Title	Direct comparison of Efficacy of the Motor Cortical Plasticity Induction and the Interindividual Variability between TBS and QPS(本文)
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Citation	
Issue Date	2021-09-30
URL	http://ir.fmu.ac.jp/dspace/handle/123456789/1615
Rights	Fulltext: Originally published in "Brain Stimul. Nov-Dec 2020;13(6):1824-1833. doi: 10.1016/j.brs.2020.10.014. © 2020 The Authors. Published by Elsevier Inc."
DOI	
Text Version	ETD

学位論文

Direct comparison of efficacy of the motor cortical plasticity induction and the interindividual variability between TBS and QPS

（**TBS** と **QPS** との運動野可塑性誘導における有効性と個人の多様性に関する直接比較検討）

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Direct Comparison of Efficacy of the Motor Cortical Plasticity Induction and the Interindividual Variability between TBS and QPS

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Running head: Comparison between TBS and QPS

Number of Figures: 5, Number of Tables: 1

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Keywords: transcranial magnetic stimulation, quadripulse stimulation, theta burst stimulation, plasticity, interindividual variability

Highlights

- Direct, head-to-head comparison of the effects and variability between TBS and QPS.
- QPS induced stronger motor cortical plasticity than TBS.
- QPS showed less interindividual variability than TBS.

Abstract

Background: Theta burst stimulation (TBS) and quadripulse stimulation (QPS) are known to induce synaptic plasticity in humans. There have been no head-to-head comparisons of the efficacy and variability between TBS and QPS.

Objective: To compare the efficacy and interindividual variability between the original TBS and QPS protocols. We hypothesized that QPS would be more effective and less variable than TBS.

Methods: Forty-six healthy subjects participated in this study. Thirty subjects participated in the main comparison experiment, and the other sixteen subjects participated in the experiment to obtain natural variation in motor-evoked potentials. The facilitatory effects were compared between intermittent TBS (iTBS) and QPS5, and the inhibitory effects were compared between continuous TBS (cTBS) and QPS50. The motor-evoked potential amplitudes elicited by transcranial magnetic stimulation over the primary motor cortex were measured before the intervention and every 5 min after the intervention for one hour. To investigate the interindividual variability, the responder/nonresponder/opposite-responder rates were also analyzed.

Results: The facilitatory effects of QPS5 were greater than those of iTBS, and the inhibitory effects of QPS50 were much stronger than those of cTBS. The responder rate of QPS was significantly higher than that of TBS. QPS had a smaller number of opposite responders than TBS.

Conclusion: QPS is more effective and stable for synaptic plasticity induction than TBS.

Introduction

Transcranial magnetic stimulation (TMS) is a technique to noninvasively modulate human brain activity. When delivered in repetitive patterns (rTMS), the amplitude of motor-evoked potentials (MEPs) to TMS increases or decreases for several minutes to hours after the intervention, which is called “after-effects”. Because MEP amplitudes can reflect motor cortical excitability, rTMS has the potential to change cortical excitability even after intervention [1-4]. The phenomenon is believed to be produced by motor cortical plasticity, mainly reflecting synaptic plasticity, i.e. long-term potentiation (LTP)-like or long-term depression (LTD)-like effects. There is evidence that rTMS alters the efficacy of glutamate synaptic transmission within the primary motor cortex (M1) through N-methyl-D-aspartate receptor (NMDAR)-dependent LTP/LTD-like effects [5, 6]. Since these fascinating capabilities of rTMS were recognized, the utility of rTMS has enormously increased in basic research, behavioral and cognitive neuroscience, and clinical settings. Conventional rTMS is a rhythmic stimulation, e.g., 5 Hz rTMS for induction of LTP-like effects and 0.9 Hz rTMS for induction of LTD-like effects, and patterned rTMS is not a simple, rhythmic stimulation [7, 8]. The representative patterned rTMSs are theta burst stimulation (TBS) and quadripulse stimulation (QPS).

TBS, one of the popular patterned rTMSs, consists of bursts of 3 pulses at 50 Hz, repeated at 5 Hz (theta rhythm), for a total of 600 pulses. The TBS machine employs biphasic stimulus pulses. Two main protocols to induce bidirectional effects on cortical excitability are intermittent TBS (iTBS) and continuous TBS (cTBS). iTBS repeats 2 s trains of TBS (10 bursts, 30 pulses) and 8 s off, 20 times (600 pulses in total). iTBS induces a facilitatory effect, as shown by a transient MEP increment. The cTBS contains

a single uninterrupted train of TBS bursts for 40 s (600 pulses in total). cTBS induces an inhibitory effect, as shown by a transient MEP decrease. The stimulus intensity is set at 80% of the active motor threshold (AMT) [9, 10].

QPS is another patterned rTMS. QPS utilizes bursts of four monophasic TMS pulses separated by interstimulus intervals (ISI) of 5 ms (short ISI) or 50 ms (long ISI), and bursts are repeated every 5 s for 30 min (1440 pulses in total). Depending on the ISI, QPS also induces bidirectional cortical excitability changes: QPS with short ISIs such as QPS5 produces a long-lasting increase in MEP amplitudes, while QPS with long ISIs such as QPS50 induces a long-lasting MEP decrease for approximately one hour. The intensity of the intervention is set at 90% of the AMT [11, 12].

In addition to the efficacy, one major issue of noninvasive brain stimulation (NIBS) is high interindividual variability. Approximately 30 – 50% of participants failed to show expected after-effects [13-17]. Nakamura et al. reported that the effects of QPS are relatively consistent across subjects, indicating less interindividual variability [18]. Thus, we performed a comparison between TBS and QPS in the present paper to confirm the finding by Nakamura et al. [18].

Both the efficacy and variability are important factors in choosing NIBS protocols in neuroscience research, and even more in a therapeutic setting, but scientific evidence has been insufficient. To select a better protocol between TBS and QPS to induce plasticity in human brains, we conducted the present study. To our knowledge, there have been no direct comparisons of the efficacy and variability between TBS and QPS. From the previous literature on TBS and QPS [13, 16, 18, 19, 20], we hypothesized that QPS induces greater plasticity than TBS, and we performed a direct comparison of the

degree of the after-effects between TBS and QPS. We also compared the interindividual variability between TBS and QPS in the same individuals.

