Abnormal Cortical Synaptic Plasticity in Primary Motor Area in Progressive Supranuclear Palsy

Antonella Conte1,2, Daniele Belvisi1, Matteo Bologna2, Donatella Ottaviani1, Giovanni Fabbrini1,2, Carlo Colosimo1, David R. Williams3 and Alfredo Berardelli1,2

1Department of Neurology and Psychiatry “Sapienza,” University of Rome, Viale dell’Università, 30, 00185 Rome, Italy, 2Neuromed Institute, “Sapienza,” University of Rome, Pozzilli (IS), Italy and 3Van Cleef Roet Centre for Nervous Diseases, Monash University, Melbourne 3004, Victoria, Australia

Address correspondence to Prof. Alfredo Berardelli, Department of Neurology and Psychiatry, “Sapienza,” University of Rome, Viale dell’Università, 30, 00185 Rome, Italy. Email: alfredo.berardelli@uniroma1.it.

No study has yet investigated whether cortical plasticity in primary motor area (M1) is abnormal in patients with progressive supranuclear palsy (PSP). We studied M1 plasticity in 15 PSP patients and 15 age-matched healthy subjects. We used intermittent theta-burst stimulation (iTBS) to investigate long-term potentiation (LTP) and continuous TBS (cTBS) to investigate long-term depression (LTD)-like cortical plasticity in M1. Ten patients underwent iTBS again 1 year later. We also investigated short-interval intracortical inhibition (SICI) and intracortical facilitation (ICF) in M1 with paired-pulse transcranial magnetic stimulation, tested H reflex from upper limb flexor muscles before and after iTBS, and measured motor evoked potential (MEP) input–output (I/O) curves before and after iTBS. iTBS elicited a significantly larger MEP facilitation after iTBS in patients than in healthy subjects. Whereas in healthy subjects, cTBS inhibited MEP, in patients it significantly facilitated MEPs. In patients, SICI was reduced, whereas ICF was normal. H reflex size remained unchanged after iTBS. Patients had steeper MEP I/O slopes than healthy subjects at baseline and became even more steeper after iTBS only in patients. The iTBS-induced abnormal MEP facilitation in PSP persisted at 1-year follow-up. In conclusion, patients with PSP have abnormal M1 LTP/LTD-like plasticity. The enhanced LTD-like cortical synaptic plasticity parallels disease progression.

Keywords: cortical plasticity, motor cortex excitability, progressive supranuclear palsy, theta-burst stimulation

Introduction

Progressive supranuclear palsy (PSP) is a sporadic neurodegenerative disease clinically characterized by supranuclear vertical ophthalmoplegia, pseudobulbar palsy, parkinsonian features, and dementia (Litvan et al. 1996; Williams et al. 2005; Williams and Lees 2009). Histopathological studies show hyperphosphorylated tau protein deposition forming fibrillary aggregates (globoid neurofibrillary tangles) in neurons (Dickson 1999) and glia of numerous cerebral areas including the cerebral neocortex, pallidum, subthalamic nucleus, substantia nigra, periacqueductal gray matter, superior colliculi, and dentate nucleus (Hauw et al. 1994; Daniel et al. 1995). Another pathological feature of PSP is a significant loss of cortical interneurons in the presupplementary motor area, primary motor cortex (M1), and motor thalamus (Halliday et al. 2005). Reductions in cortical interneuronal activity have been shown on positron–emission tomography in PSP, with altered activation of cortical interneurons expressing benzodiazepine receptors in the frontal lobes (Foster et al. 2000).

Cortical interneurons in M1 can also be tested with the transcranial magnetic stimulation (TMS) technique. Paired-pulse TMS has provided evidence of reduced intracortical inhibition (short-interval intracortical inhibition, SICI) attributed either to M1 hyperexcitability due to the loss of γ-aminobutyric (GABA)-A intracortical inhibitory interneurons or to an M1 disinhibition related to the reduced pallidothalamic inhibitory input (Kühn et al. 2004).

