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Impaired long-term potentiation-like motor cortical plasticity in progressive supranuclear palsy

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HIGHLIGHTS

- Study of motor cortical plasticity in patients with progressive supranuclear palsy (PSP) compared to healthy controls.
- This is the first report that the motor cortical plasticity is impaired in patients with PSP.
- The degree of motor cortical plasticity inversely correlated with the degree of bradykinesia.

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ABSTRACT

Objective: To elucidate long-term potentiation (LTP)-like effects on the primary motor cortical (M1) in progressive supranuclear palsy (PSP) and its relationships with clinical features.
Methods: Participants were 18 probable/possible PSP Richardson syndrome (PSP-RS) patients and 17 healthy controls (HC). We used quadripulse stimulation (QPS) over the M1 with an interstimulus interval of 5 ms (QPS-5) to induce LTP-like effect and analyzed the correlations between the degree of LTP-like effect and clinical features. We also evaluated cortical excitability using short interval intracortical inhibition (SICI), intracortical facilitation (ICF) and short interval intracortical facilitation (SICF) in 15 PSP patients and 17 HC.
Results: LTP-like effect after QPS in PSP was smaller than HC and negatively correlated with Unified Parkinson's Disease Rating Scale Part III (UPDRS-III) score, especially bradykinesia, but not with either age or any scores of cognitive functions. The SICI was abnormally reduced in PSP, but neither ICF nor SICF differed from those of normal subjects. None of these cortical excitability parameters correlated with any clinical features.
Conclusions: LTP induction was impaired in PSP. The degree of LTP could reflect the severity of bradykinesia. The bradykinesia may partly relate with the motor cortical dysfunction.
Significance: The degree of motor cortical LTP could relate with the severity of motor symptoms in PSP.

1. Introduction

Progressive supranuclear palsy (PSP) is a neurodegenerative disorder characterized by intracellular 4 repeat tau aggregation in broad brain regions that presents atypical parkinsonism and/or cognitive impairments. Pathological studies (Halliday et al., 2005) have demonstrated neuronal loss in the primary motor cortex (M1). However, the presence of motor cortical dysfunction and its relation with the motor symptoms remain unclear in PSP.

A few studies have demonstrated M1 functional abnormalities in PSP. Paired-pulse transcranial magnetic stimulation (TMS) has revealed reduced short-interval intracortical inhibition (SICI) (Kühn et al., 2004; Kujirai et al., 1993), which suggests dysfunction of gamma-aminobutyric (GABA) interneurons within the M1 (Hanajima et al., 1998; Ziemann et al., 1996). A cerebellar inhibition (CBI) experiment using paired-pulse TMS revealed abnormal cerebello-motor cortical connection in PSP (Shirota et al., 2010).

Abbreviations: PSP-RS, Progressive supranuclear palsy with Richardson's syndrome; MEP, Motor evoked potential; UPDRS-III, Unified Parkinson's Disease Rating Scale Part III; PSPRS-J, Japanese version of the PSP Rating Scale; MMSE, Mini-Mental State Examination; FAB, Frontal Assessment Battery.

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Abnormal cortical plasticity is a recent topic in neurophysiological research of neurological disorders. In Parkinson's disease (PD), long-term potentiation (LTP)-like effects were reduced. L-DOPA intakes could restore the reduced LTP-like effects after paired associative stimulation (PAS) (Morgante et al., 2006; Ueki et al., 2006) or QPS (Moriyasu et al., 2022) but did not restore that induced by intermitted theta burst stimulation (iTBS) (Suppa et al., 2011) . By contrast, two papers reported that LTP after theta-burst stimulation (TBS) was abnormally enhanced in patients with PSP in association with reduced SICI (Bologna et al., 2017a; Conte et al., 2012). Here, we aimed to investigate the motor cortical physiological changes in PSP by studying the LTP induction, intracortical inhibitory and facilitatory functions of M1. To induce LTP-like effects on M1, we used a stable non-invasive brain stimulation technique, quadripulse stimulation (QPS), which showed smaller inter-individual variability than TBS (Hanajima et al., 2017; Nakamura et al., 2016; Tiksnadi et al., 2020). We also analyzed the relation between the physiological parameters and clinical symptoms.

