No significant correlations were detected between SICI and UPDRS III score (SICI by PA: $R = -0.13$, $P < 0.75$; SICI by AP: $R = 0.27$, $P < 0.67$), disease duration (SICI by PA: $R = 0.25$, $P < 0.56$; SICI by AP: $R = 0.21$, $P < 0.74$) or DED in the PD group (SICI by PA: $R = -0.24$, $P < 0.96$; SICI by AP: $R = 0.42$, $P < 0.48$).

Discussion

Our observation that SICI with AP-directed currents was normal in PD patients suggests that the GABA-A-mediated inhibitory system of M1 may not be abnormal in PD. We observed that SICI using conventional PA currents was reduced in PD, as reported previously. This combination of SICI outcomes is similar to those of focal dystonia, in which SICI was normal with AP-directed currents and abnormal with PA-directed currents (Hanajima et al. 2008).

One possible explanation for this discrepancy is the changes in I-wave components contributing to MEP generation by PA-directed currents in PD. In healthy subjects, PA-directed currents induced I1 waves with low stimulus intensity around the AMT, and with increasing intensity the later I-waves, including I3 waves, were also recruited to produce MEP in relaxed muscles. If the contribution of the later I-waves to MEP generation decreased and that of I1 waves increased when using PA currents in subjects with PD, then SICI studied with PA currents should decrease without dysfunction of GABA-A-mediated inhibition. The observation that the slope of the input–output relationship between TMS intensity and MEP size increased in PD patients (Valls-Solé et al. 1994) suggests I-wave recruitment changes in PD.

As a second possible explanation, a recent study by Ni et al. (2011) demonstrated that the physiological features of I3 waves induced by PA currents differed from those induced by AP currents. If so, another alternative explanation is that the inhibitory neurons for PA current-induced I3 waves are affected by PD and those for AP current-induced I3 waves are intact. The inhibitory neurons for I2 waves or other I-waves to PA currents may also be abnormal, in which case GABA-A mediated inhibition is involved. Nonetheless, we can say that the GABA-A-mediated inhibition of M1 is not completely abnormal in PD because inhibitory interneurons induced by AP-directed currents are not affected.

A third possible explanation involves the contamination of facilitation. Previously, the reduction of SICI in PD was suggested to be due to superimposition of short-interval intracortical facilitation when using CS with higher intensity, such as 90–100% of the resting motor threshold or above 130% of the AMT as determined by using rectified electromyography (MacKinnon et al. 2005). AMT defined by rectified electromyography was ~87% of the AMT defined by a standard method in normal subjects (Hanajima et al. 2007). Our CS intensity of 90% AMT as determined by our standard method is ~100% AMT as determined by rectified electromyography, which is definitely lower than the high intensities (130% AMT) that could induce additional high-threshold intra-cortical facilitation. Although we therefore consider that the higher threshold facilitation was not superimposed on SICI, we cannot exclude the possibility that other facilitation could be superimposed on SICI by PA-directed currents even with weaker CS stimulation. Even in this case, we can say that some portion of the inhibitory interneuron function is not affected.

We cannot completely exclude another abnormality in M1 GABA-A-mediated inhibition in PD because confounding factors may affect the outcomes of SICI experiments. In PD, the input–output curve with AP-directed currents may be abnormal, SICI for 1-mV control responses to AP-directed currents may be abnormal, or using a CS at 70% of the AMT may exhibit abnormal aspects. As the aim of this study was not to exclude these possibilities, we expect that these issues will be resolved in the near future. We also note that in any of the above possibilities, a portion of the GABAergic neurons must be preserved in PD.

We identified no clear, significant correlations between the degree of SICI and UPDRS, disease duration, or -DOPA daily dose. However, we draw no firm conclusions about this lack of correlations due to the small number of patients we studied.

Based on the above observations and arguments, we conclude that a portion of the GABA-A-mediated inhibitory interneurons are preserved in M1 in PD. We also stress that abnormal SICI studied with conventional PA-directed currents may not always indicate an involvement of GABA-A-mediated inhibition, and thus SICI using AP-directed currents may provide new additional information about GABA-A-mediated inhibition of M1.

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Conflict of interest All authors have no disclosure or conflict interest.

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RESEARCH ARTICLE

Reduced interhemispheric inhibition in mild cognitive impairment

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Abstract In mild cognitive impairment (MCI), the corpus callosum is known to be affected structurally. We evaluated callosal function by interhemispheric inhibition (IHI) using transcranial magnetic stimulation (TMS) in MCI patients. We investigated 12 amnestic MCI patients and 16 healthy age-matched control subjects. The IHI was studied with a paired-pulse TMS technique. The conditioning TMS was given over the right primary motor cortex (M1) and the test TMS over the left M1. Motor evoked potentials were recorded from the relaxed first dorsal interosseous muscle. We also studied other motor cortical circuit functions; short-latency afferent inhibition (SAI), short-interval intracortical inhibition (SICI) and intracortical facilitation (ICF). Both the amount of IHI and SAI were significantly reduced in MCI patients as compared with control subjects, whereas SICI or ICF did not differ between them. The degree of IHI significantly correlated with neither the mini-mental state examination score nor the degree of SAI. Our results suggest that transcallosal connection between bilateral M1 is primarily involved in MCI, regardless of SAI dysfunction.

Keywords Mild cognitive impairment · Alzheimer's disease · Corpus callosum · Interhemispheric inhibition · Short-latency afferent inhibition · Transcranial magnetic stimulation

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Introduction

Mild cognitive impairment (MCI) is a cognitive disorder, which is considered to be a transitional state between normal aging and dementia such as Alzheimer's disease (AD) (Winblad et al. 2004; Gauthier et al. 2006). Recent studies using new magnetic resonance imaging (MRI) techniques, such as voxel-based morphometry and diffusion tensor imaging studies, revealed specific changes in the white matter including the corpus callosum in MCI and AD patients (Di Paola et al. 2010). Pathological study also showed corpus callosum atrophy in AD, which must cause interhemispheric disconnection (Tomimoto et al. 2004). However, it is still unclear what functional changes reflect the corpus callosal atrophy in MCI and AD. We hypothesize that in these disorders, functions of cortico-cortical connections are damaged. In this paper, we evaluated the cortico-cortical connections in MCI using transcranial magnetic stimulation (TMS).

TMS, a non-invasive human brain stimulation method, is applied to AD patients to evaluate cortical excitability (Pepin et al. 1999; Alagona et al. 2001). Especially, short-latency afferent inhibition (SAI) (Tokimura et al. 2000) is known to be reduced in AD (Di Lazzaro et al. 2002). However, interhemispheric inhibition (IHI) between bilateral primary motor cortices (M1s) has not been studied. In

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this paired-pulse TMS technique, motor evoked potentials (MEPs) to a test TMS over one hemisphere are suppressed by a conditioning TMS over the other hemisphere at interstimulus intervals (ISIs) around 10 ms (Ferbert et al. 1992). The inhibition is considered to be produced by an intracortical inhibition at the target M1 activated by the excitatory transcallosal inputs from the conditioning M1 (Chen 2004).

In the present paper, we evaluated callosal function in MCI patients using IHI. We also compared other parameters such as SAI for estimating cortico-cortical connection between the sensory cortex and M1, and short-interval intracortical inhibition (SICI) and intracortical facilitation (ICF) for estimating intracortical circuit functions of M1 (Kujirai et al. 1993).

Methods

Participants

We examined 12 amnestic MCI patients and 16 healthy elderly control subjects. Subjects were all right-handed by self-report. MCI patients were recruited from the departments of Neurology, the University of Tokyo and the Osaka City University hospitals. The diagnosis of amnestic MCI was made by board-certified neurologists on the basis of the consensus recommendation by the International Working Group on Mild Cognitive Impairment (Winblad et al. 2004). The mean age was 72.3 ± 9.3 years (mean ± SD) for MCI patients (7 women and 5 men) and 68.1 ± 4.9 years for control subjects (11 women and 5 men). All patients complained with amnesia, and the average mini-mental state examination (MMSE) (Folstein et al. 1975) score at the time of examination was 25.3 ± 2.4 (range 21–29). The average duration of the disease was 3.3 ± 1.8 years (range 1 to 6). In all the patients, MRIs revealed hippocampal atrophy. It was judged by board-certified neuroradiologists, who had no clinical information, by visual inspection. Some other neuroimaging studies confirmed their findings. Among 12 MCI patients, all 7 patients who were studied with Pittsburgh Compound-B (PIB) positron emission tomography (PET) had abnormal amyloid deposition (Klunk et al. 2004). The other 5 patients underwent ^{123}I-IMP single-photon emission computed tomography (SPECT), and a perfusion reduction at the temporo-parietal cortex was revealed in all of them. Based on these results, we concluded that all our patients were high- to intermediate-grade MCI due to AD pathology following the recommendations from the National Institute on Aging and Alzheimer's Association workgroup (Albert et al. 2011). Among 12 MCI patients, 5 patients had taken donepezil regularly.

All participants or their caregivers gave their written informed consent to participate in this study. The procedures done here were approved by the Institutional Review Boards of both Universities in accordance with the ethical standards of the Declaration of Helsinki on the use of human subjects in experiments.

Recording

Surface electromyograms were recorded from the bilateral first dorsal interosseous (FDI) muscles with 9-mm-diameter Ag/AgCl surface electrodes placed with a belly-tendon montage. Responses were input to an amplifier (Biotop; GE Marquette Medical Systems Japan, Japan) through filters set at 100 Hz and 3 kHz. They were then digitized with a sampling rate of 10 kHz and stored in a computer for later offline analyses (TMS bistim tester; Medical Try System, Japan).