Unlike paired-pulse TMS, repetitive TMS (rTMS) investigates complex circuits underlying cortical plasticity mechanisms in M1. A plasticity-inducing rTMS technique is theta-burst stimulation (TBS). TBS elicits long-lasting changes in the excitability of human M1 (Huang et al. 2005). The after-effects of TBS depend on how TBS is delivered: continuous TBS (cTBS) typically results in MEP and SICI decrease, whereas intermittent TBS (iTBS) leads to MEP and SICI increase (Huang et al. 2005). The mechanisms underlying TBS-induced after-effects on cortical excitability resemble the synaptic plasticity phenomena described after electrical stimulation of M1 in animal brain slice preparations, namely, long-term potentiation (LTP) and long-term depression (LTD) (Castro-Alamancos et al. 1995; Hess and Donoghue 1996). In humans, iTBS may therefore facilitate motor cortical responses through LTD-like plasticity, whereas cTBS depresses them through LTD-like plasticity (Huang et al. 2005) in M1. In patients with Parkinson’s disease (PD), recent studies with TBS showed that iTBS and cTBS failed to induce significant changes in M1 excitability (Eggers et al. 2010; Suppa et al. 2011). Impaired cortical synaptic plasticity may play a pathophysiological role also in motor disorders manifesting with other forms of parkinsonisms, for example, PSP, and may also be instrumental in determining its clinical features. No data are yet available on the mechanisms underlying cortical synaptic plasticity in PSP, an akinetic parkinsonian syndrome with severe motor symptoms. Nor is it known whether the altered inhibitory interneuron activity in M1 reported in pathological studies (Halliday et al. 2005) influences M1 excitability as well as cortical plasticity.

In this study, we used iTBS and cTBS to investigate LTP- and LTD-like cortical synaptic plasticity in patients with PSP and healthy subjects. To investigate whether possible alterations in iTBS-induced plasticity correlate with paired-pulse TMS alterations in patients, we also delivered paired-pulse TMS to evaluate SICI and intracortical facilitation (ICF) in M1. To investigate whether possible changes in the susceptibility to TBS-induced plasticity depended on differences in cortico-spinal excitability between patients with PSP and healthy subjects, we tested input–output (I/O) curves (Ridding and...
Materials and Methods

Subjects
We recruited 15 patients with PSP from the movement disorders outpatient clinic at the Department of Neurology and Psychiatry, Sapienza, University of Rome, and 15 age-matched healthy subjects. Patients’ clinical and demographic features are summarized in Table 1. All patients had a diagnosis of PSP based on National Institute of Neurological Disorders and Stroke (NINDS) PSP criteria (Litvan et al. 1996). The clinical features were compatible with the PSP phenotype described by Williams et al. (2005) as Richardson’s syndrome. All patients had a symmetric akinetic-rigid syndrome, which responded poorly to levodopa. Twelve patients had supranuclear gaze palsy and the other 3 had slowing of vertical saccadic eye movements. None of the patients had cerebellar signs. Patients were clinically evaluated using the Unified Parkinson’s Disease Rating Scale (UPDRS) part III (Fahn and Elton 1987), PSP Rating Scale (PSPRS) (Golbe and Ohman-Strickland 2007), Hoehn and Yahr (HY) scale (Hoehn and Yahr 1967), and Frontal Assessment Battery (FAB) (Dubois et al. 2000). Magnetic resonance imaging (MRI) scans showed that all the patients studied had varying degrees of brainstem, basal ganglia, and frontal lobe atrophy. All patients underwent a neurophysiological experimental session to assess M1 cortical excitability with single and paired-pulse TMS and TBS. Of the 15 patients enrolled, 10 participated in a 1-year follow-up iTBS session.

All the patients were studied in the morning after overnight withdrawal of dopaminergic medications. Clinical and neurophysiological variables were assessed independently by 2 different groups of investigators and the neurophysiologists were blinded to the clinical scores. The experimental procedures were approved by the institutional review board and conducted in accordance with the Declaration of Helsinki. All the participants gave their signed informed consent to the experimental procedures.