Subjects and Methods

Subjects

One paper reported that large sample sizes, at least 30 participants, are needed to reliably detect a difference in response amplitude of ~20% following TBS between two groups because of the large interindividual variability [21]. Thus, we studied 30 subjects in the main experiment. Forty-six normal subjects (21 – 40 years of age, mean age ± SD: 24.8 ± 5.4, 20 females) participated in the present study. Thirty participants were enrolled in the “real stimulation” experiment: “comparison of efficacy between TBS and QPS” and “comparison of the interindividual variability”. The other 16 participants were enrolled in the “sham stimulation” experiment to evaluate the natural variability of MEP amplitudes using the baseline variance method [18, 22]. All participants were right-handed (Edinburgh Handedness Inventory [23] mean score ± SD: 96.4 ± 7.9%), and none of them had any contraindications to TMS [8]. None took any medication on a regular basis or had any neurological or psychiatric diseases. All participants gave written informed consent to participate in this study. This study was approved by the Ethics Committee of Fukushima Medical University (Protocol No. 2744) and was carried out in accordance with the ethical standards of the Declaration of Helsinki.

MEP recording

Subjects were seated on a comfortable reclining chair. Electromyogram was recorded from the right first dorsal interosseous (FDI) muscle via surface electrodes attached on the belly of the muscle (negative electrode) and the metacarpophalangeal joint of the

index finger (positive electrode). The ground electrode was attached on the right wrist. Responses were amplified and bandpass filtered (10 Hz – 3 kHz, Multi Amplifier 1000, DIGITEX LAB Co. Ltd., Japan). Signals were digitized at 5 kHz, and data were stored in a computer for later offline analyses (MultiStim tracer; Medical Try System, Japan). Single-pulse TMS was applied to the left primary motor cortex (M1) of the hand motor area using a hand-held 70-mm diameter figure-of-eight coil connected to a monophasic Magstim 200^2 stimulator (The Magstim Co., Ltd., Whitland, Dyfed, UK). The coil was placed tangentially on the scalp at 45 degrees relative to the mid-sagittal line in which the electrical current was induced in the posterior-anterior (PA) direction perpendicular to the central sulcus. The hotspot was defined as the optimal site for eliciting the largest MEP. The spot was marked on the scalp with a waterproof pen alongside 2 additional orientation marks needed for exact repositioning of the coil throughout the experiments. The stimulus intensity was adjusted to elicit MEPs at approximately 1 mV in the relaxed condition. We recorded 15 MEPs at each time point. The intertrial interval was set at 4.5 – 5.5 s and jittered randomly for the MEP measurements. In all recording sessions, we monitored EMG activities from FDI to keep those at rest. When some activities were seen in the monitoring, we asked the subject to keep it at rest and discarded responses recorded in the active condition in the data analyses.

Theta burst stimulation (TBS)

TBS was applied over the left M1 hand motor area using Magstim Super Rapid^2 plus stimulator (Magstim Co., Ltd.), which produced biphasic pulses. Following the original method reported by Huang et al. (2005), a figure-of-eight coil (internal wing diameter of

70 mm) was placed tangentially on the scalp, 45 degrees lateralized to the midsagittal line, to induce the current in the PA-AP direction, perpendicular to the central sulcus. We applied the original protocol of TBS, which consisted of a burst of three pulses at 50 Hz, repeated at 200 ms intervals [9]. We employed iTBS (2 s trains of TBS and 8 s off, repeated every 10 s for a total of 600 pulses) for LTP-like effect induction and cTBS (40 s train of TBS without interruption for a total of 600 pulses) for LTD-like effect induction. Stimulus intensity was set at 80% AMT. AMT was defined as the lowest intensity to elicit MEPs in the right FDI larger than 200 μV in at least five of ten consecutive trials while the subjects maintained a weak voluntary contraction of the target muscle.

Quadripulse stimulation (QPS)

QPS consisted of four repeated monophasic TMS pulses every 5 s for 30 min. The pulses were delivered by four monophasic Magstim 200^2 stimulators connected with a special customized combining module (Magstim Co., Ltd.) through a figure-of-eight coil (internal wing diameter of 70 mm). The coil was placed tangentially on the scalp, 45 degrees lateral to the midsagittal line, and the current was induced in the PA direction, perpendicular to the central sulcus. We employed QPS5 (ISI = 5 ms) and QPS50 (ISI = 50 ms) for LTP/LTD-like effect induction, respectively [11]. The intensity of TMS pulses for QPS was set at 90% AMT.

Sham stimulation

To evaluate the natural variability of MEP amplitudes, we recorded MEPs after sham intervention from 16 volunteers who did not participate in real stimulation experiments. Sham stimulation of TBS or QPS was given to two groups: sham-iTBS in 8 participants and sham-QPS5 in 8 participants. In the sham condition (sham-iTBS or sham-QPS5), the coil was disconnected from the stimulator and was positioned over the left M1, and another coil produced the same sound as the real iTBS or real QPS5 by placing it 1 m behind the participant's head. Fifteen MEPs were collected every 5 min until 60 min after the intervention in the same manner as the real stimulation experiments.

Study design

Comparison of the degree of plasticity induction between TBS and QPS

Thirty subjects participated in the crossover experiments of real stimulation, which consisted of 4 interventions (i.e., two excitatory protocols: iTBS and QPS5, and two inhibitory protocols: cTBS and QPS50). Thus, each participant received all 4 protocols in a randomized order. Successive interventions were separated by at least one week in each subject. The median and range of intervisit intervals between visit 1 and visit 2 were 9 days (7 – 139 days), between visit 2 and 3 were 10 days (7 – 307 days), and between visit 3 and 4 were 10 days (7 – 216 days).

Figure 1 shows the timeline of the main experiment. First, the hotspot of the left M1 hand motor area and the stimulus intensity to elicit approximately 1 mV MEP were determined. Next, the AMT was measured. Stimulus intensity for 1 mV MEP (SI_{1mV}) and AMT were measured at the beginning of each session. To avoid the influence of

contraction of a target muscle on the after-effects of TBS [24-26] or QPS, subjects sat on the reclining chair while keeping their hand at rest, and we started to record the baseline MEPs at least 15 min after the end of the AMT measurement. To obtain the baseline MEP, we recorded 15 MEPs 3 times every 5 min before the intervention. We used the mean size of all 45 MEPs as the baseline MEP amplitude (the time of baseline is shown by “B”, see Fig. 1). After the intervention, MEPs were recorded every 5 min until 60 min (T5, T10, T15, T20, T25, T30, T35, T40, T45, T50, T55, and T60). The one-hour follow-up time was divided into four periods of quarter hour duration (Q1, Q2, Q3, Q4). We used the mean amplitude of three time points (quarter of hour) to follow the time course of MEP amplitudes [i.e., Q1: (T5+T10+T15)/3; Q2: (T20+T25+T30)/3; Q3: (T35+T40+T45)/3; and Q4: (T50+T55+T60)/3] (see Fig. 1). The MEP changes were evaluated by the MEP ratio, the ratio of the mean peak-to-peak amplitude at Q1–Q4 to that at baseline.