2. Methods

2.1. Participants

We enrolled 18 patients with probable/possible PSP Richardson syndrome (PSP-RS) (eight females; age, 76.9 ± 1.7 years; disease duration, 3.4 ± 0.4 years) based on the movement disorder society (MDS-PSP) criteria (Höglinger et al., 2017), and 17 healthy controls (HC) (10 females; age 73.7 ± 1.4 years). The disease subtype was classified based on the MDS-PSP criteria (Höglinger et al., 2017) and multiple allocation extinction rules (Grimm et al., 2019). We excluded patients with alcoholism, illegal drug abuse, seizure episodes, and other neurological/psychiatric disorders. Table 1 summarizes their clinical and demographic features. Among the 18 patients, 11 were treated with L-DOPA (Pt.1, 5, 6, 8, 9, 11, 12, 13, 15, 16 and 18), while the other patients were naive to L-DOPA. In the 11 previously treated patients, L-DOPA was stopped for > 18 hours before this study. Clinical evaluations were performed using the Movement Disorders Society Unified Parkinson's Disease Rating Scale (MDS-UPDRS) Part III; Japanese version of the PSP Rating Scale (PSPRS-J); and cognitive batteries, including Mini-Mental State Examination (MMSE) and Frontal Assessment Battery (FAB). In the evaluation of subscores of the MDS-UPDRS, the scores on the side of the recorded FDI were used. Used were "limb rigidity on the recorded side" (scores 3.3b to 3.3d or 3.3c to 3.3e), "limb bradykinesia on the recorded side" (scores 3.4a to 3.8a or 3.4b to 3.8b; total scores for finger tapping, hand movement, pronation/-supination and foot /toe tapping on the recorded side), "limb tremor on the recorded side" (scores 3.15a to 3.17c or 3.15b to 3.17d; total score for resting and postural tremor of the limb on the recorded side).

No participants had contraindications to TMS (Rossi et al., 2009, 2021). All of them provided written informed consent for study participation. The study protocol was approved by the Medical Ethics Committee of the Tottori University (No.17B033). We used the right-hand muscle for evaluation because the motor symptoms were symmetrical except one patient in whom we used the left hand because she had difficulty in relaxing the right hand during the experiment.

2.2. Motor-evoked potential recording

The participants sat in a comfortable chair. Motor evoked potentials (MEPs) were recorded from the right first dorsal interosseous (FDI) muscle using a belly-tendon montage in all the participants except one patient in whom we used the left FDI because she was not able to keep the right FDI relaxed during the experiment. Responses were sent to an amplifier (BA-1008, Miyuki Giken Co. Ltd., Japan) through a 3-kHz low-pass filter with a time constant of 0.01 s, and the signals were digitized at 10 kHz and stored on a computer for subsequent offline analyses (MultiStim tracer; Medical Try System, Japan). Finally, peak-to-peak MEP amplitudes were measured.

2.3. Transcranial magnetic stimulation (TMS)

TMS was administered over the hand area of the M1, contralateral to the target FDI, using a figure-of-eight coil (each wing with a 70-mm external diameter; The Magstim Co. Ltd, Whitland, Dyfed, UK) connected to a magnetic stimulator (Magstim 200; The Magstim Company Ltd.). The coil was tangentially placed over the scalp at an angle of approximately 45° from the midsagittal line to induce a current in the latero-posterior to medio-anterior direction in the brain. The hotspot for the hand muscle was determined as the point with the largest MEP response elicited. The hotspot was marked with a marker to reposition the coil at the same site throughout the experiments. The resting motor threshold (RMT) was defined as the lowest stimulator output eliciting ≥50 μV MEPs in half of the trials in the relaxed FDI. We defined the active motor threshold (AMT) as the lowest stimulator output sufficient for eliciting ≥200 μV MEPs in half of the trials under slight voluntary FDI contraction (Rossi et al., 2021). Each stimulus intensity was shown as percent of the maximum stimulator output (%MSO).

2.4. Quadripulse stimulation

LTP-like effect on the M1 was induced by QPS, which comprised bursts of four monophasic subthreshold TMS pulses (90% of the AMT) repeated at 5-s intervals for 30 min (360 bursts) (Hamada et al., 2008). QPS was delivered over the M1 through a hand-held figure-of-eight coil using four monophasic stimulators (Magstim 200 square; The Magstim Co, Ltd) connected with a specially designed combining module (The Magstim Co, Ltd). We employed an inter-stimulus interval of 5 ms (QPS-5), which is the optimal interval for inducing LTP in the human M1 (Hamada et al., 2008) (Fig. 1A).

Fig. 1B shows the timeline of our experiment. Clinical features and the baseline motor thresholds (RMT/AMT) were initially assessed for each patient. We recorded 20 MEPs elicited by single-pulse TMS to obtain the baseline MEP amplitude before QPS-5. The intensity was set to elicit around 0.5-mV MEPs in the relaxed FDI. After QPS-5, we obtained 20 MEPs at 5-min intervals for 30 min (5, 10, 15, 20, 25, 30 min) using the same intensity as that before QPS-5. At each time point, we applied 20 single single-pulse TMSs at random intervals of 5 to 7sec. This procedure is the same as the original report of QPS by Hamada et al (2008).