Transcranial magnetic stimulation

Throughout the experiments described below, subjects were seated on a comfortable chair and the FDI muscles were relaxed, as confirmed by an oscilloscope monitor. For TMS stimulation, monophasic TMS pulses were delivered by magnetic stimulators (Magstim 200; Magstim Co., Whitland, Dyfed, UK). The intervals between the trials were set at 8 ± 0.5 s. In advance, we measured the resting and active motor thresholds (RMT and AMT) and the central motor conduction time (CMCT) for each muscle to exclude cortico-spinal tract impairments. RMT was determined as the lowest stimulator output intensity capable of eliciting MEPs of 50 μV peak-to-peak amplitude in the relaxed FDI muscle in more than 5 of 10 consecutive trials. AMT was determined as the lowest stimulator output intensity to evoke MEPs of 100 μV peak-to-peak amplitude when the participant maintained a very slight contraction of FDI muscle (5–10% of the maximum voluntary contraction) in more than 5 of 10 consecutive trials. We also evaluated the CMCT as described previously (Ugawa et al. 1989).

Experiment 1: Interhemispheric inhibition (IHI)

The test stimulus (TS) was given over the left M1, and the conditioning stimulus (CS) over the right M1 preceding TS by 4, 6, 8, 10 and 12 ms. For both stimuli, we used a figure-of-eight coil (outer diameter of each wing was 7 cm) positioned over the optimum point for FDI (about 5 cm lateral to the vertex). The coil for TS was placed tangentially over the scalp and angled 45° to the parasagittal plane

so that current flowed in an anteromedial-to-posterolateral direction at the center of the coil. The coil for CS was set toward the sagittal plane so that current flowed in a medial-to-lateral direction at the center of the coil. The intensities of TS and CS were both adjusted to elicit MEPs of 0.5–1 mV peak-to-peak amplitude in the relaxed muscles on average when they were given alone. Eight conditioned trials for each ISIs were randomly intermixed with 16 unconditioned trials in which TS was delivered alone.

Experiment 2: Short-latency afferent inhibition (SAI)

We compared the amount of IHI with SAI, which is previously known to be reduced in AD (Di Lazzaro et al. 2002), and analyzed whether or not the two measures of cortical inhibition were correlated with each other. For SAI, TS was TMS over the left M1, and CS was the right median nerve stimulation at the wrist. The median nerve was stimulated with a 0.2-ms-duration square-wave electric pulses (cathode proximal) preceding TS by 20 ms. The CS intensity was set at just above the level to evoke a visible thumb twitch. Ten conditioned trials were randomly intermixed with 20 unconditioned trials in which TS was delivered alone.

Experiment 3: Short-interval intracortical inhibition (SICI) and intracortical facilitation (ICF)

We evaluated whether intracortical excitability of M1 was also abnormal or not. Nine out of 12 MCI patients and 13 out of 16 control subjects participated in SICI and ICF experiments. Paired pulses of CS and TS were given through the same coil over the left M1 using a bistim module (Magstim Co., Whitland, Dyfed, UK). We set the CS at 90% of AMT. CS was given before the TS at ISIs of 2, 3 and 4 ms for SICI, and 8, 10 and 15 ms for ICF. Nine conditioned trials for each ISIs were randomly intermixed with 18 unconditioned trials in which TS was delivered alone.

Data analyses

Age, body height, RMT, AMT, CMCT and control MEP size for each experiment were compared between MCI and control groups using Student's t test. Among MCI groups, age, MMSE score and disease duration were compared between patients with and without donepezil using Student's t test.

For the three experiments, the ratio of the mean peak-to-peak amplitude of conditioned MEPs to that of unconditioned MEPs was calculated for each ISI in each subject. We compared MCI and control groups using this grand mean of MEP size ratio for each ISI in every experiment.

Experiments 1 and 3

To compare the conditioning stimulus effects on the MEP size ratio between MCI patients and control subjects, we used two-way repeated measures analysis of variance (ANOVA) using group (MCI patients and control subjects) as a between-subjects factor and ISI as a within-subject factor. The dependent variable was the MEP size ratio. When necessary, Greenhouse–Geisser correction was used to correct for non-sphericity.

Experiment 2

To compare the SAI effect between MCI patients and control subjects, we used Student's t test. The size ratios were also compared between patients with and without donepezil.

Correlations between IHI and MMSE or SAI were analyzed using linear regression analyses. IHI was represented by the size ratio at an ISI of 10 ms in this analysis.

Statistical analyses were performed using PASW Statistics 18.0.0 (IBM Corporation, NY, USA). P values less than 0.05 were judged as significant.

Results

There were no significant differences in age, body height, RMT, AMT, CMCT and control MEP size for each experiment between the two groups (Table 1). Among MCI groups, there were no significant differences in age, MMSE score and disease duration between those with and without donepezil (Table 2).

Experiment 1: IHI

The mean time courses showed IHI reduction in MCI patients compared to control subjects [F (1,26) = 14.3, $P = 0.001$]. There was significant effect of ISI [F (4,104) = 3.8, $P = 0.02$], but no significant interaction between group and ISI [F (4,104) = 1.4, $P = 0.24$] (Fig. 1). There was no significant difference between MCI patients with and without donepezil [group F (1,10) = 0.005, $P = 0.95$; ISI F (4,40) = 0.5, $P = 0.63$; group × ISI F (4,40) = 1.1, $P = 0.35$].

Experiment 2: SAI

The amount of SAI was significantly reduced in MCI patients (0.85 ± 0.43) compared with the control subjects (0.50 ± 0.25; $P = 0.01$, Fig. 2). There was no significant difference between MCI patients with (0.90 ± 0.32) and without donepezil (0.82 ± 0.52; $P = 0.78$).

Table 1 Comparison of the electrophysiological values between the groups

	MCI (n = 12)	Control (n = 16)	P value
Age (years)	72.3 ± 9.3	68.1 ± 4.9	0.13
Body height (cm)	157.9 ± 6.4	156.5 ± 7.6	0.69
RMT (%MSO)	46.3 ± 12.5	46.9 ± 7.7	0.88
AMT (%MSO)	32.0 ± 7.9	33.6 ± 6.6	0.56
CMCT (ms)	6.7 ± 1.3	6.8 ± 0.49	0.89
MEP size (mV)			
Experiment 1 TS	0.87 ± 0.61	0.75 ± 0.35	0.52
Experiment 1 CS	0.53 ± 0.27	0.63 ± 0.38	0.45
Experiment 2 TS	0.87 ± 0.41	0.77 ± 0.36	0.49
Experiment 3 TS	0.68 ± 0.35	0.55 ± 0.39	0.43

Values are shown as mean ± SD

MCI mild cognitive impairment, *RMT* resting motor threshold, *AMT* active motor threshold, *%MSO* percentage of maximum stimulator output, *CMCT* central motor conduction time, *MEP* motor evoked potential, *TS* test stimulus, *CS* conditioning stimulus

Table 2 Characteristics of mild cognitive impairment patients

	With donepezil (n = 5)	Without donepezil (n = 7)	P value
Age (years)	76.2 ± 3.7	69.4 ± 11.3	0.18
MMSE score	25.0 ± 2.2	25.4 ± 2.6	0.78
Disease duration (years)	4.2 ± 1.5	2.6 ± 1.7	0.12

Values are shown as mean ± SD

MMSE mini-mental state examination

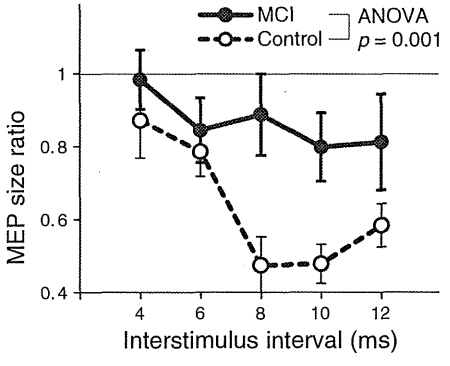

Fig. 1 Mean time courses of interhemispheric inhibition (IHI). IHI was decreased in mild cognitive impairment (MCI) patients (*dots*) compared to control subjects (*circles*). The *horizontal axis* shows interstimulus interval, and the *vertical axis* the motor evoked potential (MEP) size ratio. *Error bars* show the standard errors

Experiment 3: SICI and ICF

Neither SICI [group F (1,20) = 3.3, P = 0.08; ISI F (2,40) = 2.6, P = 0.09; group × ISI F (2,40) = 0.3, P = 0.72] nor ICF [group F (1,20) = 0.2, P = 0.70; ISI F (2,40) = 2.4, P = 0.11; group × ISI F (2,40) = 0.8, P = 0.44] differed significantly between MCI patients and control subjects (Fig. 3).

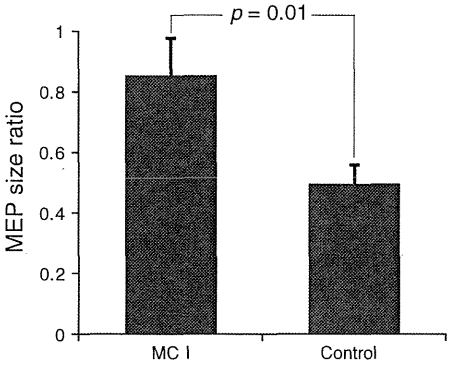

Fig. 2 Short-latency afferent inhibition (SAI). The size ratio at an interstimulus interval of 20 ms was significantly larger in mild cognitive impairment (MCI) patients compared to control subjects. The *vertical axis* shows the motor evoked potential (MEP) size ratio at an ISI of 20 ms. Error bars show the standard errors

No significant correlation was found between IHI and MMSE score in MCI patients (R^2 = 0.002, P = 0.91, Fig. 4a). No significant correlation was found between IHI and SAI in MCI patients (R^2 = 0.15, P = 0.22), control subjects (R^2 = 0.09, P = 0.26) or the whole participants (R^2 = 0.02, P = 0.48, Fig. 4b).