Figure 1

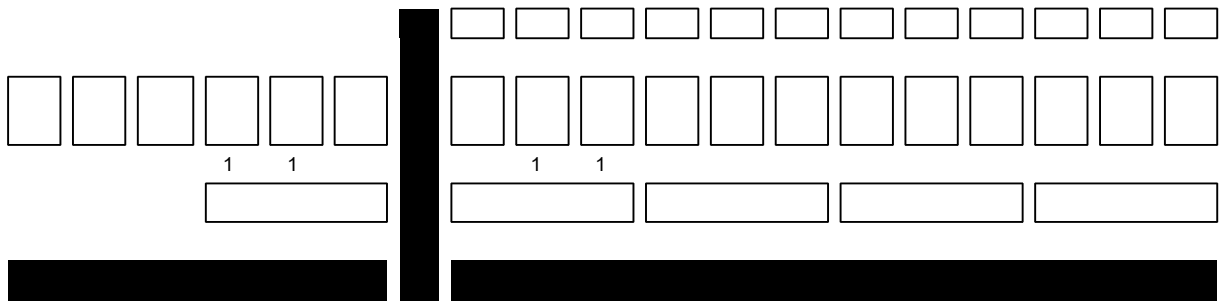

Figure 1. The study design for each intervention.

The stimulus intensity to elicit MEPs with an approximately 1 mV peak-to-peak MEP amplitude (SI_{1mV}) and AMT were measured. After 15 min of resting, 15 single pulse stimuli (SPs) at SI_{1mV} were given in one session, and 3 sessions were repeated. MEPs in 3 sessions were averaged as a baseline value (B). After an intervention of QPS or TBS, 15 SPs were given at one time point, and MEPs were averaged at 5 min intervals for 60 min (T5, T10, T15, T20, T25, T30, T35, T40, T45, T50, T55, and T60). The after-effect was analyzed using the MEP ratio (MEPs at a certain time point/baseline MEP). One-hour follow-up time after the intervention was divided into four periods of 15 min duration (Q1, Q2, Q3, and Q4). MEPs were compared between these four periods.

Relationship of the degree of plasticity induction between TBS and QPS

We investigated the relationship of MEP changes induced by the intervention between TBS and QPS. For this analysis, we used an index showing the degree of MEP changes induced by the intervention: ΔMEP. ΔMEP was defined as (MEP_Q – MEP_B)/MEP_B. MEP_B (baseline MEP) was the mean size of MEPs before intervention. MEP_Q (MEP after intervention) was the average MEP size at Q1 to Q4. The relation between TBS-induced ΔMEP and QPS-induced ΔMEP was tested by linear regression analysis.

Interindividual variability of TBS and QPS

The interindividual variability of responses to TBS and QPS was investigated by the following approaches. We used the MEP ratio at Q1, Q2, Q3, and Q4 in this evaluation. First, we used the simple classic dichotomy criteria of responders and nonresponders [13, 18, 20]. This approach was based on whether the MEP ratio was larger or smaller than 1.0 (1.0 means that the post-MEP was the same in amplitude as that at baseline). Second, we also used the trichotomy approach [18], which classified the subjects into three groups: “responder”, “nonresponder”, and “opposite-responder” compared with natural variability obtained in this study. To obtain the reference amplitude ratio for responder evaluation, we obtained the mean and standard deviation (SD) of the MEP ratio after sham intervention. Shapiro-Wilk tests revealed the normal distribution of the MEP ratio after sham stimulation, and then the natural variability was defined as the range of their mean ± 2 SD.

When the MEP ratio was in the natural variability range, the subject was classified as “nonresponder”. When the MEP ratio was out of the natural variability range, subjects were classified into “responder” or “opposite responder”. As reported by a previous paper [22], the trichotomy method based on the baseline variance is a scientifically reliable and more rigorous approach to confirm the effects of intervention because large false positive results can be contaminated in the dichotomy criteria [22]. However, in this paper, we used the dichotomy method to analyze the variability to compare the present results with those of previous papers in addition to the trichotomy method.

Statistical analysis

Data were analyzed using IBM SPSS Statistics ver. 25.0 for Windows. The baseline MEP amplitude, SI_{1mV}, and AMT were compared using paired Student's *t*-test or one-way analysis of variance (ANOVA).

To confirm the previously reported LTP/LTD-like effects of TBS or QPS, we performed one-way repeated measures ANOVA with the factor of time (B, Q1–Q4) as within subject factors on raw amplitude data (mV) in each intervention. When a significant main effect was observed, a post hoc *t*-test with Bonferroni corrections was conducted.

Next, we directly compared the efficacy between excitatory protocols, i.e., iTBS and QPS5, and between the inhibitory protocols, i.e., cTBS and QPS50. To consider the potential confounding effects (baseline MEP and SI_{1mV}), we performed repeated measures analysis of covariance (ANCOVA) with the factor of time (Q1–Q4) as the within subject factor and intervention (TBS and QPS) as the between subject factor using the MEP ratio. Prior to conducting ANOVA and ANCOVA, Shapiro-Wilk tests were conducted to assess the normality of the data. The Greenhouse-Geisser correction was used to correct nonspherical data when necessary.

In the analysis of interindividual variability, the rates of responders, nonresponders, and opposite responders were compared between TBS and QPS using the Chi-squared test.

A value of $P < 0.05$ was set as the statistically significant level in all analyses.

Results

No side effects were observed throughout the experiments.