2.5. Cortical excitability (intracortical inhibition/facilitation) studied with paired-pulse TMS

We evaluated SICI, intracortical facilitation (ICF) and short interval intracortical facilitation (SICF) in 15 PSP-RS patients and all HC, using the paired-pulse TMS techniques before QPS. We did not measure the cortical excitability parameters in several patients who were not able to endure a long examination. The paired-pulse TMS techniques used two magnetic stimulators (Magstim 200 Square) connecting with a Bistim module (Kujirai et al., 1993; Ziemann et al., 1998). For studying SICI and ICF, the intensity of conditioning stimulus was set at 90% AMT and that of the test stimulus was set to elicit 0.5 mV MEPs in the relaxed FDI. The inter-stimulus intervals (ISIs) were 3 ms and 4 ms for SICI as well as 10 ms for ICF. To study SICF, the first stimulus (S1) was

Table 1
Clinical characteristics of 18 patients with PSP-RS.

Subject	Age (years)	Gender	Disease duration (years)	RMT	AMT	Baseline MEP intensity	MMSE	FAB	LEDD	Part III	PSPRS-J
1	70	M	1	34	26	35	14	8	600	43	31
2	77	F	2	42	29	57	16	6	0	85	55
3	72	M	2	29	25	34	28	15	0	22	19
4	62	M	2	47	32	63	24	15	0	31	29
5	81	F	2	38	27	43	21	13	200	44	24
6	90	F	2	45	31	46	17	12	400	67	52
7	69	M	2	47	36	55	19	10	0	40	27
8	87	F	2	50	43	57	13	7	200	41	23
9	74	M	3	39	33	49	24	10	550	61	32
10	73	F	3	46	36	53	17	10	0	30	39
11	80	M	4	34	26	44	26	13	300	27	29
12	84	F	4	25	21	31	24	7	150	70	41
13	86	M	4	48	36	59	29	8	400	60	38
14	73	M	5	33	28	73	20	8	0	25	27
15	81	F	5	68	45	95	24	9	300	36	28
16	74	M	5	42	35	51	29	11	300	32	23
17	81	F	6	62	44	61	19	6	0	67	51
18	71	M	7	37	27	45	NA	NA	500	76	73
Mean	76.9		3.4	42.6	32.2	52.8	21.4	9.9	216.7	47.6	35.6
± SE	1.7		0.4	2.5	1.6	3.6	1.2	0.7	49.8	4.6	3.3

PSP-RS, progressive supranuclear palsy Richardson's syndrome; F, female; M, male; RMT, the resting motor threshold; AMT, the active motor threshold; MEP, Motor evoked potential; MMSE, Mini-Mental State Examination; FAB, Frontal Assessment Battery; LEDD, levodopa equivalent daily dose; Part III, MDS-Unified Parkinson's Disease Rating Scale Part III; PSPRS-J, Japanese version of the PSP Rating Scale.
Data are shown as means ± standard error (SE).