Transcranial Magnetic Stimulation Techniques

Single- and Paired-Pulse TMS
Subjects were comfortably seated in an armchair, and their right arm was maintained relaxed in the same position throughout the experiment. Single-pulse TMS was delivered through a monophasic Magstim 200 stimulator (Magstim Co., Whitanld, Dyfed, UK) connected to a figure-of-eight coil (external wing 9 cm in diameter) placed tangentially over the left M1 in the optimal position (hot spot) for eliciting motor evoked potentials (MEPs) in the right first dorsal interosseus (FDI) muscle. The hot spot was marked on the scalp with a soft-tip pen. Resting motor threshold (RMT) was calculated as the lowest intensity evoking 5 MEPs of at least 50 μV in 10 consecutive trials. Test TMS consisted in 20 single pulses delivered at the intensity able to evoke single MEPs at about 1 mV peak-to-peak in amplitude. The same intensity was used for testing MEP amplitudes throughout the experiment. Single-pulse TMS was also used to obtain I/O curve in a subgroup of 8 patients and 8 healthy subjects before and after iTBS. For I/O curves, stimulus intensities were individually adapted according to the intensity able to evoke a mean MEP of about 1 mV in each subject. Ten MEPs were recorded at 80%, 90%, 100%, 110%, and 120% of the 1 mV intensity. Peak-to-peak amplitudes of MEP were measured for each trial to obtain the mean MEP amplitudes for each stimulation intensity (Rosenkranz et al. 2007).

Short-interval paired-pulse stimulation was delivered through 2 monophasic magnetic stimulators (The Magstim Company Ltd) connected by a Y cable to a figure-of-eight coil placed over the cortical motor area. The coil was positioned to find the optimal site for evoking a MEP in the contralateral FDI muscle and held tangentially to the scalp with the handle pointing back and away from the midline at 45°.

Short-interval paired-pulse TMS (to test SICI and ICF) was delivered according to the technique described by Kujirai et al. (1993). A subthreshold (80% active motor threshold, AMT) conditioning pulse was delivered at 3- and 10-ms interstimulus intervals (ISIs) before test pulse. Test TMS pulses were collected using an intensity needed to evoke MEPs of about 1 mV amplitude. Twenty trials were acquired for each condition. Paired-pulse TMS was studied in 15 patients.

Theta-Burst Stimulation
TBS was delivered through a high-frequency biphasic magnetic stimulator (Magstim SuperRapid—The Magstim Company Ltd) connected to a figure-of-eight coil placed over the left M1. In the session testing LTP-like plasticity, rTMS was delivered using the iTBS protocol (Huang et al. 2005) and consisted in bursts of 3 pulses at high frequency, 50 Hz, repeated at intervals of 200 ms, in short trains lasting 2 s, with a pause of 8 s between consecutive trains, for a total number of 600 pulses. In the LTD-like plasticity session, rTMS was delivered using the cTBS protocol and consisted in bursts given in a continuous train lasting 40 s (600 pulses in total) (Huang et al. 2005). The stimulation intensity for iTBS and cTBS was set at 80% of AMT obtained with the biphasic magnetic stimulator. AMT was determined as the lowest intensity evoking 5 MEPs of at least 200 μV in 10 consecutive trials during a mild tonic contraction (20% of maximal voluntary contraction) (Rossini et al. 1994). As the variable for measuring LTP and LTD-like TBS-induced plasticity in M1, we collected 20 MEPs before (I0) and 5

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<th>Disease duration (years)</th>
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Note: MMSE, mini-mental state examination.
MEP sizes after iTBS with factor iTBS (absolute MEP values at assessment. Repeated measures ANOVA was used to analyze changes in for evoking 1mV-MEPs in patients at baseline and at one year follow-up run to test iTBS-induced effects in healthy subjects. Paired sample -test showed that RMT and AMT in patients remained unchanged at the 1-year follow-up session.

Results

Clinical Scores

In patients with PSP, mean clinical scores at baseline were PSPRS 38.2 ± 3.0; UPDRS 32.0 ± 3; HY 3.6 ± 0. Fab 10.5 ± 0.8 (Table 1). In the 10 patients who underwent the 1-year follow-up session, PSPRS scores and UPDRS but not HY, significantly worsened from baseline values (PSPRS: P = 0.002; UPDRS: P = 0.05; HY: P = 0.17).

RMT, AMT, Intensity for 1 mV MEP and EMG Root Mean Square (Single MEP Traces and During iTBS)

Unpaired Student’s -test for RMT, AMT values, 1 mV MEP intensity, and EMG root mean square amplitude in healthy subjects and patients showed no significant differences for either TMS variables in the 2 groups tested (Table 2). Paired-sample -test showed that RMT and AMT in patients remained unchanged at the 1-year follow-up session.