We compared the baseline physiological measures among the interventions. One-way ANOVA showed no significant difference in the baseline MEP amplitudes ($F_{3,119}$ = 1.708; P = 0.169, η^2 = 0.042). There were also no significant differences in the SI_{1mV} ($F_{3,119}$ = 0.039; P = 0.990, η^2 = 0.001). The AMT showed no difference between iTBS and cTBS (T = -1.703; P = 0.099), or between QPS5 and QPS50 (T = -0.713; P = 0.481).

Time course of MEP amplitudes in TBS and QPS

We studied the time courses of MEP amplitudes in each intervention. As illustrated in Fig. 2, both iTBS and QPS5 increased the averaged MEP amplitude, while cTBS and QPS50 decreased the averaged MEP amplitude. Shapiro-Wilk tests revealed normal distributions of the data (all P > 0.05). A one-way repeated measures ANOVA revealed no significant effect of time on MEP amplitude in iTBS ($F_{2.517,72.997}$ = 0.511; P = 0.644, η^2 = 0.017). On the other hand, QPS5 had a significant effect of time ($F_{3.089,89.591}$ = 6.283; ***P* = 0.001**, η^2 = 0.178). A post hoc *t*-test using the Bonferroni correction revealed that QPS5 significantly increased the MEP amplitudes at Q2 and Q4 (P < 0.05). In inhibitory protocols, one-way repeated measures ANOVA showed a significant effect of time on MEP amplitudes in QPS50 ($F_{4,116}$ = 18.993; ***P* < 0.001**, η^2 = 0.396), but not in cTBS ($F_{2.679,77.694}$ = 1.239; P = 0.301, η^2 = 0.041). Post hoc *t*-tests using the Bonferroni

correction revealed that QPS50 significantly decreased the MEP amplitudes at all periods (***P* < 0.05**) (see Fig. 2).

Figure 2

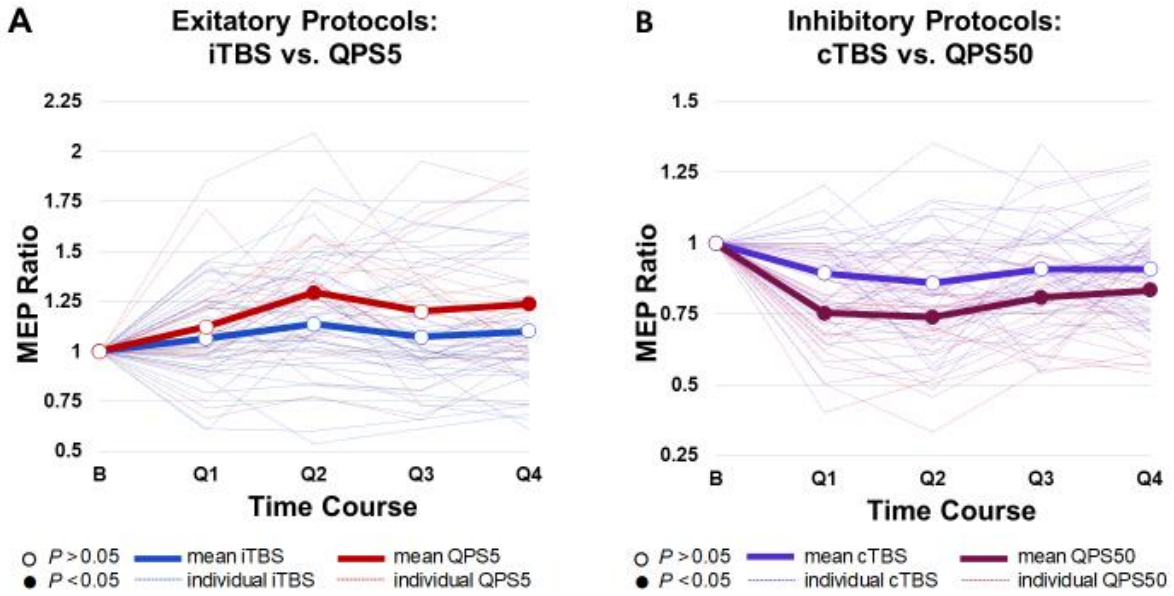

Figure 2. Comparison of the MEP ratio between TBS and QPS.

(A) Facilitatory intervention: iTBS vs. QPS5; (B) Inhibitory intervention: cTBS vs. QPS50. B: baseline (before intervention); Q1: the first quarter hour after intervention (T5+T10+T15); Q2: second quarter hour (T20+T25+T30); Q3: third quarter hour (T35+T40+T45); Q4: fourth quarter hour (T50+T55+T60). Thick lines show average MEP ratios from all subjects, and thin lines indicate all individual results.

Comparison of efficacy between TBS and QPS

Shapiro-Wilk tests did not show a normal distribution of the MEP ratio ($P < 0.05$), but a normal distribution of the log-transformed MEP ratio ($P > 0.05$). Hence, we used the log-transformed MEP ratio in this analysis. A repeated measures ANCOVA of the comparison between iTBS and QPS5 showed a main effect of intervention ($F_{1,56}$ = 4.476; $\boldsymbol{P = 0.039}$, $\eta^2 = 0.074$) but revealed no significant main effect of time ($F_{2.239,125.386}$ = 0.258; $P = 0.797$, $\eta^2 = 0.005$) or a significant interaction between intervention and time ($F_{2.239,125.386} = 0.554$, $P = 0.596$, $\eta^2 = 0.010$) (Fig. 2A). There was no significant interaction between baseline MEP and time ($F_{2.239,125.386} = 0.557$, $P = 0.594$, $\eta^2 = 0.01$) or SI_{1mV} and time ($F_{2.239,125.386} = 0.124$, $P = 0.904$, $\eta^2 = 0.002$). In the inhibitory protocols, there was a significant main effect of intervention ($F_{1,56} = 16.238$; $\boldsymbol{P < 0.001}$, $\eta^2 = 0.225$) without any significant interaction between intervention and time ($F_{3,168} = 1.272$, P = 0.286, $\eta^2 = 0.022$) or main effect of time ($F_{3,168} = 0.510$, $P = 0.676$, $\eta^2 = 0.009$) (Fig. 2B). We also observed no significant interaction between baseline MEP and time ($F_{3,168}$ = 1.238, $P = 0.298$, $\eta^2 = 0.022$) or SI_{1mV} and time ($F_{3,168} = 0.769$, $P = 0.513$, $\eta^2 = 0.014$). These results indicate that QPS induced greater bidirectional synaptic plasticity in the M1 compared to TBS in a similar manner of time.