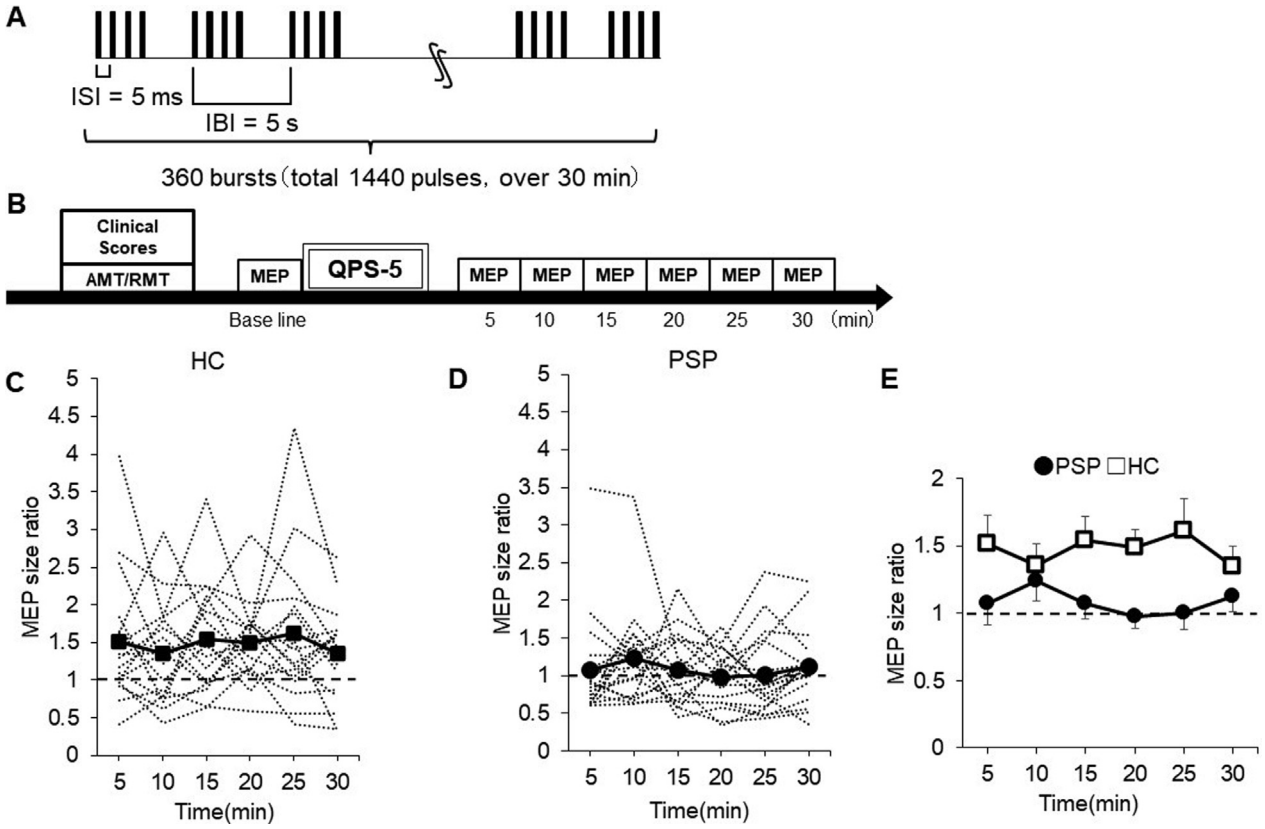

Fig. 1. A. The protocol for quadripulse stimulation (QPS). QPS composes bursts of four monophasic subthreshold transcranial magnetic stimulation (TMS) pulses [90% of the active motor threshold (AMT)] administered once 5 seconds [inter-burst interval (IBI) of 5 s] for 30 min (total 360 bursts, 1440 pulses). Inter-stimulus intervals (ISI) of the four TMS pulses are set at 5 ms to induce LTP-like effects (QPS-5). **B**. The timeline of the experiment. Before QPS-5, we evaluated the clinical scores, measured the active/resting motor threshold (AMT/RMT), and recorded 20 motor evoked potentials (MEPs) at baseline. Short interval intracortical inhibition and intracortical facilitation (SICI/ICF) and short-interval intracortical facilitation (SICF) were also studied. After QPS-5, 20 MEPs were obtained at 5, 10, 15, 20, 25, and 30 min. **C. D.** Time courses of the mean MEP size ratios of healthy controls (HC) (C) and progressive supranuclear palsy Richardson's syndrome (PSP-RS) patients (D). The abscissa represents the time points after QPS while the ordinate indicates the ratio of a MEP amplitude at each time to the baseline amplitude. The dotted lines show individual time courses, and the bold lines show the average time courses. The squares represent HC, and dots PSP-RS patients. E. The mean time courses of HC (squares) and PSP patienst (dots) for comparison.

set at the same intensity as the test stimulus of SICI/ICF and the second stimulus (S2) at the same as the conditioning stimulation for SICI/ICF. The S1 preceded the S2 at ISIs of 1.2 ms and 1.5 ms. The test trials (one stimulus given alone or S1 alone for SICF) and conditioned trials (both stimuli administered) were randomly intermixed using software (Pulse Timer II; Medical Try System, Tokyo, Japan). Ten trials were performed for each condition in one session. The participants were asked to relax the tested hand. Trials contaminated with voluntary contraction were excluded from the subsequent offline analyses.

2.6. Statistical analyses

We used unpaired t-test to compare the age, AMT/RMT and baseline MEP size between PSP-RS patients and HC, and Pearson's chi-squared test in comparison of the gender distribution.

The MEP size ratio was defined as the mean MEP amplitude at each time point divided by the mean MEP amplitude at the baseline. To analyze the effect of QPS-5 on the MEP size, we used a two-way repeated measures analysis of variance (ANOVA) for the within-subject factors "GROUP" (two levels: "PSP-RS" and "HC") and "TIME" (six points: 5, 10, 15, 20, 25, and 30 minutes). For conditions with significant F values, we evaluated group differences using the post hoc Tukey's test.

Regarding SICI, we used a two-factors ANOVA for the within-subject factors "GROUP" (two levels: "PSP-RS" and "HC") and "TIME" (two points: 3 ms and 4 ms). For analysis of ICF, we used paired t-test. To assess SICF, we used a two-factors ANOVA for the within-subject factors "GROUP" (two levels: "PSP-RS" and "HC") and "TIME" (two points:1.2 ms and 1.5 ms).

