ULS converges, it yields more-accurate parameter estimates and standard errors than does WLSMV. However, WLSMV generally outperforms ULS in convergence rates. Thus, Forero et al.[13] suggest the use of ULS. In the case of nonconvergence, however, they suggest using WLSMV, because this method might converge when ULS does not. In this case, whereas the ULS algorithm did converge, it converged to an incorrect value (i.e., a percent of variance explained that was greater than 1.0), so WLSMV was used.

The chi-square test was used to analyze, additionally, the differences in the distribution of responses for each item of the MDS-UPDRS between PD patients of Japanese and English groups.

Results

Cognitive Pretesting

A total of 12 patients with PD and their examiners were interviewed using a structured interview format typical in cognitive pretesting. During the first round of cognitive pretesting, minor word changes were suggested for features of dopamine dysregulation syndrome, urinary problems, and time spent with dyskinesia. In response to comments from patients and caregivers, we enlarged the size of characters used in questions from Part IB and Part II. No items were identified as problematic during a second round of cognitive pretesting conducted with 10 patients with PD. The modified version of the scale was approved as the Official Working Draft of the Japanese MDS-UPDRS for testing in a larger group of patients with PD.

Data Analysis

Demographics

Participants' demographic characteristics are shown in Table 1. The Japanese data set included 365 native-Japanese–speaking patients with PD who were examined using the MDS-UPDRS. In the Japanese sample, there was a greater proportion of female patients, compared to the English sample. The two cohorts were similar on age and duration of disease, but the distribution of H & Y stages were significantly different between the two cohorts ($P < 0.0005$; Table 1).

Primary Analysis: CFA

Table 2 displays the CFA models for each part of the MDS-UPDRS. For all four parts of the Japanese version, the CFI was 0.93 or greater, in comparison to the English-language factor structure. Our prespecified criterion was a CFI of 0.90 or greater; thus, we conclude that the English factor structure was confirmed in the Japanese data set.

Secondary Analysis: EFA

The factor structure of the EFA for the English version has been used as the basis for all CFAs, but our EFA of the Japanese

TABLE 1 Demographics of Japanese patients with PD in comparison with the MDS-UPDRS (English version) data

	English	Japanese	*P* Value
Total N	876	365	ns
% male	63.2	45.2	<0.0005
Age (mean ± SD)	68.2 ± 10.8	69.0 ± 9.2	ns
Disease duration (mean years ± SD)	8.3 ± 6.7	7.8 ± 6.1	ns
Years of education	NA	12.6 ± 2.7	ns
H & Y stage			<0.0005
0	0	2	
1	63	28	
2	467	164	
3	174	116	
4	109	42	
5	53	11	

SD, standard deviation; NA, not available; ns, not significant.

TABLE 2 Confirmatory factor analysis model fit

Part I: Nonmotor aspects of experiences of daily living (a two-factor model)[a]	
Japanese	CFI = 0.93; RMSEA = 0.09 (351 patients)
English language	CFI = 0.97; RMSEA = 0.05 (849 patients)
Part II: Motor aspects of experiences of daily living (a three-factor model)	
Japanese	CFI = 0.99; RMSEA = 0.07 (356 patients)
English language	CFI = 0.99; RMSEA = 0.05 (851 patients)
Part III: Motor examination (a seven-factor model)	
Japanese	CFI = 0.94; RMSEA = 0.08 (336 patients)
English language	CFI = 0.95; RMSEA = 0.08 (801 patients)
Part IV: Motor complications (a two-factor model)	
Japanese	CFI = 1.00; RMSEA = 0.06 (350 patients)
English language	CFI = 1.00; RMSEA = 0.00 (848 patients)

[a]Dopamine dysregulation syndrome was not included in this analysis because it did not load on any factor in the U.S. version.

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data set differs from that of the English-language data set in some aspects. The results of the EFA for the English and Japanese versions are shown in Table 3, including the number of factors and their associated eigenvalues and percent variance.