SCI and ICF

Between-group repeated measures ANOVA for SCI and ICF showed a significant effect of factor ISI (F1, 28 = 133.6; P < 0.00001), factor group (F1, 28 = 8.43, P = 0.004) and a significant interaction of factors ISI and group (F1, 28 = 23.85, P < 0.0001). Post hoc analysis showed that SCI but not ICF significantly differed in patients and healthy subjects (SCI: P < 0.0001; ICF: P = 0.21) (Table 2).

Intermittent Theta-Burst Stimulation

Testing iTBS-induced plasticity in the 15 patients with PSP and 15 age-matched healthy subjects, between-group repeated measures ANOVA for MEP size showed a significant effect of factor group (F1, 28 = 13.05, P < 0.0001), iTBS (F2, 84 = 24.25, P < 0.0001) and a significant interaction of factor iTBS and group (F2, 84 = 8.32, P < 0.0001). Post hoc analysis showed that the amount of MEP facilitation differed significantly at all time points in the 2 groups (P1: P = 0.0003; P2: P = 0.008; P3: P = 0.001), whereas the MEP size at T0 did not (P = 0.54) (Fig. 1).

Repeated measures ANOVA testing iTBS-induced effects on M1 separately in healthy subjects showed a significant effect of factor iTBS (F2, 82 = 3.74; P = 0.03). Post hoc analysis showed that the increase in MEP size was significant at all time points (P1: P = 0.003; P2: P = 0.0001; P3: P = 0.006).

In 7 patients of the 15 patients, paired-sample -test for the H reflex size showed no significant difference after iTBS (H reflex amplitude pre-iTBS: 1.73 ± 0.21 mV vs. H reflex amplitude post-iTBS: 1.64 ± 0.19 mV, P = 0.30).

In the 10 patients who underwent the follow-up study, repeated measures ANOVA for the iTBS-induced facilitation at baseline and at 1-year follow-up showed a significant effect of factor iTBS (F2, 27 = 18.89, P < 0.000001), but no significant effect of factor 1-year follow-up session (F1, 9 = 2.37, P = 0.15) and a nonsignificant interaction between the 2 factors (F2, 27 = 0.56, P = 0.64). The iTBS-induced MEP facilitation in patients
was higher though not statistically significant higher at 1-year follow-up than at baseline (Fig. 2).

**Effects of iTBS on I/O Curve in Patients and Healthy Subjects**

Between-group repeated-measures ANOVA for MEP size in the I/O curve showed a significant effect of factor group ($F_{1,14} = 7.24, P = 0.01$), factor iTBS ($F_{1,14} = 19.92, P < 0.001$), and intensity ($F_{1,14, 6.04} = 44.53, P < 0.00001$ corrected for nonsphericity) and also a significant interaction of factor group × intensity ($F_{1,14, 6.04} = 7.04, P = 0.014$ corrected for nonsphericity), factor iTBS × intensity ($F_{2,17, 30.51} = 3.79, P = 0.03$ corrected for nonsphericity) and group × iTBS ($F_{1,14} = 7.04, P = 0.018$) but not significant interaction of factors group × iTBS × intensity. MEPs size in the I/O curves significantly differed between PSP and healthy subjects ($P = 0.01$) and significantly differed before and after iTBS ($P = 0.006$). Statistical analysis for the steepness of I/O curve showed that steepness of I/O differs significantly between patients and healthy subjects ($F_{1,14} = 7.43, P = 0.01$). Although post hoc analysis showed steeper slopes in patients than in healthy subjects before and after iTBS (Wald–Wolfowitz runs test: $P = 0.03$, $P = 0.01$) and the slopes steepened in both groups after iTBS, the difference was statistically significant only in patients (Wilcoxon’s Test: PSP: $P = 0.03$, healthy subjects: $P = 0.7$) (Fig. 3).

**Continuous iTBS**

Testing cTBS-induced plasticity in 7 of the 15 patients with PSP and in 7 age-matched healthy subjects, between-group repeated measures ANOVA for MEP size showed a significant effect of factor group ($F_{1,12} = 34.82, P < 0.0001$), cTBS ($F_{3, 56} = 4.24, P = 0.01$) and a significant interaction of factor cTBS and group ($F_{3, 56} = 14.54, P < 0.000001$). Post hoc analysis showed that whereas in healthy subjects, cTBS significantly inhibited MEP size ($F_{3, 18} = 23.55, P = 0.00002$) at all time points, in patients cTBS significantly facilitated MEP size ($F_{3, 18} = 4.16, P = 0.02$) and the increase was significant at $T_2$ ($P = 0.04$) and $T_3$ ($P = 0.03$) (Fig. 4).