Discussion

In the present study, we first showed that IHI was significantly reduced in MCI patients. SAI, another cortico-cortical connection parameter between sensory cortex and M1, was also reduced in MCI patients. However, their degrees of reduction did not correlate with each other. In contrast, SICI and ICF, reflecting the motor cortical intracortical circuit function, were not affected in MCI. We, thereafter, will discuss the above findings separately.

Abnormal IHI in MCI

Since IHI reflects the transcallosal pathways function, the above result may indicate a damage of interhemispheric cortico-cortical connection of M1 in MCI. Which mechanisms are responsible for this abnormality?

The first possibility is that the corpus callosum itself is damaged in MCI and that IHI was reduced due to reduced inputs from the contralateral M1. Many MRI studies showed structural changes in the corpus callosum in MCI and AD (Chua et al. 2008; Di Paola et al. 2010; Douaud

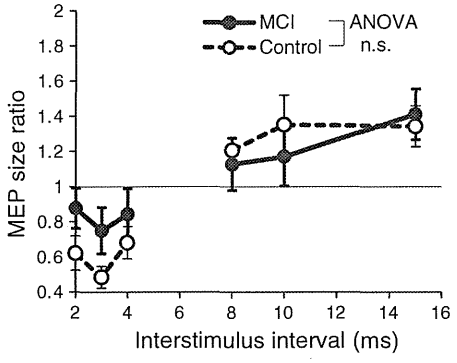

Fig. 3 Mean time courses of short-interval intracortical inhibition (SICI) and intracortical facilitation (ICF) show no significant differences between mild cognitive impairment (MCI) patients (*dots*) and control subjects (*circles*). The *horizontal axis* shows interstimulus interval, and the *vertical axis* the motor evoked potential (MEP) size ratio. *Error bars* show the standard errors

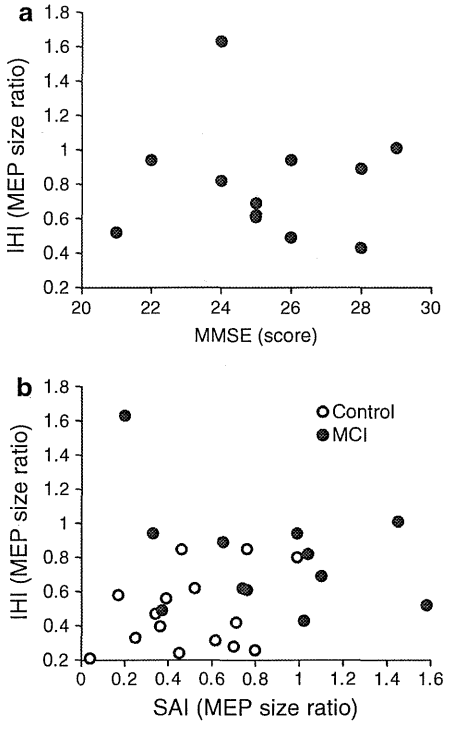

Fig. 4 **a** Correlation between interhemispheric inhibition (IHI) and mini-mental state examination (MMSE) score in mild cognitive impairment (MCI) patients. They had no significant correlation. The *horizontal axis* shows MMSE score, and the vertical axis the motor evoked potential (MEP) size ratio of IHI. **b** Correlation between IHI and short-latency afferent inhibition (SAI). They had no significant correlation in MCI (*dots*), control (*circles*) or even both groups together. The *horizontal axis* shows MEP size ratio of SAI, and the *vertical axis* for IHI

et al. 2011). Other functional MRI study showed effective connectivity is altered between primary sensorimotor cortices in amnestic MCI patients (Agosta et al. 2010). These reports support our hypothesis that the corpus callosum may be primarily involved in MCI.

The second possible explanation of the present finding is that some interneurons connecting callosal fibers in M1 are damaged. Those interneurons may be directly involved or functionally involved secondary to other interneuronal dysfunction. In a triple-pulse TMS study, for example, the interneurons related with SICI influenced some functions of the interneurons related to IHI (Lee et al. 2007). In our subjects, SICI tended to be reduced, but this reduction was not statistically significant. From these results, we cannot completely exclude a mild SICI involvement because the number of the subjects may be not many enough for detecting slight SICI abnormality. However, they were not strongly affected, and their dysfunction alone should not explain abnormal IHI shown here. Based on these arguments, we conclude this possibility unlikely even though this may explain our finding only partly.

Third, we also consider the possibility that reduced SAI could affect the amount of IHI. However, it is unlikely because the degree of abnormality did not significantly correlate between these two evaluations. We think that reduced IHI is independent of the SAI reduction. The SAI should relate to some cortical cholinergic circuit because donepezil normalized SAI in AD patients (Di Lazzaro et al. 2002, 2004, 2005; Nardone et al. 2008). The reduced IHI must not relate to abnormal cholinergic circuit. In addition, in our patients, neither IHI nor SAI was influenced by donepezil treatment.

No correlation was found between the amount of IHI and MMSE score in this study. This may be because MMSE score is not able to detect small difference in mental function in MCI. This suggests that IHI could be used for early detection of AD pathology that is not able to be picked up by ordinary mental tests.

Other cortical excitability parameters using TMS

In our MCI patients, both SICI and ICF were normal. Some previous papers reported a reduction in SICI in early-onset AD (Pierantozzi et al. 2004) and MCI converted to AD (Olazarán et al. 2010) even though there was high inter-individual variability. No consistent result has been reported concerning the ICF. They concluded that SICI and ICF were not good tools for the diagnosis of early-stage AD (Olazarán et al. 2010). In our patients, both SICI and ICF were normal; though SICI had a tendency to be reduced in MCI, SICI might be mildly reduced in MCI. We consider, however, that neither the intracortical circuits for SICI nor those for ICF are definitely involved in MCI or early stage AD.

On the other hand, SAI is reduced in AD patients, whereas a previous paper showed normal SAI in MCI

patients (Sakuma et al. 2007). This difference is probably because of the heterogeneity of MCI pathogenesis. Since more than half of our patients showed evidence of amyloid deposition, we suppose that the converting rate to AD is higher in our group. SAI may be abnormal even at an early stage in MCI patients due to AD pathology.

Functions of cortico-cortical connections might be more damaged than intracortical functions in MCI. The combination of abnormalities of the two cortico-cortical functions, SAI and IHI, may be useful for the diagnosis of early-stage MCI converting to AD. Based on the above arguments, we conclude that transcallosal connection between bilateral M1 is primarily involved in MCI, regardless of SAI dysfunction.

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Conflict of interest There is no conflict of interest.

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RESEARCH ARTICLE

On-line effects of quadripulse transcranial magnetic stimulation (QPS) on the contralateral hemisphere studied with somatosensory evoked potentials and near infrared spectroscopy

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Abstract To evaluate on-line effects of quadripulse stimulation (QPS) over the primary motor cortex (M1) on cortical areas in the contralateral hemisphere. QPS consisted of 24 bursts of transcranial magnetic stimulation (TMS) pulses with an inter-burst interval of 5 s for 2 min (for on-line effect study) or 360 bursts for 30 min (for after-effect study). Each burst consisted of four TMS pulses (i.e. QPS) separated by an interstimulus interval of 5 or 50 ms (QPS-5 or QPS-50). QPSs were delivered over the left M1. Experiment 1 [on-line effect on somatosensory evoked potential (SEP)]: Left median nerve SEPs were recorded before, during and after QPS. Experiment 2 (after effect on SEP): After-effects of QPS were evaluated by following up SEPs after the QPS sessions. Experiment 3 (on-line effect on NIRS): Near infrared spectroscopy (NIRS) was also recorded at the right hemisphere during all QPS paradigms. Both QPS-5 and QPS-50 enlarged a cortical component of the contralateral SEP during stimulation. On the other hand, concerning the after effects, QPS-5 over M1 potentiated the contralateral SEP and QPS-50 tended to depress it. In NIRS study, both QPS-5 and QPS-50 induced a significant oxy-Hb decrease (deactivation pattern) at the right hemisphere during stimulation whereas sham stimulations unaffected them. We have shown the unidirectional on-line effects evoked by QPS-5 and QPS-50 on both SEP and NIRS, and bidirectional after effects on SEP at the contralateral hemisphere. The discrepancy between on-line effect and after effect may be explained by the differences in the underlying mechanisms between them. The former may be mainly explained by pure electrophysiological property changes in the membrane or synapses. The latter may be explained by synaptic efficacy changes which need some protein syntheses at least partly. Another discrepancy shown here is the direction of on-line effects. Electrophysiological (SEP) function was potentiated by both QPSs whereas hemodynamic (NIRS) function was depressed. This may be explained by which sensory areas contribute to NIRS or SEP generation.

Keywords Near infrared spectroscopy · Optical recording · Interhemispheric connection · Transcranial magnetic stimulation · Somatosensory evoked potential

Introduction

Repetitive transcranial magnetic simulation (rTMS) is one of the methods to modulate brain activity and sometimes give some benefits to patients with neurological or psychiatric diseases; Parkinson's disease, epilepsy, depression and so on (Epstein et al. 2007; Hamada et al. 2008b; Kimiskidis 2010). Regularly given, conventional high frequency rTMS (i.e. above 5 Hz) over the primary motor cortex (M1) usually potentiates M1 (Pascual-Leone et al. 1994), and low frequency rTMS (i.e. under 1 Hz) depresses it (Chen et al. 1997). These effects are often weak and highly variable from one individual to another (Maeda et al. 2000).