The Scree plots were used to determine the number of factors to be retained from the EFA. Comparison between the Scree plots for the English and Japanese cohorts revealed similarities in shape of the plots (Fig. 1), but differences were noted in the relationship between factors and their eigenvalues and percent of variance (Table 3): For Part I: Nonmotor aspects of experiences of daily living, we extracted two factors; for Part II: Motor aspects of experiences of daily living, we extracted three components; for Part III: Motor examination, we extracted seven factors; and for Part IV: Motor complications, we extracted two factors.

Chi-square (χ^2) test (Table 4) revealed greater distribution of less-severe scores on the cognitive impairment items (Part I: item 1.1) in the Japanese group, compared to the English group ($\chi^2 = 23.457$; df = 4; $P = 0.0001$). There was no significant difference of the distribution of scores on the hallucinations and psychosis item (Part I: item 1.2) ($\chi^2 = 5.962$; df = 4; not significant). In many other items, PD patients in the English group showed greater distribution of more-severe scores, including depressed mood, pain and other sensations, lightheadedness on standing, fatigue, and sleep problems in Part I; speech, saliva and drooling, doing hobbies and other activities, tremor, and getting out of bed in Part II; speech, facial expression, rigidity, finger tapping, hand movements, pronation supination, toe tapping, leg agility, and tremor in Part III; and time spent with dyskinesia, functional impact of dyskinesias, time spent in the OFF state, complexity of motor fluctuations, and painful OFF-state dystonia in Part IV. Japanese PD patients showed greater distribution in more-severe scores than English groups in items constipation problems in Part I and postural stability in Part III.

Discussion

The overall factor structure of the Japanese version was consistent with the English version based on the CFIs for all four parts of the MDS-UPDRS in the CFA (all CFI ≥0.93). The Japanese scale was confirmed to share a common factor structure with the English scale. Therefore, this version can be designated as the official Japanese version of the MDS-UPDRS.

EFA, in which variability from sample to sample is expected, identified isolated item differences of factor structure between the Japanese and English versions of the MDS-UPDRS. However, the distribution of factors with their associated eigenvalues and percent variances were similar across the two languages.

In our study, female preponderance was noted as the previous study reported from Japan.[14] This may, in part, be because of the longer life expectancy (by approximately 6.5 years) in Japanese women, in comparison to men.

Another interesting difference between the Japanese- and English-language versions data sets for the MDS-UPDRS concerned the pattern of responses to items 1.1 (cognitive impairment) and 1.2 (hallucinations and psychosis). For the

TABLE 3 Comparison of English-language and Japanese exploratory factor structures for parts I to IV of the MDS-UPDRS

	English		Japanese	
Factor	Eigenvalues	Percent Variance	Eigenvalues	Percent Variance
Part I				
1	4.421	34.0	5.045	42.0
2	1.231	9.5	1.244	10.4
3	1.051	8.1	1.081	9.0
4	1.007	7.7	0.866	7.2
5	0.811	6.2	0.721	6.0
6	0.724	5.6	0.642	5.4
7	0.673	5.2	0.594	5.0
8	0.630	4.8	0.508	4.2
9	0.616	4.7	0.472	3.9
10	0.542	4.2	0.375	3.1
11	0.519	4.0	0.288	2.4
12	0.399	3.1	0.160	1.3
13	0.376	2.9		
Part II				
1	6.898	53.1	7.293	56.1
2	1.128	8.7	1.062	8.2
3	1.000	7.7	0.826	6.4
4	0.728	5.6	0.684	5.3
5	0.595	4.6	0.534	4.1
6	0.542	4.2	0.494	3.8
7	0.425	3.3	0.445	3.4
8	0.390	3.0	0.431	3.3
9	0.380	2.9	0.370	2.8
10	0.294	2.3	0.260	2.0
11	0.245	1.9	0.240	1.8
12	0.198	1.5	0.219	1.7
13	0.178	1.4	0.141	1.1
Part III				
1	12.112	36.7	14.451	43.8
2	5.035	15.3	4.190	12.7
3	2.173	6.6	2.429	7.4
4	2.051	6.2	1.961	5.9
5	1.615	4.9	1.668	5.1
6	1.485	4.5	1.238	3.8
7	1.104	3.3	0.922	2.8
8	0.903	2.7	0.793	2.4
9	0.720	2.2	0.685	2.1
10	0.615	1.9	0.596	1.8
11	0.552	1.7	0.558	1.7
12	0.495	1.5	0.514	1.6
13	0.479	1.5	0.472	1.4
14	0.407	1.2	0.360	1.1
15	0.403	1.2	0.348	1.1
16	0.361	1.1	0.330	1.0
17	0.323	1.0	0.246	0.7
18	0.314	1.0	0.233	0.7
19	0.267	0.8	0.203	0.6
20	0.265	0.8	0.194	0.6
21	0.223	0.7	0.183	0.6
22	0.203	0.6	0.147	0.4
23	0.164	0.5	0.138	0.4
24	0.145	0.4	0.115	0.3
25	0.141	0.4	0.099	0.3
26	0.109	0.3	0.058	0.2
27	0.091	0.3	0.027	0.1
28	0.077	0.2	0.013	0.0
29	0.055	0.2	0.004	0.0
Part IV				
1	3.811	63.9	3.656	60.9
2	0.942	15.6	1.210	20.2
3	0.640	10.7	0.725	12.1
4	0.241	4.0	0.168	2.8
5	0.208	3.5	0.130	2.2
6	0.159	2.3	0.111	1.9