Correlation between TBS and QPS effects

Regression analysis showed a significant positive linear correlation between TBS-induced ΔMEP and QPS-induced ΔMEP (Fig. 3; $R = 0.488$, $P < 0.001$). This suggests that the overall pattern of QPS after-effects is similar to that of TBS after-effects in each

subject. This indicates that the effect of either TBS or QPS would be estimated by that of the other one.

Figure

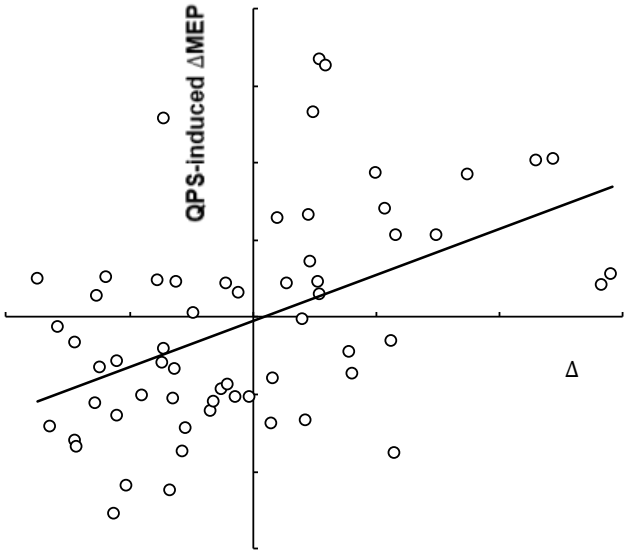

Figure 3. Correlation between TBS and QPS effects.

Positive linear correlation between TBS-induced ΔMEP (*x*-axis) and QPS-induced ΔMEP (*y*-axis). The thick line indicates the regression line.

Interindividual variability of TBS and QPS

To determine the natural variability range of MEPs, we first statistically compared the results between sham-iTBS and sham-QPS5. Unpaired *t*-test showed no significant

difference between the two sham stimulations (T = -0.329; P = 0.747). We therefore made a normal range of natural variation from all the data of the two sham interventions. The Shapiro-Wilk test revealed normal distributions of the MEP ratio in the sham stimulation (all $P > 0.05$), and then we made a normal range of size ratios based on their means and SD. The calculated MEP ratios from both sham interventions were 0.989 (SD = 0.095) at Q1, 1.003 (SD = 0.089) at Q2, 1.014 (SD = 0.090) at Q3, and 1.005 (SD = 0.084) at Q4. The ranges of natural variability were defined between 0.799 and 1.179 at Q1, 0.825 and 1.181 at Q2, 0.835 and 1.195 at Q3, and 0.836 and 1.174 at Q4 (mean ± 2SD). Based on these natural variation ranges, we classified all results as follows.

Initially, the response to the intervention of each person was categorized using dichotomy criteria of responder and nonresponder as in the previous papers [13, 18, 20]. In excitatory protocols (Fig. 4A), the responder rates of QPS5 were greater than those of iTBS (iTBS vs QPS5: 47% vs 57%, difference 10% at Q1; 57% vs 87%, difference 30% at Q2; 33% vs 70%, difference 37% at Q3; 50% vs 63%, difference 13% at Q4). The Chi-squared test showed a significant difference at Q2 (X^2 = 6.648, ***P* = 0.010**) and Q3 (X^2 = 8.076, ***P* = 0.004**), but there were no significant differences at Q1 or Q4 ($X^2 < 1.1$, $P > 0.2$). In inhibitory protocols (Fig. 4B), the responder rates of QPS50 were greater than those of cTBS (cTBS vs QPS50: 67% vs 100%, difference 33% at Q1; 67% vs 93%, difference 26% at Q2; 63% vs 90%, difference 27% at Q3; 63% vs 80%, difference 17% at Q4). The Chi-squared tests showed significant differences at Q1 (X^2 = 12.000, ***P* = 0.001**), Q2 (X^2 = 6.667, ***P* = 0.010**), and Q3 (X^2 = 5.963, ***P* = 0.015**). No significant differences were shown at Q4 (X^2 = 2.052, P = 0.152).