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Several patterned rTMSs have been reported to have more powerful modulation effects than regularly given rTMS (Huang et al. 2005, 2009). In the theta burst stimulation (TBS), one of patterned rTMSs, bursts of three TMS pulses [50 Hz; inter-stimulus interval (ISI) = 20 ms] are delivered at 5 Hz in a few special patterns. Intermittent TBS potentiates the stimulated area (M1, somatosensory cortex or premotor area) whereas continuous TBS depresses it (Huang et al. 2005; Mochizuki et al. 2005; Ishikawa et al. 2007). In 2008, quadripulse stimulation (QPS), a newly developed patterned rTMS protocol was introduced to produce a broad range of motor cortical plasticity ranging from depression to potentiation depending on an interval of the TMS pulses (Hamada et al. 2008a). QPS at an interval of 5 ms (QPS-5) induced most powerful potentiation and QPS at 50 ms interval (QPS-50) most powerful depression.

The purpose of this study is to investigate whether or not the on-line effects of QPS-5 and QPS-50 are oppositely directed similarly to the after effects. We selected QPS-5 and QPS-50 here since they had the most prominent potentiation and depression after effects, respectively. We evaluated the on-line effect and after effect of QPS-5/QPS-50 over M1 on the contralateral somatosensory evoked potentials (SEPs).

Neuroimaging studies have been used to assess the impact of rTMS on the brain. Because of their temporal resolution, only a few methods are applicable to study the brain activity changes during or just after rTMS (Siebner et al. 2009). The on-line effects of single pulse TMS or rTMS were evaluated by functional magnetic resonance imaging method (Bestmann et al. 2008), electroencephalography (Ilmoniemi and Kičić 2010) or near-infrared spectroscopy (NIRS) (Noguchi et al. 2003; Mochizuki et al. 2006). NIRS recording estimates hemoglobin (Hb) concentration changes by measuring reflected light and is not interfered with magnetic fields associated with TMS. NIRS is one of noninvasive neuroimaging methods studying rTMS on-line effects but is not a suitable method for investigation of after effect since it needs to record repeatedly at least a few times. In this paper, we used multi-channel NIRS to evaluate on-line effects of QPS on the contralateral hemisphere.

Subjects and methods

Subjects

Ten healthy volunteers (three women and seven men; age, 27–57 years old, mean ± SD, 39 ± 9 years old) participated in this study. None reported a history of neurological disorders or episodes of seizure. All subjects were right handed based on the Edinburgh Handedness Inventory (Oldfield 1971) and they all gave written informed consent to participate in the study. The experimental procedures used here were approved by the Ethics Committee of Fukushima Medical University and were carried out in accordance with Declaration of Helsinki. No side effects were noted in any individuals. Subjects sat with earplugs in a comfortable reclining chair during the experiments.

Methods

In this study, we performed three experiments as follows.

Experiment 1: On-line effects of 2 min QPS over M1 on the contralateral SEPs.
Experiment 2: After effects of 30 min QPS over M1 on the contralateral SEPs.
Experiment 3: On-line effects of 2 min QPS over M1 on the contralateral NIRS.

Electromyogram (EMG) recordings

Surface EMGs were recorded from the bilateral first dorsal interosseous muscles (FDIs) with 9 mm diameter, Ag–AgCl surface cup electrodes. The active electrode was placed over the muscle belly and the reference electrode over the metacarpophalangeal joint of the index finger. Responses were amplified with an amplifier (MA1116; Digitex Laboratory, Japan) through filters set at 20 Hz and 3 kHz, digitized at a sampling rate of 20 kHz and stored by a computer (TMS bistim tester; Medical Try System, Japan) that was used to perform the randomized conditioning test paradigm and off-line averaging in each condition.

TMS

Magstim 200^2 magnetic stimulators (The Magstim Company Ltd., UK) were used to deliver TMS. We placed a figure 8-shaped coil (7 cm external diameter at each wing; The Magstim Company Ltd., UK) over the M1 of the left hemisphere. The induced currents in the brain were set in the anteromedial direction at a 45 degree angle from the midline (Fig. 1a). M1 was defined as the "hot spot" where stimulation evoked the largest motor evoked potential (MEP) in the contralateral FDI. In two of the subjects, that position was confirmed to be over the primary motor cortex by the neuronavigation system (Spetzger et al. 1995; Boroojerdi et al. 1999). 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 same coil.

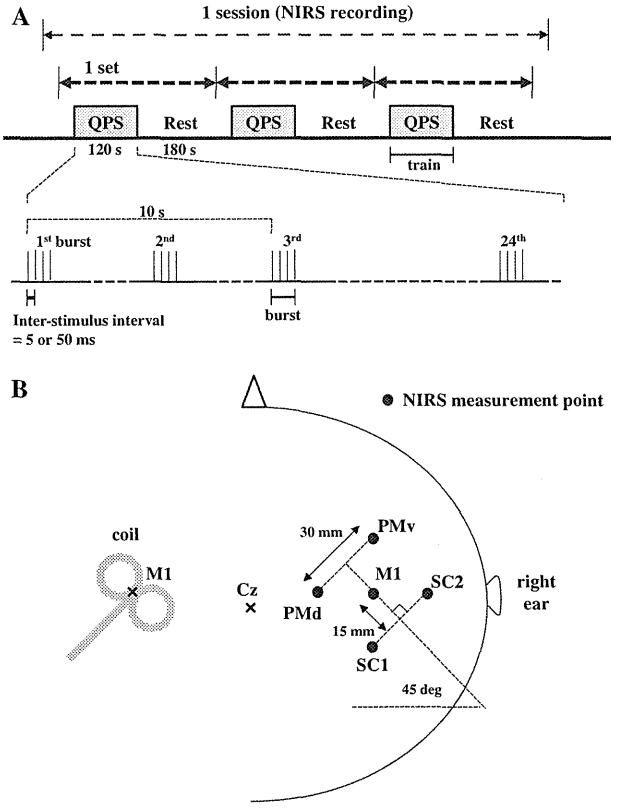

Fig. 1 **a** The paradigm for NIRS on-line effect study (Experiment 3). Two types of QPS (QPS-5 and QPS-50) over left M1 or two types of sham QPS (SHAM-5 and SHAM-50) were delivered for 120 s (1 train, 24 burst, 96 pulses). Rest time of 180 s followed the end of each QPS. This time course (120 s QPS and 180 s rest; 1 set) was repeated three times in one session (total 3 trains, 72 bursts, 288 pulses). **b** The allocations of TMS coil and NIRS measurement points. TMS coil was positioned at the left primary motor cortex (M1). The induced currents in the brain were set in the anteromedial direction at a 45 degree angle from the midline. The five measurement points were the right M1 and four points around the M1. The four measurement points were named here as the right dorsal premotor area (PMd), ventral premotor area (PMv), sensory cortex 1 (SC1) and sensory cortex 2 (SC2)

Repetitive TMSs used here were two types of QPS. QPS was reported to have stable good modulation effects on the stimulated site (Hamada et al. 2008a). In that paper (Hamada et al. 2008a), each burst consisted of four magnetic pulses (i.e. QPS) separated by an ISI of 5 or 50 ms with an inter-burst interval of 5 s (i.e. 0.2 Hz) (Fig. 1a). These QPS types designated as QPS-5 or QPS-50. QPS-5 for 30 min (360 bursts, 1,440 pulses) has a long-term potentiation (LTP) like effect (facilitatory after effect) and QPS-50 a long-term depression (LTD) like effect (inhibitory after effect) on the stimulated site (Hamada et al. 2008a).

The intensity was adjusted at 110% (for on-line effect studies; experiments 1 & 3) or 90% (for after effect study; experiment 2) of active motor threshold (AMT) at M1. We determined the AMT at that to evoke EMG activities in the active target muscle when a subject contracted the target muscles at 5–10% of maximum contraction (about 50 μV). 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 (about 200 μV) as compared to the pre-stimulus background activity in half of the trials.

For the on-line effect experiments (Experiments 1 & 3), the ISI and inter-burst interval were the same as the previous paper (Hamada et al. 2008a). To produce a considerable effect, a duration of rTMS should be longer than 2 min (Thickbroom et al. 2006), and a few times averaging is necessary for getting reliable NIRS results. To get rid of subjects' fatigue, one session must be within 20 min. Taking consideration of all the above factors together, we made one session of three trains of 24 QPS bursts (96 pulses) for 120 s which were interrupted by 180 s rest (total 72 bursts, 288 pulses; Fig. 1a). For the after effects experiment (Experiment 2), QPS was given for 30 min the same as our previous paper (Hamada et al. 2008a).

Experiment 1: on-line effect of QPS on the contralateral SEPs

Eight (three women and five men; age, mean ± SD, 40 ± 10 years old) out of 10 subjects took part in this experiment. To evaluate electrophysiological changes in the sensory cortex, we measured the left median nerve somatosensory evoked potential (SEP) during 2 min QPS.