Dotted line shows the factors selected in the English cohort.

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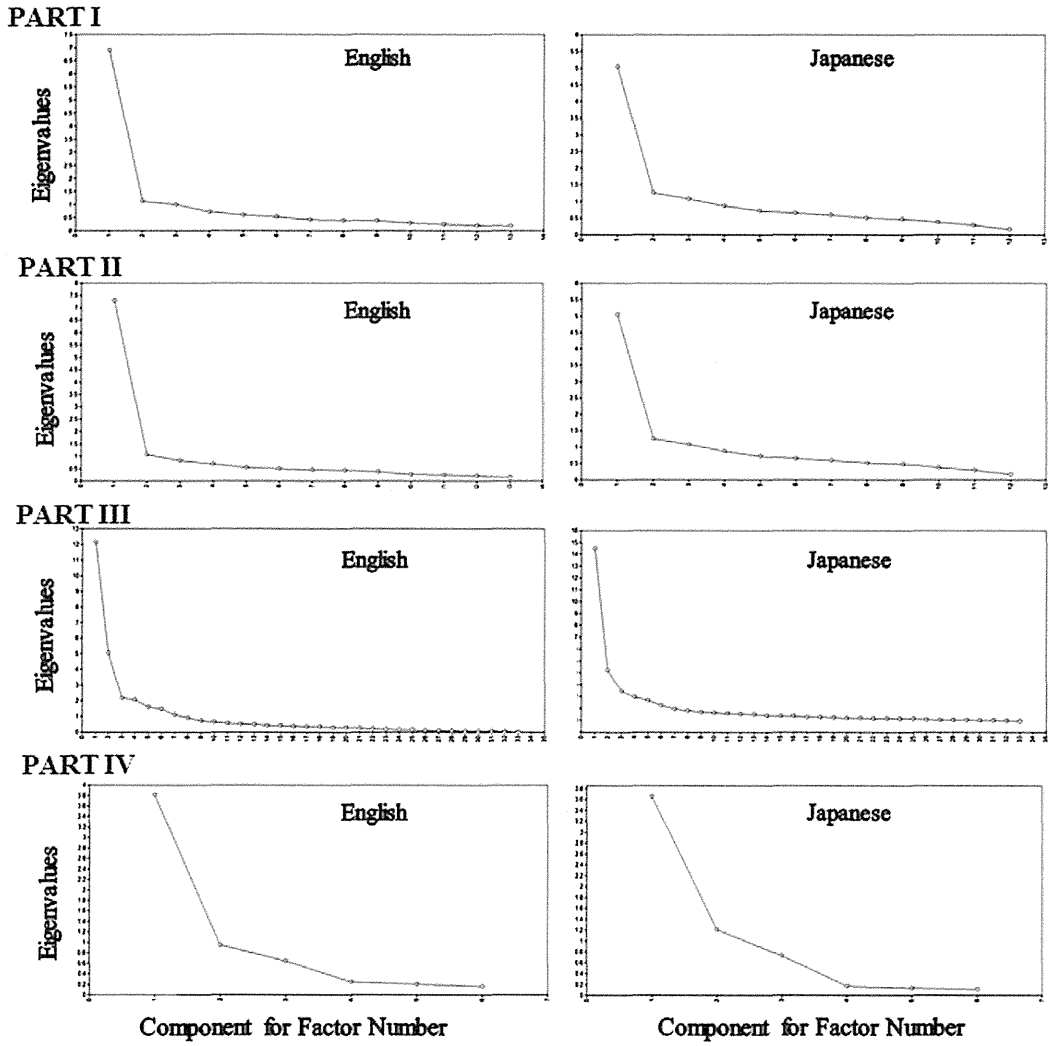