**Correlations between TMS Variables and Clinical Scores**

Spearman’s correlation coefficient showed no significant correlation either between demographic and clinical scores (PSPRS, UPDRS, HY, and FAB) or between clinical scores (PSPRS, UPDRS, HY, and FAB) and the amount of iTBS-induced MEP facilitation at baseline. Pearson’s correlation coefficient, however, showed a significant correlation between the changes in the degree of post-iTBS MEP facilitation at 1-year follow-up (ratios between the MEP size ratio at $T_2/T_0$ at 1-year follow-up and the MEP size ratio at $T_2/T_0$ at baseline) and the changes in clinical severity scores (ratios between PSPRS at 1-year follow-up and PSPRS values at baseline) ($R^2 = 0.49, P = 0.02$) (Fig. 5). No correlation was found between the degree of MEP facilitation and inhibition at paired-pulse TMS and the iTBS- and cTBS-induced facilitation.

**Discussion**

Our neurophysiological study investigating TBS-induced LTP- and LTD-like cortical synaptic plasticity in patients with PSP provided 3 new findings. The first is that iTBS produces a larger...
MEP facilitation in patients with PSP than in healthy subjects. The second is that unexpectedly, cTBS also elicits a significant MEP facilitation in patients with PSP but normal MEP inhibition in healthy subjects. A further new finding is that the expected steeper MEP I/O curve in patients with PSP than in healthy subjects became even steeper after iTBS but did so only in patients. Finally, at 1-year follow-up PSPRS scores worsened and the enhanced iTBS-induced MEP facilitation at baseline became, though not significantly, more evident. These TBS-induced changes provide hitherto unavailable information on the mechanisms underlying cortical synaptic plasticity in PSP.

To ensure that iTBS- and cTBS-induced changes in LTP- and LTD-like cortical synaptic plasticity were due to our intervention and to ensure reliable data, our experimental procedures envisaged several precautions. All participants were studied early in the morning to exclude possible confounding due to the circadian rhythm. To ensure that our findings were unaffected by possible transient unstable changes in dopaminergic neurotransmission, patients underwent experimental sessions after overnight withdrawal of dopaminergic medication. Previous studies showed that the MEP facilitation after PAS and repetitive magnetic stimulation is larger when subjects focus attention on the target muscle (attention-demanding condition) than when they look straight ahead (''relaxed'' condition) (Stefan et al. 2004; Conte et al. 2007). In these studies, attention levels were checked by delivering electrical shocks to the target hand and by asking the subjects to count the number of electrical shocks during the whole experimental procedure. Because patients with PSP may have mild cognitive deficits (as also shown by the FAB scale and mini-mental state examination), to avoid possible bias due to cognitive impairment across the subjects, we tested the patients and healthy subjects when they looked straight ahead (relaxed condition). Participants were therefore asked to look straight ahead at a PC screen placed in front of them, maintaining the target muscle relaxed with the aid of audiovisual feedback. Because RMT, AMT, and the intensity for eliciting a 1 mV MEP did not statistically differ between patients and healthy subjects, we confidently exclude the possibility that the abnormally large MEP facilitation and the reversed cTBS-induced after-effects in patients with PSP depended on differences in the intensity used for cTBS and iTBS stimulation. In the 7 patients who underwent cTBS and iTBS session, the 2 experimental interventions took place at least 1 month apart and in a randomized order to exclude carryover effects. Because we checked continuously that subjects remained relaxed during the neurophysiological sessions, we excluded the possibility that muscle contraction influenced the TBS-induced effects. Statistical analysis testing whether background EMG activity differentially influenced the iTBS responses in patients and in healthy subjects showed comparable background EMG activity during MEP assessments.
and during iTBS in both groups. Hence, differences in background EMG activity could not account for the larger MEP facilitation in patients. Concordantly, because Huang et al. (2008) reported that mild target muscle contraction sustained during the TBS intervention abolishes both iTBS- and cTBS-induced effects, we exclude the possibility that TBS-related findings in patients with PSP depended on insufficient muscle relaxation. Equally important, because the H reflex size is modulated by muscle contraction, the unchanged H reflex after iTBS further excludes changes related to an involuntary muscle contraction. Because Eggers et al. (2010) showed that in patients with Parkinson's disease, a disease in which rigidity is a key feature, cTBS left M1 excitability unchanged, we also exclude rigidity as responsible for our patients' abnormal MEP facilitation after cTBS and their enhanced response to iTBS. Similarly to previous observations that rigidity and insufficient muscle relaxation in patients with Parkinson's disease cannot explain the reduced SICI (Ridding et al. 1995; Kühn et al. 2004), we therefore believe it unlikely that in our patients with PSP, rigidity or insufficient muscle relaxation or both played a prominent role in the altered plasticity. Finally, because values for the MEP facilitation after iTBS and MEP inhibition after cTBS we found in healthy subjects match those previously reported for aged healthy subjects (Di Lazzaro et al. 2008; Suppa et al. 2011) and the iTBS-induced enhanced MEP facilitation in M1 in patients persisted almost unchanged at 1-year follow-up, baseline measurements presumably yielded reliable and reproducible MEPs.