Left median nerve SEP was recorded before, during and after QPS-5 or QPS-50 sessions. Brief electrical stimuli (0.2 ms duration) were delivered to the left median nerve at the wrist 2 s after the every onset of QPS burst (0.2 Hz). The stimulus intensity was fixed at about 1.2 times the motor threshold, which was strong enough to evoke tingling sensation radiating to the tip of the index finger. To confirm that electric stimulus delivered on median nerve constantly, we monitored antidromic sensory never action potential (SNAP) at the left index finger and averaged them. For cortical SEPs, electrodes were placed on C4′ (2 cm behind C4) and Fz according to the International 10–20 system. Before and after the QPS session, 180 responses (15 min) amplified with filters set at 1 and 1,500 Hz were averaged. During the QPS session, 72 responses were averaged for 6 min.

Experiment 2: after effect of QPS on the contralateral SEPs

Six subjects (one woman and five men; age, mean ± SD, 37 ± 5 years old) were studied in this experiment. QPS-5

or QPS-50 (360 bursts, 1,440 pulses) was delivered to the left M1 for 30 min. The recording and stimulation methods are all the same as Experiment 1. The simulation rate was 2 Hz and 500 responses were averaged for SEP.

Experiment 3: on-line effect on NIRS at the contralateral hemisphere

Nine subjects (three women and six men; age, mean ± SD, 40 ± 10 years old) took part in this experiment.

We used a NIRS system (ETG-4000; Hitachi Medical Corporation, Tokyo, Japan) having five pairs of emitter and detector. The distance between emitter and detector was 3 cm. The five measurement points (midpoints between emitters and detectors) were placed on the right M1 and four points around the M1. Those measurement points were named here as the right dorsal premotor area (PMd), ventral premotor area (PMv), sensory cortex 1 (SC1) and sensory cortex 2 (SC2) (indicated in Fig. 1b). Near-infrared laser diodes with two wavelengths, 695 and 830 nm, were used as the light sources, and transmittance data of the light beams were obtained every 100 ms. We calculated oxyhemoglobin (oxy-Hb) and deoxyhemoglobin (deoxy-Hb) concentrations from the transmittance data.

In this study (paradigm was indicated in Fig. 1a), each event period ranged from 30 s before the QPS train onset to 120 s after the end of the train. Under each condition, the average Hb concentration changes were obtained from the results of two sessions, namely 6 trains, and they were used in statistical analyses. We mostly neglected an accumulative effect during one session because the concentrations returned to the baseline before the next train, even though we cannot completely exclude a small accumulation.

Sham stimulation was performed with two coils. One non-discharging coil was positioned at the left M1, and the other was positioned 10 cm above the head and the same currents as real stimulation (QPS-5 or QPS-50) were induced in it to make sounds. Two types of sham QPS (SHAM-5 and SHAM-50) were applied.

Four different stimulation conditions (two real and two sham stimulation) were done in all the subjects. Each stimulation condition consisted of two sessions. Then, in total, eight sessions (two sessions × four conditions) were done in one subject. The subjects kept both hand muscles relaxed and no MEPs were induced by TMS during all QPS sessions. The inter-session interval was set at 20 min or longer, which was long enough for the Hb concentration changes to return to the baseline. The order of sessions was counterbalanced within and across subjects. Four sessions were done on one experimental day (two QPS and two sham sessions). Any experiments of Experiment 1, 2 and 3 were separated by 1 week or more in the same subject.

Statistical analyses

In SEP studies, repeated-measures ANOVAs (factor, TIME; Experiment 1, before, during and after QPS; Experiment 2, before and 0, 15, 30, 45, 60, 75 and 90 min after QPS) were performed for each SEP component. When an ANOVA test showed significant effects, we further performed post-hoc analyses with Bonferroni's method for multiple comparisons compensation. In the NIRS experiment (Experiment 3), we obtained a representative value of Hb concentration changes by averaging Hb data from 60 to 180 s after the onset of QPS in each condition, and used these average values (mean Hb change) in statistical comparisons. The comparisons were performed by *t* test between QPS-5 and SHAM-5 and between QPS-50 and SHAM-50 at each channel. The statistical significance was set at $P = 0.05$.

Results

None of the subjects reported any adverse effects in our experiments.

SEP studies (Experiments 1 & 2)

Experiment 1: on-line effect

Typical waveforms of SEP before, during and after QPS-5 and QPS-50 for 2 min are shown in Fig. 2. SNAP showed no changes (less than 5%), but P25 peak–N33 peak amplitudes during QPS-5 or QPS-50 were larger than those before or just after each QPS (more than 130%). Before, during and just after QPS-5 or QPS-50, the mean amplitudes of SNAP, N20 onset–peak, N20 peak–P25 peak and P25 peak–N33 peak were shown in Fig. 3. Repeated-measures ANOVA revealed no significant TIME effect on SNAP (QPS-5, $F = 0.313$, $P = 0.736$; QPS-50, $F = 0.020$, $P = 0.981$). This finding means that the left median nerve was stimulated constantly in any conditions. For amplitudes of N20 onset–peak and N20 peak–P25 peak, in either QPS-5 or QPS-50, ANOVA revealed no significant TIME effects on the amplitude (N20 onset–peak, QPS-5, $F = 3.567$, $P = 0.056$, QPS-50, $F = 2.948$, $P = 0.085$; N20 peak–P25 peak, QPS-5, $F = 2.722$, $P = 0.100$, QPS-50, $F = 1.912$, $P = 0.184$). For P25 peak–N33 peak, in contrast, repeated-measures ANOVA revealed significant TIME effects in both QPS types (QPS-5, $F = 9.157$, $P = 0.003$; QPS-50, $F = 8.440$, $P = 0.004$). Post-hoc analyses with Bonferroni method showed that the amplitudes of P25 peak–N33 peak during QPS-5 or QPS-50 were significantly larger than those before or after QPS-5 or QPS-50 ($P < 0.05$).

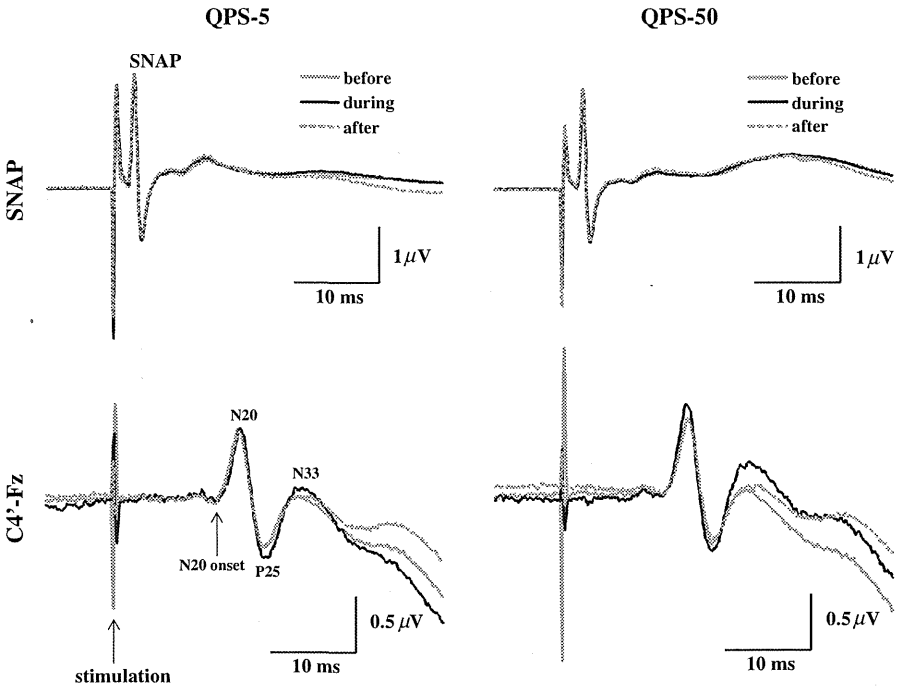

Fig. 2 Typical SEP waveforms before, during and after 2 min QPS-5 (*left column*) or QPS-50 (*right column*). The sensory nerve action potential (SNAP) showed no significant changes (less than 5%), but P25 peak–N33 peak amplitudes during QPS-5 or QPS-50 were larger than those before or just after each QPS. Before QPS, *gray lines*; during, *black lines*; after, *gray dotted lines*

Experiment 2: after effect

Before (baseline) and after 30 min QPS-5 or QPS-50, the mean amplitudes of SNAP, N20 onset–peak, N20 peak–P25 peak and P25 peak–N33 peak are shown in Fig. 4. Repeated-measures ANOVA revealed no significant TIME effect on any of SNAP, N20 onset–peak, N20 peak–P25 peak amplitudes (SNAP, QPS-5, $F = 1.524$, $P = 0.192$, QPS-50, $F = 0.705$, $P = 0.668$; N20 onset–peak, QPS-5, $F = 0.489$, $P = 0.836$, QPS-50, $F = 2.226$, $P = 0.056$; N20 peak–P25 peak, QPS-5, $F = 1.751$, $P = 0.129$, QPS-50, $F = 1.428$, $P = 0.226$). For P25 peak–N33 peak, the mean amplitude tended to be enlarged at 45 min after QPS-5 and suppressed 45 min after QPS-50 (QPS-5, 156%, QPS-50, 85%), but repeated-measures ANOVA revealed significant TIME effects only after QPS-5 (QPS-5, $F = 3.539$, $P = 0.006$; QPS-50, $F = 1.676$, $P = 0.147$) and post-hoc analyses with Bonferroni method showed that it was significantly larger at 45, 60 and 90 min after QPS-5 than the baseline ($P < 0.05$).