Figure

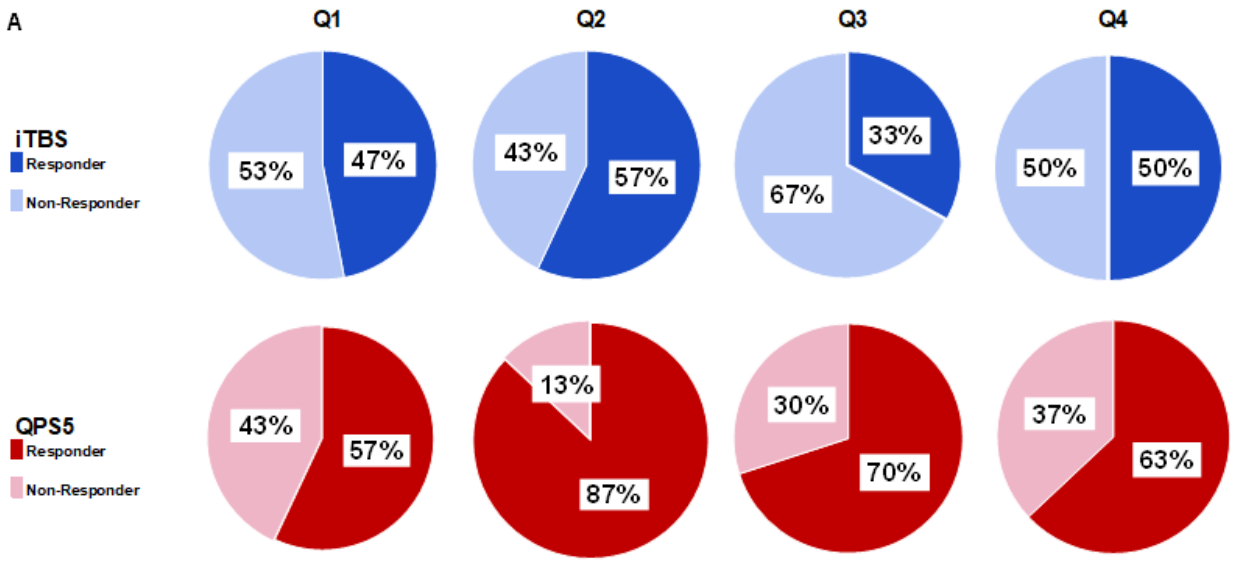

Figure B

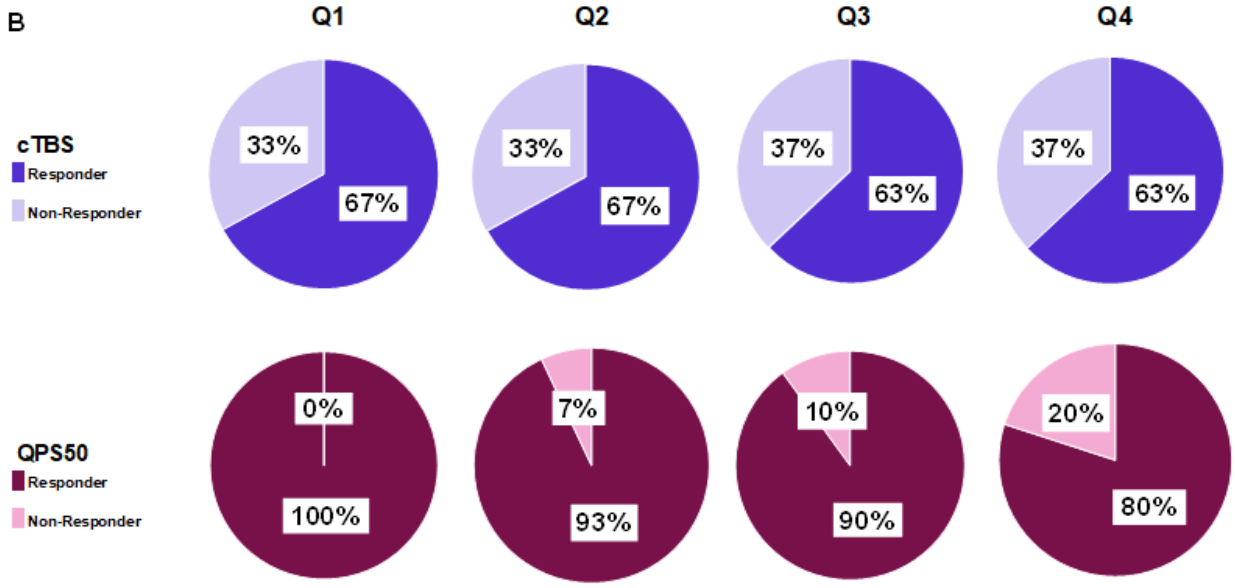

Figure 4. The profiles of interindividual variability between TBS and QPS in the dichotomic approach.

All subjects were classified into two groups, responder and nonresponder, in (A) excitatory and (B) inhibitory protocols.

In the trichotomy approach (Fig. 5A), the responder rates of QPS5 were greater than those of iTBS (iTBS vs QPS5: 30% vs 40%, difference 10% at Q1; 37% vs 67%, difference 30% at Q2; 27% vs 40%, difference 13% at Q3; 30% vs 47%, difference 17% at Q4). The nonresponder rates of QPS5 were almost the same as those of iTBS (iTBS vs QPS5: 53% vs 50%, difference 3% at Q1; 46% vs 30%, difference 16% at Q2; 40% vs 47%, difference 7% at Q3; 40% vs 46%, difference 6% at Q4). The rates of the opposite responder of QPS5 were smaller than those of iTBS (iTBS vs QPS5: 17% vs 10%, difference 7% at Q1; 17% vs 3%, difference 14% at Q2; 33% vs 13%, difference 20% at Q3; 30% vs 7%, difference 23% at Q4). The Chi squared test showed that the intervention affected the responder rate at Q2 (X^2 = 6.367, $\boldsymbol{P}$ **= 0.041**), but no significant effects were shown at other time points ($X^2 < 5.7$, $P > 0.05$). More responders were present in QPS5 than in iTBS at Q2. In inhibitory protocols (Fig. 5B), the responder rates of QPS50 were greater than those of cTBS (cTBS vs QPS50: 23% vs 63%, difference 40% at Q1; 40% vs 70%, difference 30% at Q2; 33% vs 54%, difference 21% at Q3; 30% vs 47%, difference 17% at Q4). The nonresponder rates of QPS50 were smaller than those of cTBS (cTBS vs QPS50: 74% vs 37%, difference 37% at Q1; 50%

vs 30%, difference 20% at Q2; 60% vs 43%, difference 17% at Q3; 57% vs 46%, difference 11% at Q4). The rates of the opposite responder of QPS50 were also smaller than those of cTBS (cTBS vs QPS50: 3% vs 0%, difference 3% at Q1; 10% vs 0%, difference 10% at Q2; 7% vs 3%, difference 4% at Q3; 13% vs 7%, difference 6% at Q4). The Chi-squared test revealed a significant difference in effects between the two interventions at Q1 (X^2 = 10.205, ***P* = 0.006**) and Q2 (X^2 = 6.955, ***P* = 0.031**), but there was no significant effect at other time points (X^2 < 2.6, P > 0.2). QPS50-induced LTD-like effects more frequently than cTBS at Q1 and Q2.

These above results suggest that the bidirectional plasticity induced by QPS is less variable than that induced by TBS.