We performed Spearman's Rank correlation coefficient analysis to study the correlations between the physiological measures [degree of LTP-like effect (i.e., the grand average of MEP size ratio), SICI, ICF, and SICF] and clinical scores (MDS-UPDRS Part III, PSPRS-J, MMSE, and FAB). As a representative value of the LTP-like effect induced by QPS-5, we calculated the grand average of the MEP size ratio from 5 min to 30 min. We also used an average size ratio at 3 ms and 4 ms as a representative value of SICI and an average size ratio at 1.2 ms and 1.5 ms as a representative value of SICF. For sub-score analyses of MDS-UPDRS Part III, we used each symptom score on the recorded side.

Statistical analyses were performed using SPSS Statistics (version 25.0; IBM, New York, NY, USA). Statistical significance was set at $P < 0.05$. Unless stated otherwise, data are shown as means ± standard error.

3. Results

All participants completed the study protocol without any adverse events. Clinical characteristics are shown in Table 1; no significant differences in either age ($p = 0.153$) or gender distribution ($p = 0.395$) between the patients and HC.

At the baseline, neither RMT ($p = 0.388$), AMT ($p = 0.509$) nor TMS intensity ($p = 0.653$) used for MEP follow up were different between PSP-RS and HC. The baseline MEP size was bigger in PSP-RS (0.79 ± 0.34 mV) than in HC (0.52 ± 0.16 mV) ($p < 0.01$) probably because MEP size was variable in some PSP-RS.

3.1. QPS-induced plasticity

Fig. 1C, D, E show time courses of the mean MEP size ratios of HC (squares) and PSP-RS group (dots) after QPS-5. Dotted lines show times course of the mean MEP size ratios of all individuals.

In the two-way repeated measures ANOVA, there was significant effect of "GROUP" ($F_{1,197} = 19.481$, $p < 0.01$) and no effect of "TIME after QPS" ($F_{5,197} = 0.106$, $p = 0.991$) on MEP ratio after QPS-5. There was no interaction "TIME × GROUP" ($F_{5,197} = 0.723$, $p = 0.607$).

3.2. Intrinsic cortical excitability: SICI, ICF and SICF

For SICI, the two-factors ANOVA showed a significant effect of "GROUP" ($F_{1,60} = 4.037$, $p = 0.049$), but no effect of "ISI" ($F_{1,60} = 0.091$, $p = 0.765$), and there was no interaction "ISI × GROUP" ($F_{1,60} = 0.278$, $p = 0.600$). (Fig. 2A). ICF was not different between the two groups ($p = 0.642$) (Fig. 2B). On the degree of SICF, the two-factors ANOVA showed no significant effect of "ISI" ($F_{1,60} = 0.041$, $p = 0.840$), "GROUP" ($F_{1,60} = 0.584$, $p = 0.448$) and no interaction between the two-factors"ISI × GROUP" ($F_{1,60} = 0.090$, $p = 0.766$) (Fig. 2C).

3.3. Correlations between MEP size ratio and clinical scores or between MEP size ratio and SICF/ICF

The grand average of MEP size ratio negatively correlated with the scores of the MDS-UPDRS Part III ($r = -0.627$, $p < 0.01$) (Fig. 3A). Sub-score analyses revealed that the MEP size ratio negatively correlated with bradykinesia on the recorded side ($r = -0.637$, $p < 0.01$) (Fig. 3B), while it correlated with neither rigidity on the recorded side ($r = -0.397$, $p = 0.103$) (Fig. 3C) nor tremor on the recorded side ($r = -0.131$, $p = 0.604$) (Fig. 3D). There was no correlation between the grand average MEP size ratio and either age ($r = -0.222$, $p = 0.377$), the PSPRS-J ($r = -0.453$, $p = 0.059$), MMSE ($r = 0.294$, $p = 0.252$), or FAB ($r = 0.283$, $p = 0.272$) (Fig. 3E ∼ H).

There was no correlation between the degree of LTP by QPS-5 and either the degree of SICI ($r = -0.196$, $p = 0.483$) (Fig. 4A), ICF ($r = -0.296$, $p = 0.283$) (Fig. 4B), or the degree of SICF ($r = 0.454$, $p = 0.089$) (Fig. 4C). Neither the degree of SICI, ICF nor SICF had a significant correlation with any clinical symptoms or scores.

4. Discussion

This is the first study to show both the motor cortical LTP reduction and a negative correlation between the degree of LTP and the severity of bradykinesia in PSP. SICI, which must reflect function of GABA-$_A$ inhibitory neurons in M1, was reduced in PSP similarly to the previous report (Bologna et al., 2017a) but had no correlation with clinical symptom scores.