In healthy subjects, experimental evidence suggests that TBS-induced changes originate at cortical level in M1 (Huang et al. 2005; Di Lazzaro et al. 2008). Although the PAS-technique modulates the H reflex in healthy subjects (Lamy et al. 2010), TBS, a technique that only lower subthreshold intensities (80% of the AMT) without eliciting descending activity in the cortico-spinal tract (Huang et al. 2005), makes it unlikely that changes in spinal cord excitability have a role in increasing the iTBS-induced MEP facilitation. Even though the motor neuron pools tested by the H reflex may differ from those mediating the MEP (Kiers et al. 1993; Morita et al. 1999; Nielsen et al. 1999), our findings that the H reflex size remained unchanged after iTBS, whereas MEP amplitude increased argue against a prominent role of changes in spinal excitability in determining the enhanced MEP facilitation in patients with PSP.

All confounding factors excluded, the enhanced MEP facilitation we found after iTBS and the reversed cTBS-induced effect in patients with PSP suggest that TBS-induced cortical plasticity mechanisms are altered in PSP. Studies using the PAS (Morgante et al. 2006; Ueki et al. 2006) and TBS (Eggers et al. 2010) techniques in patients with Parkinson's disease reported a lack of PAS-induced and cTBS-induced plasticity. Given that iTBS and cTBS both increased M1 excitability, the increase in patients with PSP cannot depend on the dopaminergic neuronal loss typically present in Parkinson's disease and PSP.

A possible alternative pathophysiological explanation is that the enhanced cortical plasticity (increased MEP facilitation) we found in the patients with PSP studied here may reflect glutamatergic excitatory interneuronal hyperactivity. Excessive glutamate release is a key feature in the excito-toxicity model in cultured cortical neurons, as reported in several neurodegenerative diseases (Sasaki et al. 2009; Fan et al. 2010; Nutini et al. 2011). Studies investigating glutamatergic neurotransmission in healthy humans show that ketamine—a noncompetitive NMDA receptor antagonist—able to reduce NMDA thus favoring non-NMDA transmission, decreases RMT, AMT, and increases ICF, suggesting that these TMS variables are dependent on non-NMDA transmission (Di Lazzaro et al. 2003). Because iTBS-induced after effects depend on NMDA transmission (Huang et al. 2007), the normal RMT, AMT, and ICF together with a steeper I/O curve and increased LTP-like plasticity we report in patients with PSP could therefore rely on imbalanced glutamatergic activity favoring NMDA activity. These observations notwithstanding imbalanced glutamatergic activity responsible for deregulating LTP-like plasticity does not fully explain why we found markedly impaired SICI in patients with PSP. In their study investigating glutamatergic neurotransmission with ketamine in healthy subjects, Di Lazzaro et al. (2003) found slightly altered SICI. Keeping in mind that TMS studies in humans have an intrinsic limitation, insofar as they provide only indirect evidence about cellular physiology, the unexpectedly enhanced iTBS-induced MEP facilitation and markedly impaired SICI we describe in patients with PSP nevertheless support the hypothesis that unbalanced cortical activity in M1 exists in PSP and possibly involves other neurotransmitter systems besides the glutamatergic system.