Figure

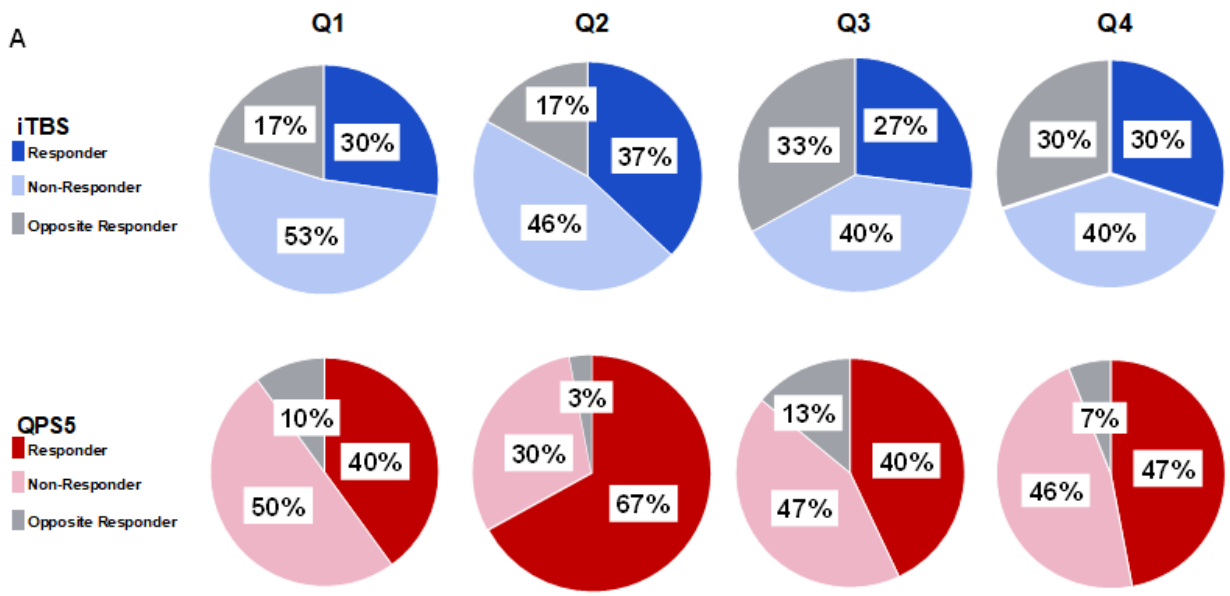

Figure B

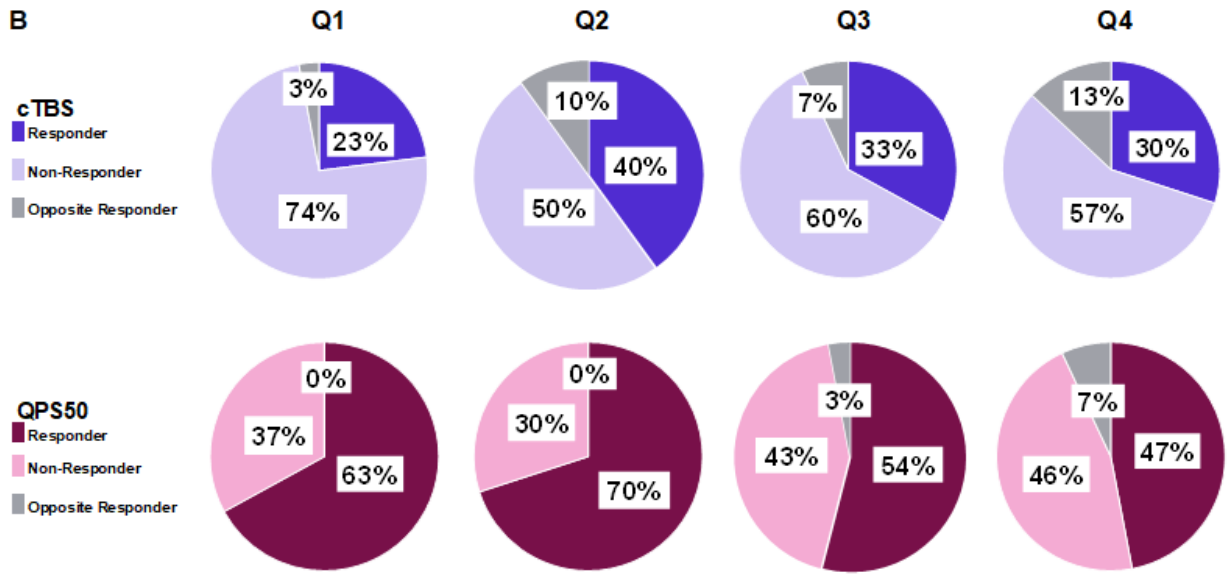

Figure 5. The profiles of interindividual variability between TBS and QPS in the trichotomic approach.

Trichotomic classifications into three groups, responder, nonresponder, and opposite responder in (A) excitatory and (B) inhibitory protocols.

Discussion

This is the first study of direct, head-to-head comparisons of the efficacy and variability between TBS and QPS. The present study revealed that QPS induced greater plasticity and more stable effects on the motor cortex than TBS.

Comparison of the degree of plasticity between TBS and QPS

The present results suggest that QPS can induce motor cortical plasticity more strongly than TBS. We speculate that one critical factor explaining strong QPS effects may be the differences in the pulse waveform between QPS and TBS. In short, the monophasic pulse used in QPS might effectively induce motor cortical plasticity compared to the biphasic pulses used in TBS.

The direction of the induced current flowing across the central sulcus has a great influence on the activation of cortical neurons. Because the complex geometry of the folded surface of the cerebral cortex gives a variety of relationships between neurons and the electrical field [27-29], the stimulation applied over M1 may have an influence on only some populations of neurons oriented in a particular direction. As shown in previous studies [30-32], the cortical neurons activated by monophasic pulse stimulation applied over the M1 depend on the induced current direction: the PA-directed currents activated different populations of M1 neurons from those activated by the AP-directed currents. Based on these characteristics, we propose several possible explanations of the strong QPS effects as follows.

One plausible explanation of the strong QPS effects is the monophasic TMS pulse in QPS. The TMS pulse used in TBS is biphasic: the induced current generated by the first phase of the TMS pulse flows in one direction, and the induced current at the second phase flows in the opposite direction. The opposite current generated by the second phase might have two unfavorable effects. One unfavorable effect is that the opposite induced current might counteract the ongoing membrane depolarization in the cortical neurons induced by the first phase, which might interfere with the activation of cortical neurons subliminally depolarized by the first phase of pulse. This is supported by a recent controllable TMS study demonstrating that biphasic pulses had higher motor thresholds than monophasic pulses [33]. The counteraction may reduce the firing cortical neurons for synaptic plasticity induction. However, contradictory results have also been reported regarding the effects of pulse waveform on motor threshold and MEP amplitude [34-37].

Another unfavorable effect is that the opposite induced current might recruit other populations of cortical neurons in addition to those activated by the first phase of TMS pulse, which may inhibit the target effect induced by the first phase of TMS pulse. Facilitatory neurons in the M1 are arranged in one particular direction to the central sulcus [32], whereas inhibitory neurons are oriented in random directions [38, 39]. The monophasic pulse by QPS and the first phase of the biphasic pulse used in TBS must preferably activate the facilitatory interneurons of M1 and inhibitory interneurons oriented in the same direction as the facilitatory interneurons. In contrast, the opposite induced current of the second phase in TBS might recruit inhibitory interneurons in

addition to those activated by the first phase, which might interfere with the facilitatory effects induced by the first phase of pulses.