4.1. Reduced LTP-like plasticity in PSP

Two papers (Bologna et al., 2017a; Conte et al., 2012) repored abnormal enhancement of intermittent TBS (iTBS) induced LTP like effect in patients with PSP-RS, and one of them (Conte et al., 2012) also reported a paradoxical LTP like effect induction by continuous TBS (cTBS). The inconsistency in the LTP induction between the previous papers and ours could be attributed to the different LTP induction mechanisms between QPS and TBS. QPS-induced LTP can solely reflect the homotopic plasticity by monophasic pluses at the glutamatergic synapses (Hamada et al., 2008) which must be reduced in PSP. In contrast, MEP changes induced by TBS should reflect a combination of the homotopic plasticity of the M1 (Huang et al., 2005) and the complex balance between cortical facilitation and inhibition (Huang et al., 2011). Combination of LTP reduction and M1 hyperexcitability due to SICI reduction should cause LTP exaggeration by iTBS. A paradoxical LTP like effects by cTBS may be explained by combination of the cTBS induced synaptic plasticity (LTD at glutamatergic synapses) and the TBS induced motor cortical intrinsic hyperexcitability.

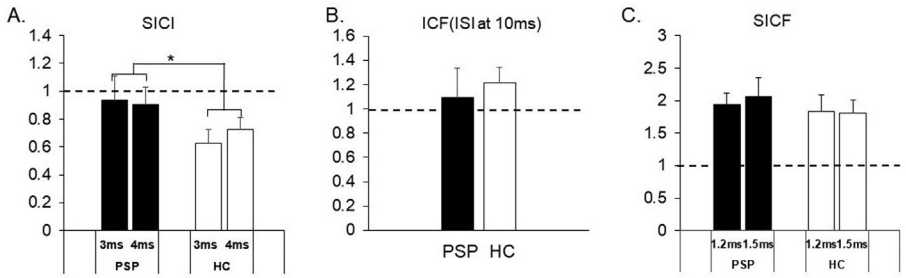

Fig. 2. Intrinsic cortical excitability: SICI, ICF and SICF in PSP-RS and HC. PSP-RS (black bars) and HC (white bars): For SICI, a two-factors analysis of variance (ANOVA) showed significant effect of the groups (PSP-RS and HC) (A). There were no differences in ICF (B) or SICF (C) between the two groups. Short interval intracortical inhibition (SICI); intracortical facilitation (ICF); short interval intracortical facilitation (SICF); progressive supranuclear palsy Richardson's syndrome (PSP-RS); healthy controls (HC).