NIRS study (Experiment 3)

Hb concentration changes during QPS-5 and SHAM-5

Oxy- and deoxy-Hb concentration changes induced by QPS-5 and SHAM-5 are shown in Fig. 5. Oxy-Hb decreased from a few seconds after the onset of QPS-5 and returned to the baseline around 3 min, whereas deoxy-Hb showed no changes. SHAM-5 induced no significant oxy- or deoxy-Hb concentration changes. The average values of oxy-Hb concentration change at 1–3 min after the onset of QPS-5 were significantly lower than those of SHAM-5 at PMv, M1, SC1 and SC2 (PMv and M1, $P < 0.01$; SC1, $P < 0.02$; SC2, $P < 0.05$).

Hb concentration changes during QPS-50 and SHAM-50

Oxy- and deoxy-Hb concentration changes induced by QPS-50 and SHAM-50 are shown in Fig. 6. Oxy-Hb decreased from a few seconds after the onset of QPS-50 and returned to the baseline around 2 or 3 min, whereas deoxy-Hb showed no changes. This pattern of QPS-50 is similar to that of QPS-5. SHAM-50 induced no significant oxy- or deoxy-Hb concentration changes. The average values of oxy-Hb concentration changes at 1–3 min after the onset QPS-50 were significantly lower than those of SHAM-50 at M1 (M1, $P < 0.05$).

Discussion

Our present results can be summarized as follows.

(1) Both 2 min QPS-5 and QPS-50 enlarged P25–N33 peak to peak amplitude at the contralateral hemisphere *during* QPS (on-line effect). (2) P25–N33 peak to peak amplitude was enlarged *after* 30 min QPS-5 over the contralateral M1 and tended to be depressed *after* 30 min QPS-50 over the contralateral M1 (after effect). (3) Two minutes QPS-5 over M1 induced a significant oxy-Hb

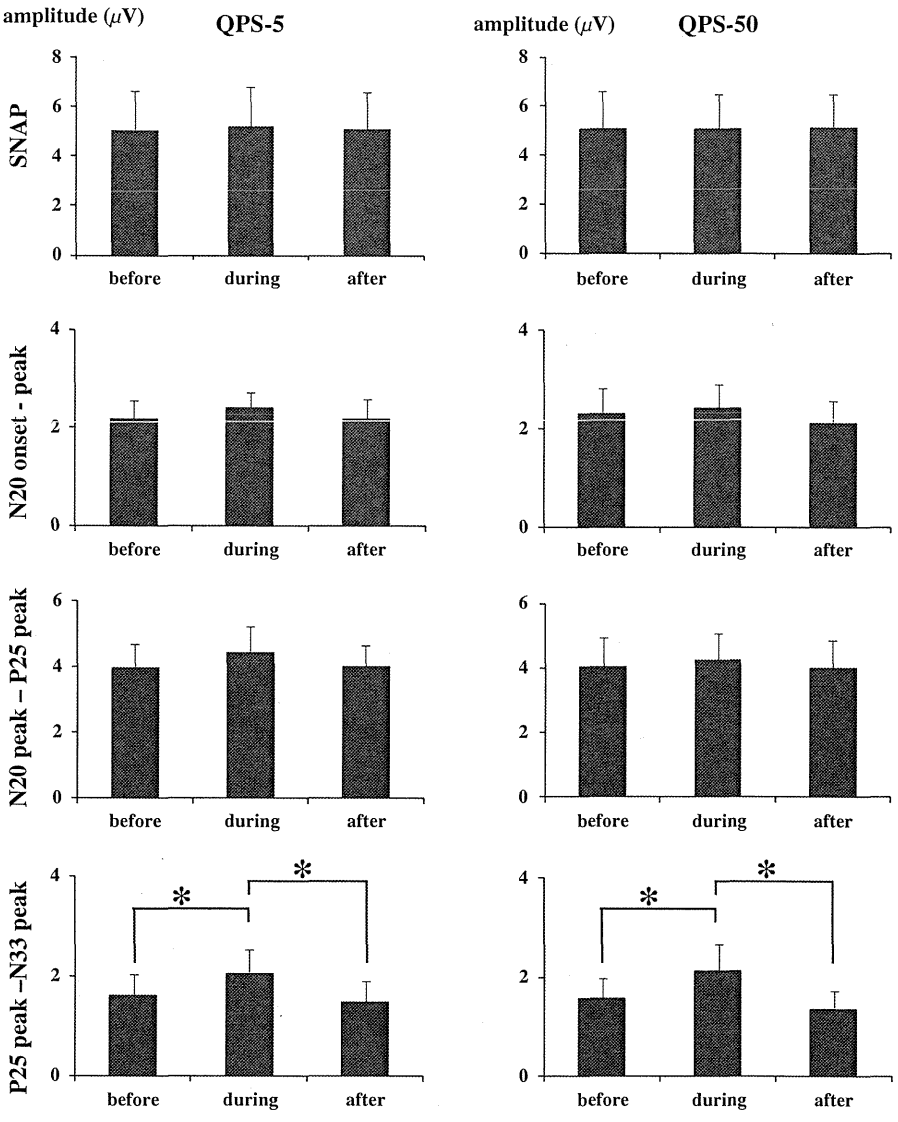

Fig. 3 Mean (± standard error) amplitudes of sensory nerve action potential (SNAP), N20 onset–peak, N20 peak–P25 peak and P25 peak–N33 peak before, during and after 2 min QPS-5 or QPS-50. Repeated-measures ANOVA and post-hoc analyses with Bonferroni method revealed that the amplitudes of P25 peak–N33 peak during QPS-5 or QPS-50 were significantly larger than those before and after QPS-5 or QPS-50 ($P < 0.05$)

decrease at the contralateral M1, PMv, SC1 and SC2 *during* QPS (on-line effect). (4) Two minutes QPS-50 over M1 also induced significant oxy-Hb decrease at the contralateral M1 *during* QPS (on-line effect).

We recorded SEP and NIRS at the contralateral hemisphere. These were a kind of indirect (not direct) effects through the corpus callosum. We may make more firm discussions if based on the ipsilateral hemisphere recordings. However, we had no chance to record ipsilateral responses under the coil because of methodological limitations. Even with these limitations, it is conspicuous that QPS-5 and QPS-50 had the same directional on-line effects at the contralateral hemisphere.

On-line and after effects of QPS on the contralateral SEPs

Both QPS-5 and QPS-50 enlarged P25–N33 peak to peak amplitude at the contralateral hemisphere during QPS. Both QPS-5 and QPS-50 over M1 have facilitatory on-line effects on the contralateral SEPs. TMS pulses in QPS-5 are given at 200 Hz, and those in QPS-50 at 20 Hz, which are a kind of high-frequency TMS pulses. High-frequency rTMS had a facilitatory on-line effect under the coil in animals (Collingridge et al. 2004). Short high-frequency TMS bursts were also reported to have facilitatory on-line effects in humans (Huang and Rothwell 2004; Hanajima et al. 2009). We could not conclude that both QPS-5 and QPS-50 had similar facilitatory on-line effects on the stimulated site based on our data, but could say that both QPS-5 and QPS-50 induced the same directional on-line effects on the contralateral hemisphere.

As regards the after effects of 30 min QPS, QPS-5 potentiated and QPS-50 depressed the M1 after QPS over M1 (Hamada et al. 2008a). In the other patterned rTMS, the continuous TBS (cTBS) depressed and intermittent TBS (iTBS) potentiated the M1 after TBS over M1 (Huang et al.

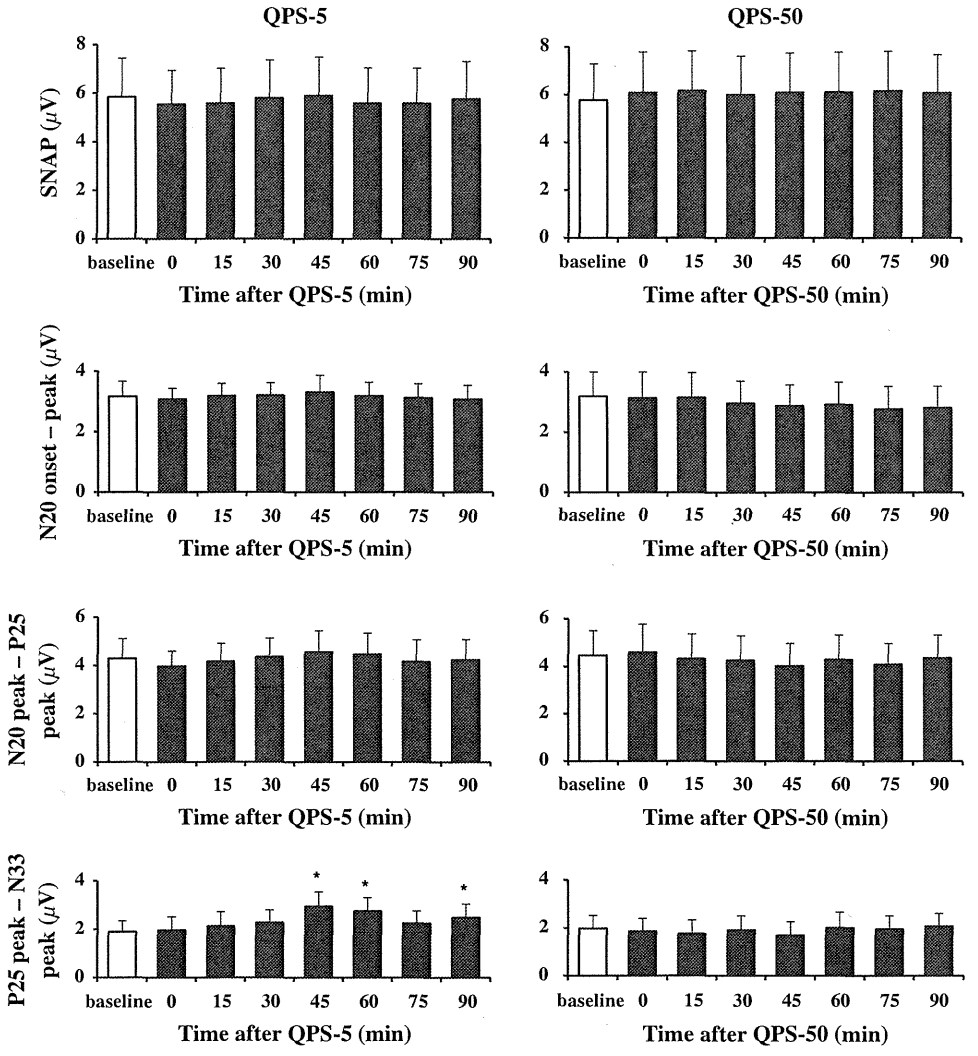

Fig. 4 Mean (± standard error) amplitudes of sensory nerve action potential (SNAP), N20 onset–peak, N20 peak–P25 peak and P25 peak–N33 peak before and after QPS-5 or QPS-50. Repeated-measures ANOVA and post-hoc analyses with Bonferroni method showed that the amplitudes of P25 peak–N33 peak at 45, 60 and 90 min after QPS-5 were significantly larger than the baseline ($P < 0.05$)