Consistent with our patients' altered SICI, our finding that iTBS produced a stronger effect in patients than in healthy subjects suggests that the altered TBS-induced plasticity depends at least partly on inhibitory interneuron loss in M1. Evidence from animal studies using a GABA-receptor blockade—induced with bicuculline—suggests that GABAergic inhibitory circuits have an important modulating effect on LTP at cortical synapses (Hess et al. 1996; Grover and Yan 1999; Casasola et al. 2004; Matsuyama et al. 2008). The enhanced MEP facilitation after iTBS together with the reduced SICI in patients with PSP might possibly depend on altered inhibitory interneuronal activity in M1. Several TMS studies showed that SICI is increased by pharmacological enhancement of GABA? neurotransmission (Kujirai et al. 1993; Ziemann et al. 1996; Ilc et al. 2002; Di Lazzaro et al. 2006) and the interneurons mediating SICI are thought to synapse onto corticospinal neurons closer to the axon initial segment (Alle et al. 2009). Conversely, the increased response to iTBS intervention in PSP could reflect an impairment of the GABAergic interneuronal population responsible for electrotonically attenuating synaptic events (Xiang et al. 2002). Even though no studies have investigated GABAergic subpopulations in PSP, the altered SICI in PSP might therefore reflect the loss of specific GABAergic inhibitory interneuronal populations (Kawaguchi et al. 1995; Kawaguchi and Kubota 1997; Gupta et al. 2000; Markram et al. 2004). The lack of correlation we found between abnormal SICI activity and the enhanced MEP facilitation after iTBS could support the hypothesis that the altered inhibitory interneuron activity in M1 and the higher propensity to undergo changes in synaptic plasticity coexist but are not necessarily causally related to each other. Although in this study we were unable to investigate whether SICF contributes to SICI abnormalities (Peurala et al. 2008) and whether TBS induces after effects on SICI, addressing these issues would give further insight into cortical pathophysiological mechanisms in PSP.

Some information on the pathophysiological mechanisms underlying the enhanced iTBS-induced MEP facilitation in PSP come from MEP I/O curve measurements. As expected (Kühn et al. 2004), patients with PSP had significantly steeper I/O curves at baseline than healthy subjects. Because no significant
parallels disease progression. The enhanced LTP-like cortical synaptic plasticity and LTD-like cortical synaptic plasticity is altered in patients with PSP. The lack of correlation between TBS-induced after effects and clinical features of PSP patients at baseline can be explained by considering that TBS explores M1 cortical plasticity alone, whereas the PSPRS clinical scale evaluates multiple functions of the nervous system.

Collectively, the altered SICI, steeper I/O curve, enhanced MEP facilitation after iTBS and MEP facilitation after LTD-like plasticity inducing protocol suggest that the inhibitory interneuronal activity fails to limit the enhanced M1 output gain in patients with PSP, thus increasing their susceptibility to changes in cortical synaptic efficacy. Consistent with our hypothesis that SICI and TBS abnormalities depend on inhibitory interneuron loss in M1, in a postmortem study, Halliday et al. (2005) reported that in the primary motor cortex from patients with PSP, neuronal loss was confined to inhibitory interneurons. The hypothesis that TBS abnormalities depend on the loss of cortical inhibitory interneurons leaves open the possibility that in PSP changes in M1 depend also on decreased pallidothalamic inhibition (Hardman and Halliday 1999).

The lack of correlation between TBS-induced after effects and clinical features of PSP patients at baseline can be explained by considering that TBS explores M1 cortical plasticity alone, whereas the PSPRS clinical scale evaluates multiple functions including eye movement abnormalities, postural alterations, and other motor symptoms. Nevertheless, the significant correlation we found with the changes in clinical severity scores and the more pronounced changes in iTBS variables at 1-year follow-up suggest that TBS-induced changes in plasticity parallel disease progression and might therefore provide a surrogate marker of disease progression. In conclusion, LTP-like cortical synaptic plasticity is altered in patients with PSP. The enhanced LTP-like cortical synaptic plasticity parallels disease progression.

Notes
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References

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