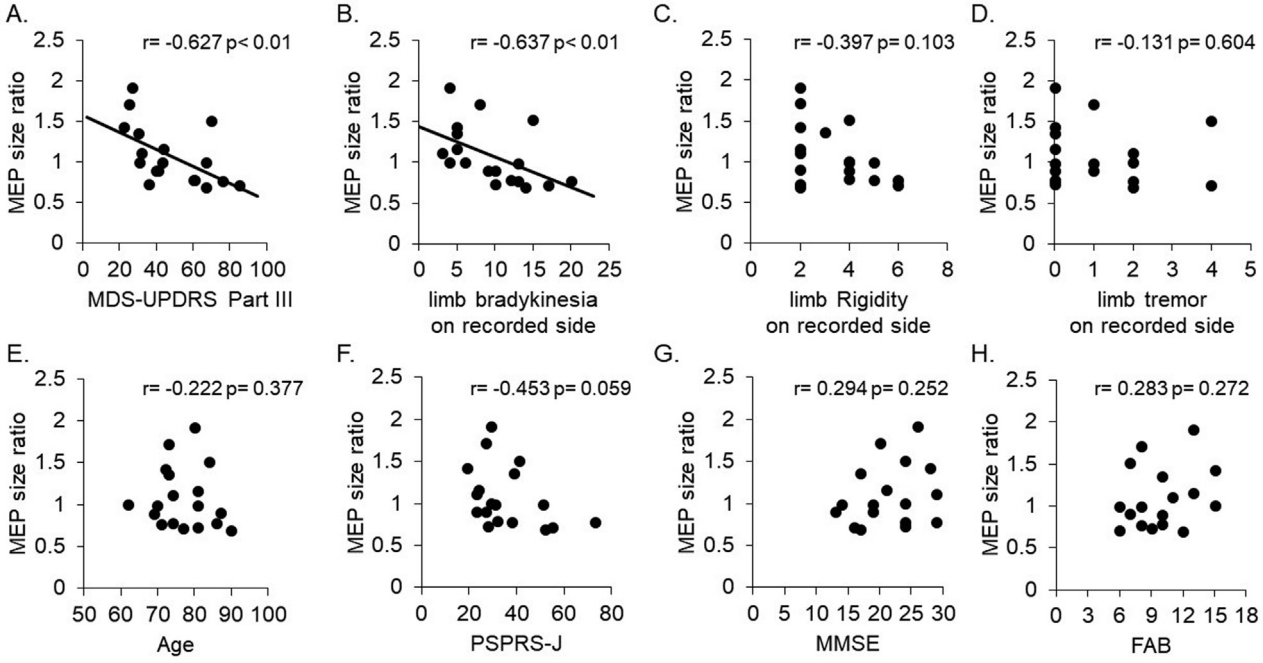

Fig. 3. Correlation between clinical features and MEP size ratio after QPS-5 in PSP. Black dot (●) shows each participant. The abscissa in each diagram indicates the Movement Disorders Society Unified Parkinson's Disease Rating Scale (MDS-UPDRS) Part III (A), limb bradykinesia on the recorded side (B), limb rigidity on the recorded side (C), limb tremor on the recorded side (D), age (E), scores of the Japanese version of the PSP Rating Scale (PSPRS-J) (F), mini-Mental State Examination (MMSE) (G), and frontal Assessment Battery (FAB) (H). The ordinate indicates the grand average MEP size ratio. The MEP size ratio negatively correlated with the scores of the MDS-UPDRS Part III, limb bradykinesia on the recorded side. Motor evoked potential (MEP); progressive supranuclear palsy (PSP); quadripulse stimulation (QPS) over the M1 with an interstimulus interval of 5 ms (QPS-5).

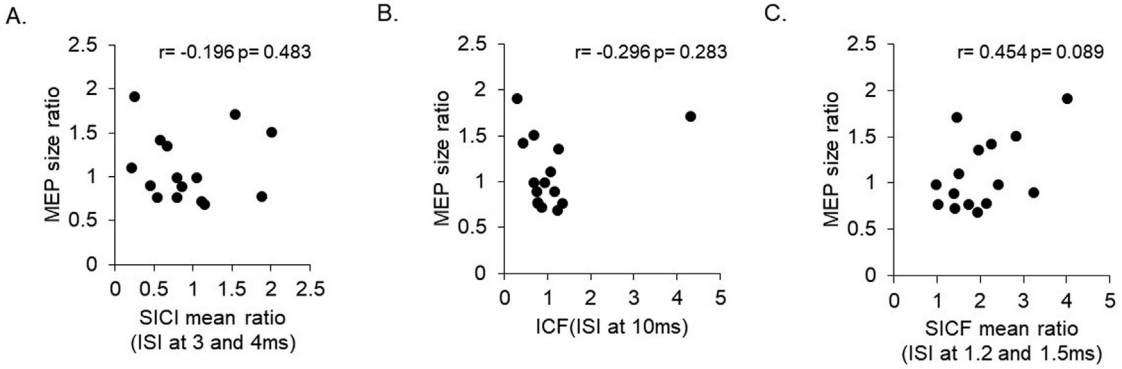

Fig. 4. Correlations between the amount of SICI/ICF, SICF and MEP size ratio after QPS-5 in PSP**.** There was no correlation between the degree of long-term potentiation (LTP) by QPS-5 and the degree of SICI (A) or ICF (B). There was no correlation between the degree of LTP by QPS-5 and the degree of SICF (C). Short interval intracortical inhibition (SICI); intracortical facilitation (ICF); short interval intracortical facilitation (SICF); motor evoked potential (MEP); progressive supranuclear palsy (PSP); quadripulse stimulation (QPS) over the M1 with an interstimulus interval of 5 ms (QPS-5).

The reduced LTP-like effect after QPS was also observed in PD (Moriyasu et al., 2022). Most of previous papers using PAS (Bagnato et al., 2006; Kojovic et al., 2012; Morgante et al., 2006) or TBS (Eggers et al., 2010; Kishore et al., 2012; Suppa et al., 2011) reported impaired LTP induction in PD. Only one paper reported normal LTP like effect induced by TBS in PD (Zamir et al., 2012). Based on the above whole arguments, we conclude that the LTP should be involved in PD and PSP.

4.2. What mechanisms for the LTP reduction?

We consider that the reduced motor cortical LTP may reflect cortical neuronal degenerations at M1 or direct involvement of M1 in PSP-RS. Neuronal loss or Tau-positive neurofibrillary degenerations were observed in the motor cortices in PSP (Halliday et al., 2005). Similar pathophysiological speculation is also applied to Alzheimer disease. The LTP reduction seen in Alzheimer disease (AD) (Bologna et al., 2020; Di Lorenzo et al., 2016) was also explained by the cortical pathology (Battaglia et al., 2007; Koch et al., 2012; Di Lorenzo et al., 2020). The dysfunctions of the basal ganglia-thalamo-cortical loops or reduction of cortical dopamine directly projected from the ventral tegmental area may also explain the LTP reduction in PD. These mechanisms could also contribute to the LTP reduction in PSP-RS.