2005). According to the contralateral hemisphere, reversed after-effects were induced by TBS (Suppa et al. 2008). The cTBS over M1 induced a facilitatory after-effect on the contralateral M1, and iTBS induced an inhibitory one. Reciprocal connection may be present between the bilateral M1s. Which effect would be produced in the contralateral sensory cortex? Some dense mutual interactions are present between motor and sensory cortices within the same hemisphere, and an activation of one produces a reciprocal suppressive effect on the other (Enomoto et al. 2001; Tamura et al. 2004; Mochizuki et al. 2004). Based on these previous papers, the activation (or deactivation) of left M1 induced by QPS-5 (QPS-50) was speculated to inhibit (facilitate) the right M1 activities and facilitate (inhibit) the right sensory cortical activities. This speculation is completely consistent with the present findings that P25–N33 peak to peak amplitude was enlarged after QPS-5 over the contralateral M1 and depressed after QPS-50 over the contralateral M1. Reciprocal connections between bilateral M1 s and between ipsilateral M1 and S1may explain the present findings of after effects induced by 30 min QPS.

Mentioned above, the on-line effects of QPS-5 and QPS-50 over M1 on the contralateral SEP were SEP amplitude enhancement and were unidirectional, and their after effects were bidirectional. This discrepancy between the on-line and after effects of QPS would be explained by the differences in the underlying mechanisms. The on-line effects may be mainly explained by pure electrophysiological property changes in the membrane or synapses (short term changes) or some biochemical changes without protein syntheses. On the other hand, the after effect may be explained by some synaptic efficacy changes (LTP and LTD like

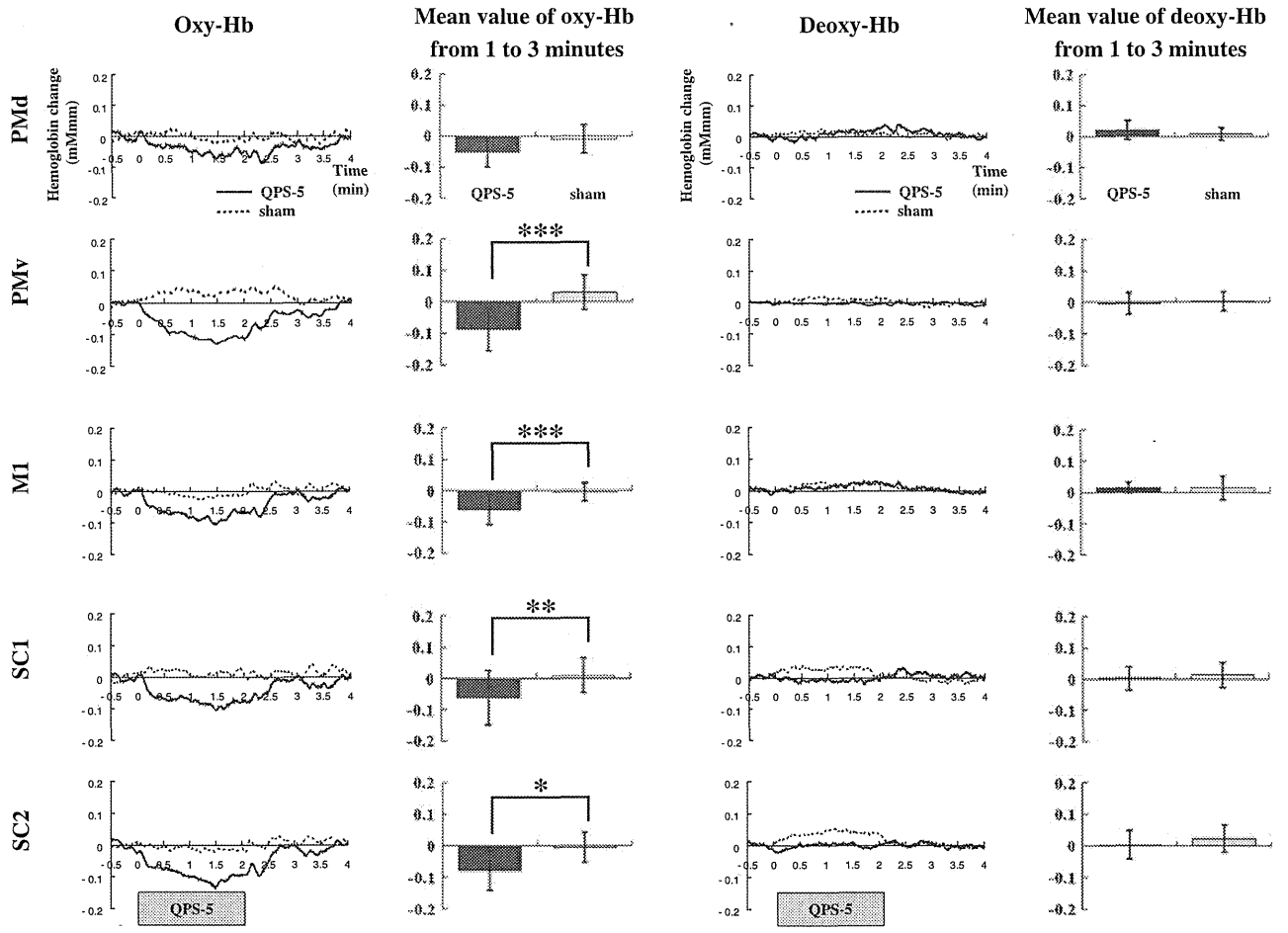

Fig. 5 Oxy-Hb (first and second columns) and deoxy-Hb (*third* and *fourth columns*) concentration changes induced by QPS-5 (*thick lines* and *dark gray boxes*) and SHAM-5 (*dotted lines* and *light gray boxes*). Oxy-Hb decreased from a few seconds after the onset of QPS-5 and returned to baseline around 3 min. The average oxy-Hb changes at 1–3 min of QPS-5 were significantly lower than those of SHAM-5 at PMv, M1, SC1 and SC2. $*P < 0.05$; $**P < 0.02$; $***P < 0.01$

effects) which partly need some protein syntheses (Malenka and Bear 2004).

NIRS findings

Three different patterns of NIRS changes have been reported in natural brain activation and TMS stimulation. First, large oxy-Hb increase and small deoxy-Hb decrease were observed in natural brain activation (activation) (Chance et al. 1988; Villringer et al. 1993; Kleinschmidt et al. 1996). Another is large oxy-Hb decrease and small deoxy-Hb increase in natural deactivation (deactivation) (Wenzel et al. 2000; Fabbri et al. 2003). The other one is large deoxy-Hb decrease without any significant oxy-Hb change. This pattern is observed only after a single pulse TMS under the coil (Mochizuki et al. 2006). The pattern observed in the present study, large oxy-Hb decrease and small deoxy-Hb increase, is almost the same as that seen in natural deactivation among the above three patterns. We speculate that some deactivation must occur at the motor cortex and some surrounding areas both during QPS-5 and during QPS-50 over the contralateral M1.

As discussed above, both QPS-5 and QPS-50 induced same facilitatory on-line effects on the contralateral SEPs. On the other hand, our NIRS data revealed that QPS-5 and QPS-50 induced the oxy-Hb decrease (deactivation pattern) at the contralateral hemisphere. Then, what can explain the oxy-Hb concentration decrease in sensory cortex with SEP enhancement? This may be explained by the structures contributing to NIRS or SEP generation. The amplitude of SEP components reflects functional activity of a certain sensory cortical area, such as 3b, 1 or 2. In contrast, NIRS value over the sensory cortex may reflect activity of the whole sensory cortex. These may explain the above discrepancy.