Figure 1 Scree plots for the English and Japanese exploratory factor analyses.

hallucination item, the Japanese and English frequencies for each rating option were very similar (77% and 78%, respectively), but cognitive impairment ratings were different in the two cultures. A much greater percentage (62.2%) of Japanese had 0 scores, in comparison to the English-speaking sample (48.9%). In general, among reports in Western cultures, cognitive impairment and hallucinations are shared or overlapping behaviors and such data have been used to argue shared common pathogeneses.[15,16] Results of the chi-square test indicate that severity of motor and nonmotor symptoms are generally more severe in patients of English groups than those of Japanese groups. Even after taking these differences into consideration, the present results from the Japanese sample may indicate that cognitive impairment is less frequent or viewed differently and thereby may be underreported for cultural reasons in Japan, in comparison to the Western culture.

Contrary to majority of items, constipation problems and postural stability were rated more severe in Japanese patients than English patients. Differences in genetic factor, eating habits, and amount of daily exercise between two populations are possible factors to produce different response to the former item. The reason why postural stability was rated more severely in Japanese groups remains unknown. Factors including examiner's manner to pull patients may be clarified in future.

In conclusion, the CFI for the Japanese version of the MDS-UPDRS was 0.93 or greater. Therefore, the Japanese version meets the criterion for designation as an official translation of the MDS-UPDRS. This is the first Asian- or non-Indo-European–language translation of the MDS-UPDRS. The Japanese version of the MDS-UPDRS is available from the MDS website (http://www.movementdisorders.org/publications/rating_scales/). The establishment of additional non-English translations will further facilitate the understanding of PD symptoms and help accelerate qualified clinical trials and discussions worldwide.

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TABLE 4 Distribution of responses by MDS-UPDRS by language[a]