4.3. Relationship between QPS-induced LTP-like effect and clinical features

The conspicuous finding of this study was that LTP-like effect induced by QPS-5 negatively correlated with the total scores of the MDS-UPDRS Part III (motor symptoms), especially with the score of bradykinesia on the recorded side. Similar negative correlation between the degree of LTP-like effects after QPS-5 and motor symptoms was shown in PD patients (Bologna et al., 2018; Moriyasu et al., 2022). On the other hand, the degree of LTP-like effects after QPS-5 correlated with neither rigidity nor tremor on the recorded side in the present investigation. No correlation with rigidity, inconsistent with the QPS induced LTP-like effects in PD (Moriyasu et al., 2022), may be explained by the fact that the rigidity involves dominantly the axial muscles symmetrically in PSP, but it involves limb muscles considerably unilaterally in PD. The present results suggest that abnormal M1 cortical plasticity may contribute to the severity of bradykinesia in PSP-RS at least partly. However, the reduction of LTP induced by TBS did not correlate with bradykinesia in AD patients (Bologna et al., 2020). The pathological mechanism for the plasticity reduction may be different between movement disorders and cognitive disorders, and the degree of the plasticity may relate with motor symptoms only in movement disorders. This issue may be solved by studies of neuroplasticity in many kinds of neurological disorders. However, it is out of scope of the present study and may be one of future research projects.

In contrast, it did not correlate with the PSPRS-J scores. The PSPRS-J includes numerous clinical features in patients with PSP; however, the MDS-UPDRS Part III can evaluate only motor symptoms of parkinsonism. The motor cortical plasticity impairment may tightly relate with motor symptoms in PSP.

4.4. Intrinsic cortical excitability in PSP

Reduced SICI and normal ICF in the present study were consist with previous reports (Benussi et al., 2018; Bologna et al., 2017b; Conte et al., 2012; Kühn et al., 2004; Di Lazzaro et al., 2021). Neither any clinical scores nor the degree of LTP-like effects correlated with the degree of SICI. These suggest that GABAergic inhibitory interneurons of M1 are functionally disturbed in PSP irrespective of the severity of bradykinesia. Many previous papers reported reduced SICI in PD and other atypical parkinsonian syndromes (Bologna et al., 2017b; Di Lazzaro et al., 2021). However, its correlation with motor symptoms such as bradykinesia has not been detected (Bologna et al., 2018). Reduced SICI may be sensitive to Parkinsonian pathophysiolgy but the amount of SICI could not reflect the degree of the parkinsonian motor symptoms. One possibility is that SICI is involved and severely impaired at the early stage of disease and does not change in parallel with symptom progression because of the floor effect.

To our knowledge, this is the first investigation of SICF in PSP. We showed normal SICF in PSP. SICF may be produced by EPSP temporal summation at motor cortical output neurons (Ziemann, 2020; Ziemann et al., 1998). SICF has been known to be enlarged in Parkinson's disease with L-DOPA induced dyskinesias (Guerra et al., 2019) and normalized by Safinamide, a monoamine oxidase type-B inhibitor with anti-glutamatergic properties (Guerra et al., 2022). We cannot exclude the possibility that SICF could be also abnormally enlarged in PSP when using S2 with stronger intensity. Even though, we can say that SICF preserved in PSP. This indicates that response of motor cortical output neuron (glutamatergic neurons) to a single pulse TMS is preserved in PSP whereas the glutamatergic synaptic plasticity is involved (reduction of QPS-5 induced LTP) in the motor cortex.

Limitations.

This study has several limitations. First, because PSP is a rare neurological disease with faster progression comparing with PD, we studied only relatively small number of PSP patients. Second, we studied only early staged PSP patients because patients at late-stage do not cooperate with us during several long experiments. However, we showed some abnormal findings even in the early-stage patients. Third, we studied PSP-RS patients only and did not compare the results between the subtypes of PSP because we could not recruit many patients with the other rarer PSP subgroups enough for analyses. Studies of advanced stage patients and patients of different subtypes may be a future project. Fourth, SICI, ICF, and SICF could not be performed in all the patients, only in 15 of 18 PSP patients. In addition, we did not use many stimulus intensities to study cortical excitability measures in the present investigation. We need more precise examinations to decide those parameters changes in PSP in the future. We measured 10 MEPs for each condition in paired pulse TMS studies. More MEPs for one condition may be better considering the intertrial variability of MEPs. Fifth, average MEP size before QPS was bigger in PSP than HC probably because in some PSP-RS MEP size was variable and difficult to set exactly the same size. We can't exclude the possibility that the difference in the baseline MEP size must be one confounding factor to explain the LTP reduction in PSP in the present study. Finally, no pathologically confirmed PSP patients were included in the preset paper. Further studies are warranted to confirm our findings.

5. Conclusion

We revealed abnormal LTP reduction and negative correlation between LTP-like plasticity induced by QPS-5 and the degree of bradykinesia in patients with PSP. The degree of QPS-5 induced plasticity could be a physiological biomarker for severity of motor symptoms, such as bradykinesia, in PSP. To confirm this possibility, we need further investigation on this point in many patients with PSP.

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Declaration of interest

We have nothing to declare.

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