Our results revealed that the on-line effects were the same directional between QPS-5 and QPS-50 in contrast to

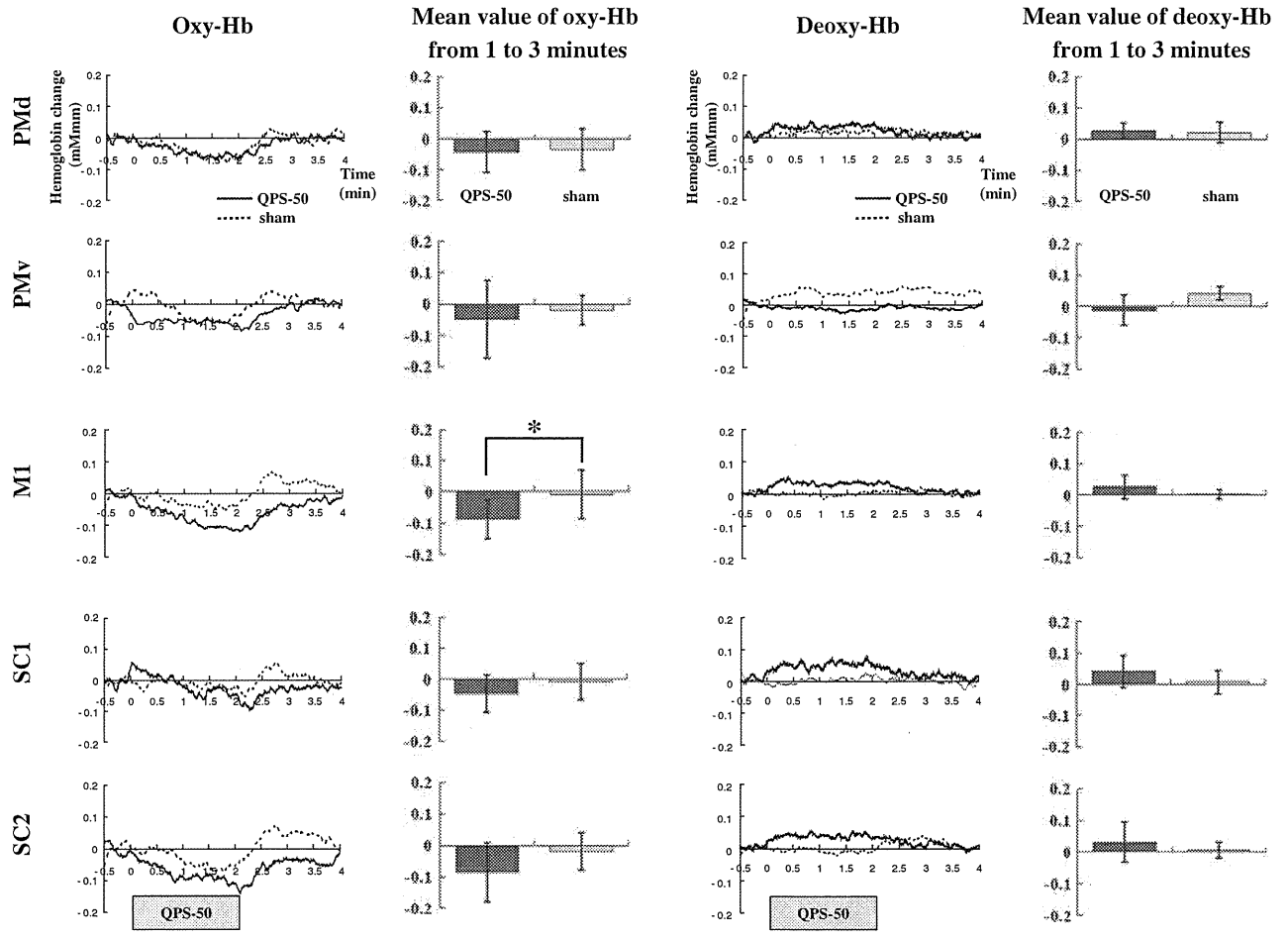

Fig. 6 Oxy-Hb (*first* and *second columns*) and deoxy-Hb (*third* and *fourth columns*) concentration changes induced by QPS-50 (*thick lines* and *dark gray boxes*) and SHAM-50 (*dotted lines* and *light gray boxes*). Oxy-Hb decreased from a few seconds after the onset of QPS-50 and returned to the baseline around 2–3 min. The average oxy-Hb changes at 1–3 min of QPS-50 were significantly lower than those of SHAM-50 at M1. $*P < 0.05$

their oppositely directed after effects. Based on these, we conclude that the underlying mechanisms are different between the on-line effects and after effects. The former may be mainly produced by pure electrophysiological property changes in the membrane or synapses. The latter may be produced by some synaptic efficacy changes which partly need some protein syntheses.

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LETTER TO THE EDITOR

Neurophysiological analysis of the cauda equina in POEMS syndrome

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Keywords Magnetic stimulation · POEMS syndrome · Crow-Fukase syndrome · Cauda equina · Spinal nerve

Sir,

In POEMS syndrome (Crow-Fukase syndrome), the proximal conduction of peripheral nerves innervating leg muscles is difficult to assess using conventional nerve conduction studies (NCSs) when F-waves or H-reflexes are not detectable. Recently, we developed a novel magnetic stimulation method to measure cauda equina conduction time (CECT) using a powerful coil known as a magnetic augmented translumbosacral stimulation coil (MATS coil) [1–3]. This method allows us to investigate CECT even in patients with peripheral neuropathy [3]. In this study, we applied our method to a patient with POEMS syndrome.

The patient was a 72-year-old man who was unable to walk 5 months after onset. Neurological findings at 6 months after onset revealed weakness with muscular atrophy (Medical Research Council scale for muscle strength grades: proximal arm 4, distal arm 3, proximal leg 3 and distal leg 1), distal dominant sensory disturbance and areflexia of the extremities. Whole-body computed tomography revealed hepatomegaly and multiple enlarge lymph nodes. We made the diagnosis of POEMS syndrome on the basis of skin hemangioma, skin pigmentation, hirsutism, leg edema, hepatomegaly, lymphadenopathy, monoclonal protein of immunoglobulin G (λ type), and subacute motor and sensory polyneuropathy. Conventional NCSs were performed on the right side. In the median nerve, the amplitude of compound muscle action potentials (CMAPs) was severely reduced to 0.4 mV. Neither a pathological temporal dispersion nor a conduction block was detected. Motor conduction velocity (MCV) between wrist and elbow was slowed to 24 m/s with prolonged distal latency (5.6 ms). Sensory nerve action potentials (SNAPs) were not evoked. For the lower extremities, neither CMAPs in the tibial nerve nor SNAPs in the sural nerve were evoked. Additionally, neither F-waves in the median and tibial nerves nor H-reflexes in the tibial nerve were evoked. Needle electromyography (nEMG) was performed in the biceps brachii, first dorsal interossei, rectus femoris, and tibialis anterior muscles on the right side. Abundant spontaneous activities were recorded during relaxation in only the first dorsal interossei and tibialis anterior muscles. In all the contracted muscles, recruitment of motor unit potentials was reduced during voluntary contraction (contraction of the tibialis anterior muscle was impossible). MATS coil stimulation was performed to measure CECT. CMAPs were recorded from the biceps femoris muscle. This particular proximal muscle was selected since it had experienced much less atrophy than the distal muscles. The most distal part of the cauda equina was activated by MATS coil stimulation over the first sacral spinous processes (S1) [1–3]. The most proximal part of the cauda equina was activated by MATS coil stimulation over the first lumbar spinous processes (L1) [2, 3].

As shown in Fig. 1a, this method demonstrated severely prolonged CECT (right 8.1 ms, left 8.0 ms; normal values

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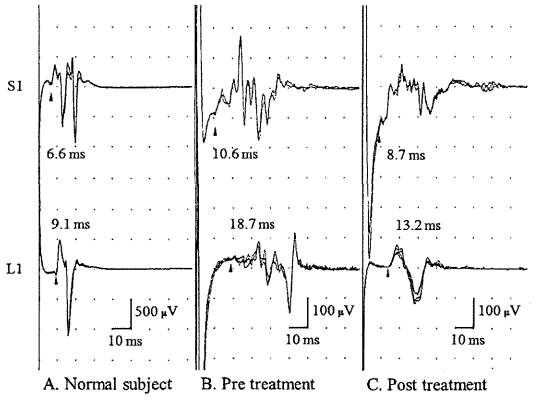

Fig. 1 MATS coil stimulation method. The CMAPs recorded from the right biceps femoris muscle in a normal subject (**a**) and in a patient with POEMS syndrome before therapy (**b**) and after therapy (**c**). In the biceps femoris muscle, H-reflexes can contaminate the CMAP evoked by S1 level MATS coil stimulation. For this reason, CMAP onset latency (i.e., cauda equina conduction time [CECT]) is used as the neurophysiological parameter of the cauda equina

are 2.4 ± 0.8 ms). Thereafter, the patient was successfully treated with autologous peripheral blood stem cell transplantation (auto-PBSCT). One year after auto-PBSCT, the patient could walk again with the aid of a walker. MATS coil stimulation demonstrated a shortened but still abnormal CECT (right 4.5 ms, left 4.0 ms, Fig. 1b).

The findings of nEMG suggested that axonal degeneration was prominently observed in the distal muscles in a patient with POEMS syndrome. MATS coil stimulation also showed severely prolonged CECT before auto-PBSCT. This result is compatible with the demyelinating lesions in the cauda equina. Moreover, CECT was reduced after auto-PBSCT, which was compatible with the remyelinating process. In electrophysiological research of this disorder, the function of proximal peripheral nerves has received little attention. On the other hand, previous papers on autopsies have noted that the demyelinating lesions exist predominantly in the proximal portions of the peripheral nerves, although axonal loss is prominently observed in the distal portions [4, 5]. On the basis of this prior research, we conclude that our electrophysiological findings strongly support the pathological findings of these previous papers (i.e., the demyelinating lesions in the proximal portions of the peripheral nerves). We also conclude that the demyelinating lesions in the cauda equina before auto-PBSCT and the remyelinating process after auto-PBSCT can be observed in this disorder.

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Conflict of interest The authors have no potential conflicts of interest.

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