	English		Japanese			English		Japanese	
Part I									
Cognitive impairment*	Frequency	%	Frequency	%	Daytime sleepiness	Frequency	%	Frequency	%
0	428	48.86	227	62.19	0	212	24.2	104	28.49
1	256	29.22	93	25.48	1	216	24.66	73	20.00
2	121	13.81	25	6.85	2	364	41.55	147	40.27
3	53	6.05	17	4.66	3	59	6.74	32	8.77
4	17	1.94	3	0.82	4	16	1.83	8	2.19
999	1	0.11	0	0.00	999	9	1.03	1	0.27
Total	876	100	365	100.00	Total	876	100	365	100.00
Hallucinations and psychosis	Frequency	%	Frequency	%	Pain and other sensations*	Frequency	%	Frequency	%
0	687	78.42	280	76.71	0	303	34.59	148	40.55
1	89	10.16	38	10.41	1	289	32.99	117	32.05
2	51	5.82	26	7.12	2	130	14.84	60	16.44
3	35	4	14	3.84	3	106	12.1	31	8.49
4	13	1.48	4	1.10	4	39	4.45	4	1.10
999	1	0.11	3	0.82	999	9	1.03	5	1.37
Total	876	100	365	100.00	Total	876	100	365	100.00
Depressed mood*	Frequency	%	Frequency	%	Urinary problems	Frequency	%	Frequency	%
0	471	53.77	223	61.10	0	325	37.1	144	39.45
1	265	30.25	84	23.01	1	281	32.08	118	32.33
2	81	9.25	36	9.86	2	137	15.64	60	16.44
3	45	5.14	21	5.75	3	88	10.05	32	8.77
4	12	1.37	0	0.00	4	38	4.34	10	2.74
999	2	0.23	1	0.27	999	7	0.8	1	0.27
Total	876	100	365	100.00	Total	876	100	365	100.00
Anxious mood	Frequency	%	Frequency	%	Constipation problems*	Frequency	%	Frequency	%
0	413	47.15	192	52.60	0	384	43.84	90	24.66
1	307	35.05	116	31.78	1	287	32.76	120	32.88
2	96	10.96	39	10.68	2	119	13.58	74	20.27
3	41	4.68	15	4.11	3	70	7.99	63	17.26
4	17	1.94	1	0.27	4	9	1.03	18	4.93
999	2	0.23	2	0.55	999	7	0.8	0	0.00
Total	876	100	365	100.00	Total	876	100	365	100.00
Apathy	Frequency	%	Frequency	%	Lightheadedness on standing*	Frequency	%	Frequency	%
0	584	66.67	249	68.22	0	490	55.94	238	65.21
1	141	16.1	61	16.71	1	216	24.66	78	21.37
2	88	10.05	27	7.40	2	103	11.76	37	10.14
3	52	5.94	20	5.48	3	51	5.82	10	2.74
4	8	0.91	7	1.92	4	9	1.03	1	0.27
999	3	0.34	1	0.27	999	7	0.8	1	0.27
Total	876	100	365	100.00	Total	876	100	365	100.00
Features of DDS	Frequency	%	Frequency	%	Fatigue*	Frequency	%	Frequency	%
0	747	85.27	315	86.30	0	217	24.77	141	38.63
1	57	6.51	23	6.30	1	335	38.24	128	35.07
2	44	5.02	20	5.48	2	184	21	57	15.62
3	19	2.17	4	1.10	3	81	9.25	33	9.04
4	6	0.68	0	0.00	4	50	5.71	4	1.10
999	3	0.34	3	0.82	999	9	1.03	2	0.55
Total	876	100	365	100.00	Total	876	100	365	100.00
Sleep problems*	Frequency	%	Frequency	%					
0	280	31.96	138	37.81					
1	202	23.06	103	28.22					
2	207	23.63	81	22.19					
3	140	15.98	39	10.68					
4	40	4.57	3	0.82					
999	7	0.8	1	0.27					
Total	876	100	365	100.00					
Part II									
Speech*	Frequency	%	Frequency	%	Doing hobbies and other activities*	Frequency	%	Frequency	%
0	252	28.77	159	43.56	0	227	25.91	130	35.62
1	236	26.94	78	21.37	1	289	32.99	99	27.12
2	233	26.6	82	22.47	2	185	21.12	65	17.81
3	126	14.38	43	11.78	3	81	9.25	41	11.23

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TABLE 4 (Continued)