These two unfavorable effects of biphasic pulse, counteraction of membrane depolarization and additional inhibitory interneuron activation, might contribute to the weaker and shorter motor cortical plasticity induced by TBS compared to that induced by QPS using monophasic pulse. This explanation was supported by the paired-pulse TMS experiments in the original TBS and QPS papers: QPS influences intracortical facilitation but not inhibitory circuits of the M1 [11], whereas TBS modulates both intracortical facilitation and inhibition in the same way [9]. Several comparison studies between monophasic pulses and biphasic pulses in rTMS have shown supportive results [14, 38-41]. A direct comparison of monophasic QPS and biphasic QPS showed that monophasic QPS had stronger and longer effects than biphasic QPS in inducing motor cortical plasticity [18].

The stimulation pattern should be another factor to explain the difference between TBS and QPS. In TBS, the difference in stimulation pattern of the same burst must determine the direction of synaptic plasticity induction: intermittent or continuous. In QPS, on the other hand, the interval of TMS single pulses must determine the direction of plasticity: 5 ms or 50 ms, which is consistent with an original BCM theory. This pattern difference may explain the difference in interindividual variability between the two methods.

Taken together, the differences in both the pulse waveforms and pattern of stimulation might result in different degrees of plasticity induction between TBS and QPS.

Other factors, e.g., total number of pulses and duration of the intervention, might also be responsible for the difference in efficacy between the two interventions. Previous studies of TBS showed that doubling the total pulse stimuli reversed the after-effects [26, 42]. A previous study of QPS also revealed that a smaller stimulus number and shorter duration of the intervention induced smaller after-effects compared to the original QPS protocols [18].

Regardless of the above discussions, the true explanations remain to be resolved. Whatever the mechanism, however, we demonstrated that QPS is more effective than TBS in inducing motor cortical plasticity.

Interindividual variability

As shown in many previous studies, there is a large interindividual variability in a variety of NIBS, such as rTMS [43-47], including TBS [13, 16, 19]. Nevertheless, QPS appears to show less variability, as reported by our and other groups [18, 48].

The interindividual variabilities of TBS and QPS in the present study are not largely different from those in previous studies. The responder rate (33 – 57% on dichotomy) of iTBS in the present study was similar to those in previous papers: 52% (dichotomy) reported by Hamada et al. [13] and 43% (dichotomy) by Lopez-Alonso et al. [19]. The responder rate of cTBS in the present study was better (63 – 67% on dichotomy) than 42 – 43% (dichotomy) in previous papers [13, 16].

There is a slight difference in responder/nonresponder rates between the present study and the previous studies, which might be explained by the difference of the method for

analysis: for example, interindividual variability in QPS was analyzed at Q1, Q2, Q3 and Q4 in the present study, whereas it was analyzed at all time points in the previous study [18]. Likewise, other factors, such as age, influence interindividual variability. Among NIBSs, however, QPS must have the highest responder rates.

On the other hand, there were no previous studies of the trichotomy interindividual variabilities of TBS. The responder rates of QPS5 (57 – 87% on dichotomy and 40 – 67% on trichotomy) and QPS50 (80 – 100% on dichotomy and 47 – 70% on trichotomy) were comparable with those in previous papers reported by Nakamura et al. [18] and Simeoni et al. [48]. Analysis with trichotomy also confirmed less interindividual variability of QPS.

Taken together, the results of the present study confirmed the lower interindividual variability of QPS compared with TBS in the plasticity induction effect.

Study limitations

Other factors could also influence the induction of synaptic plasticity in NIBS. The recognized factors are muscle contraction [24-26, 49], physical activity [50], time [51, 52], age [45, 53], attention [54-56], pharmacology [57], and genetics [58]. We controlled for confounding factors such as age, handedness, medication, and history of neurological or psychiatric diseases. We excluded the influence of muscle contraction. However, we did not perform the experiment on the same time of the day or we did not analyze genetics in the subjects [17, 19]. These factors might influence the difference in the time course of after-effects of TBS between the present study and the previous

studies. However, the present head-to-head comparisons may exclude some of those factors from the main influential factors.

The other limitation of the study was the stimulus intensity, which was not identical between TBS and QPS, i.e., TBS 80% AMT and QPS 90% AMT. We did not equalize the stimulus intensity because the aim of the present study was head-to-head comparison between TBS and QPS under the original protocols. The comparison of the two protocols at the same intensity, e.g. 90% AMT, should be performed in future studies.

Recent papers reported that at least 20 MEPs are required at each recording to obtain reliable estimates of MEP amplitudes [59, 60], but 15 MEPs were recorded at each time point in the present study. The suboptimal number of MEPs might influence the precision for evaluation of the after-effects of interventions. Considering this issue, in the main experiments, we used an average of 45 MEPs at three time points as one period in the analyses of the time course of the intervention.

Several behavioral studies have used TBS to modulate performance [61-63]. Recently, QPS was also applied for behavioral experiments [64, 65]. The results of MEP changes by rTMS are not necessarily in parallel with those of behavioral modulation. Differences in the efficacy of behavioral or cognitive performances between TBS and QPS are yet unknown, but the findings of MEPs in the present study can be a criterion to choose protocols.

The last limitation of the QPS study is that most studies of QPS have been performed by one group and only one study was published by another group [48], as mentioned in a recent review paper [12].

Regardless of the several limitations, the direct comparison between TBS and QPS has suggested superiority of QPS to TBS. The advantages of TBS to QPS are the shorter duration of the intervention and the cheaper equipment. These issues always cause some limitations of using QPS in clinical practice.

Conclusions

Upon direct head-to-head comparison, we found that QPS produces larger after-effects in comparison with TBS. We also revealed that QPS had less interindividual variability than TBS.

Conflict/Declaration of Interests

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Funding

This work was supported in part by grants from the Research Project Grant-in-aid for Scientific Research from the Ministry of Education, Culture, Sports, Science and Technology (Grant 16K09724) to TM, and those to YU (Grants 22390181, 25293206, 15H05881, 16H05322), the Research Committee on Degenerative Ataxia from the Ministry of Health, Labor and Welfare of Japan to YU.

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