	English		Japanese			English		Japanese	
4	22	2.51	3	0.82	4	84	9.59	29	7.95
999	7	0.8	0	0.00	999	10	1.14	1	0.27
Total	876	100	365	100.00	Total	876	100	365	100.00
Saliva and drooling*	Frequency	%	Frequency	%	Turning in bed	Frequency	%	Frequency	%
0	341	38.93	186	50.96	0	277	31.62	122	33.42
1	115	13.13	49	13.42	1	378	43.15	144	39.45
2	203	23.17	64	17.53	2	111	12.67	48	13.15
3	157	17.92	46	12.60	3	55	6.28	31	8.49
4	53	6.05	18	4.93	4	50	5.71	19	5.21
999	7	0.8	2	0.55	999	5	0.57	1	0.27
Total	876	100	365	100.00	Total	876	100	365	100.00
Chewing and swallowing	Frequency	%	Frequency	%	Tremor*	Frequency	%	Frequency	%
0	549	62.67	241	66.03	0	189	21.58	118	32.33
1	230	26.26	81	22.19	1	360	41.1	154	42.19
2	54	6.16	22	6.03	2	212	24.2	69	18.90
3	34	3.88	18	4.93	3	72	8.22	17	4.66
4	3	0.34	3	0.82	4	36	4.11	7	1.92
999	6	0.68	0	0.00	999	7	0.8	0	0.00
Total	876	100	365	100.00	Total	876	100	365	100.00
Eating tasks	Frequency	%	Frequency	%	Getting out of bed*	Frequency	%	Frequency	%
0	363	41.44	158	43.29	0	180	**20.55**	**101**	27.67
1	265	30.25	114	31.23	1	317	36.19	140	38.36
2	187	21.35	79	21.64	2	199	22.72	73	20.00
3	42	4.79	8	2.19	3	104	11.87	35	9.59
4	10	1.14	5	1.37	4	70	7.99	15	4.11
999	9	1.03	1	0.27	999	6	0.68	1	0.27
Total	876	100	365	100.00	Total	876	100	365	100.00
Dressing	Frequency	%	Frequency	%	Walking and balance	Frequency	%	Frequency	%
0	220	25.11	82	22.47	0	184	21	74	20.27
1	322	36.76	176	48.22	1	336	38.36	156	42.74
2	211	24.09	67	18.36	2	105	11.99	38	10.41
3	76	8.68	28	7.67	3	172	19.63	61	16.71
4	42	4.79	12	3.29	4	74	8.45	33	9.04
999	5	0.57	0	0.00	999	5	0.57	3	0.82
Total	876	100	365	100.00	Total	876	100	365	100.00
Hygiene	Frequency	%	Frequency	%	Freezing	Frequency	%	Frequency	%
0	342	39.04	126	34.52	0	453	51.71	176	48.22
1	367	41.89	160	43.84	1	182	20.78	74	20.27
2	88	10.05	47	12.88	2	89	10.16	40	10.96
3	33	3.77	25	6.85	3	90	10.27	49	13.42
4	38	4.34	7	1.92	4	56	6.39	25	6.85
999	8	0.91	0	0.00	999	6	0.68	1	0.27
Total	876	100	365	100.00	Total	876	100	365	100.00
Handwriting	Frequency	%	Frequency	%					
0	161	18.38	106	29.04					
1	251	28.65	151	41.37					
2	222	25.34	75	20.55					
3	146	16.67	22	6.03					
Part III									
Speech*	Frequency	%	Frequency	%	Arising from chair	Frequency	%	Frequency	%
0	189	21.58	148	40.55	0	422	48.17	197	53.97
1	379	43.26	143	39.18	1	245	27.97	106	29.04
2	213	24.32	53	14.52	2	78	8.9	24	6.58
3	69	7.88	15	4.11	3	71	8.11	22	6.03
4	22	2.51	4	1.10	4	55	6.28	16	4.38
999	4	0.46	2	0.55	999	5	0.57	0	0.00
Total	876	100	365	100.00	Total	876	100	365	100.00
Facial expression*	Frequency	%	Frequency	%	Gait	Frequency	%	Frequency	%
0	96	10.96	88	24.11	0	202	23.06	81	22.19
1	300	34.25	137	37.53	1	351	40.07	187	51.23
2	361	41.21	109	29.86	2	167	19.06	47	12.88
3	89	10.16	23	6.30	3	97	11.07	36	9.86
4	26	2.97	7	1.92	4	55	6.28	14	3.84
999	4	0.46	1	0.27	999	4	0.46	0	0.00
Total	876	100	365	100.00	Total	876	100	365	100.00
Rigidity, neck	Frequency	%	Frequency	%	Freezing of gait	Frequency	%	Frequency	%
0	260	29.68	134	36.71	0	655	74.77	250	68.49
1	247	28.2	97	26.58	1	95	10.84	50	13.70
2	274	31.28	92	25.21	2	60	6.85	30	8.22
3	73	8.33	36	9.86	3	26	2.97	13	3.56

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