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Quadripulse Stimulation: A Replication Study with A Newly Developed Stimulator

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Abstract

Quadripulse stimulation (QPS) is a promising patterned repetitive transcranial magnetic stimulation protocol, which allows the modulation of brain activity for over one hour after the stimulation. Recently, Deymed Diagnostic developed a new stimulator specifically designed to deliver QPS (DuoMAG MP-Quad, https://deymed.com/duomag-qps). The properties of the after-effect with this new stimulator were expected to parallel those obtained with another stimulator, the Magstim stimulator, which is currently used in the psychological and clinical research but not commercially available anymore. Nevertheless, experimental validation of DuoMAG MP-Quad was still warranted. We thus studied the QPS after-effect induced by this stimulator. As a result, motor evoked potentials were found to be bidirectionally modulated by the QPS for more than one hour, consistent with previous studies using the Magstim stimulator. Moreover, the degree of the after-effect was comparable to the after-effect induced by the other stimulator. Taken together, we conclude that the newly developed QPS stimulator is as effective as the Magstim stimulator.

Quadripulse stimulation (QPS) is a patterned repetitive transcranial magnetic stimulation (rTMS) protocol [1]. The after-effect of QPS, compared to another patterned rTMS protocol–theta burst stimulation, was reported to be stronger and less variable across participants [2]. Moreover, the after-effect of QPS is not affected by gene-polymorphisms of BDNF [3], often influencing the rTMS after-effect [4]. Therefore, QPS emerges as a promising rTMS protocol for neuro-modulational research and treatment.

Recently, Deymed Diagnostic has developed a new stimulator specifically designed for QPS (DuoMAG MP-Quad, https://deymed.com/duomag-qps), which appears as a promising QPS-stimulator [5]. However, the after-effect induced by the DuoMAG MP-Quad has not yet been systematically investigated. The degree of after-effect may differ between QPS-stimulators considering that the waveform of stimulation pulses slightly differs between manufacturers [6]. We thus studied the QPS after-effects induced by the DuoMAG MP-Quad stimulator.

The participants were thirteen healthy adult volunteers comprising five females, 20–24 years of age (mean ± standard deviation: 21.5 ± 1.3). They were right-handed without a history of neurological or psychiatric disorders. Our study comprised two sessions with a within-subject design, applying two different types of QPS: QPS

with an interpulse-interval of 5 ms (QPS5) and 50 ms (QPS50). These two protocols are

expected to potentiate and depress the stimulated region most effectively [1]. The two

sessions were separated by over a week, while their order was randomly assigned and

counterbalanced across the participants. QPS was delivered over the left primary motor

cortex (M1) using DuoMAG MP-Quad (Deymed Diagnostic s.r.o., Hronov, Czech

Republic) with a butterfly-shaped 70-mm air-cooling coil (DuoMAG 70BF Air Cooled

Coil; Deymed Diagnostic s.r.o., Hronov, Czech Republic). Throughout the session,

motor evoked potentials (MEPs) were recorded from the right first dorsal interosseous

(FDI) muscle using a Brainsight surface-electromyogram (Rogue Research Inc.,

Montreal, Canada).

In each session, we first localized the hotspot, defined as the location evoking

the largest MEPs, for the right FDI, and measured active motor threshold (AMT),

defined as the intensity evoking MEPs larger than 100 μV in 5 out of 10 trials, with a

slight contraction of the right FDI (~10 % of maximum voluntary contraction). We then

measured 30 MEPs at the intensity evoking ~500 μV of MEPs in the relaxed FDI as a

baseline (pre-QPS). We further assessed alertness of the participants with a Stanford

Sleepiness Scale (SSS; one participant presenting SSS > 4 was excluded) [7].

Subsequently, we applied QPS over the hotspot with one burst of four monophasic

pulses delivered every 5 s for 30 min with a intensity of 90% AMT [1]. After applying

QPS, we measured 20 MEPs every 10 min until 90 min after QPS (post-10 to post-90)

using the same intensity as for the pre-QPS. The coil position was monitored with a

Brainsight (Rogue Research Inc.) to confirm stable coil position.

To evaluate the overall after-effect in QPS5 and QPS50, we first compared the

MEPs between pre- and post-QPS (post-10 to post-90) for each QPS protocol. The

grand mean MEP amplitudes of post-QPS normalized to pre-QPS (normalized MEP)

was 1.71 ± 0.41 (from below mean $\pm$ standard deviation) in QPS5 and 0.82 ± 0.23 in

QPS50 (Fig. 1A). Two-tailed paired Student's t-tests of the absolute MEP amplitude

between pre- and post-QPS revealed significant enlargement after QPS5 ($P < 0.001$, d'

$= 1.40$) and reduction after QPS50 ($P = 0.019$, $d' = -0.80$).

To evaluate the time-course of MEPs, we separated the time-course into three

time-blocks (post-10–30, post-40–60, and post-70–90), then averaged MEPs among

each time-block [2]. The mean of normalized MEP in post-10–30, post-40–60, and post-

70–90 was 1.51 ± 0.36, 1.79 ± 0.48, 1.79 ± 0.48, respectively, for QPS5 (Fig. 1B), and

0.84 ± 0.32, 0.80 ± 0.26, and 0.83 ± 0.17, respectively, for QPS50 (Fig. 1C) (see

Supplementary Fig. 1 for the individual time courses of MEPs). Repeated-measures

one-way ANOVA revealed significant effect of time-block in QPS5 ($P < 0.001$, $\eta^2 =$

0.60) and moderate effect of time-block in QPS50 ($P = 0.051$, $\eta^2 = 0.24$). Post-hoc

paired t-tests of the absolute MEP amplitude with correction for multiple comparisons

using the Holm's method also showed significant enlargement by QPS5 in all time-

blocks (post-10–30, $P = 0.002$, $d' = 1.14$; post-40–60, $P = 0.001$, $d' = 1.35$; post-70–90,

$P = 0.001$, $d' = 1.42$), together with a significant reduction by QPS50 in post-40–60 and

post-70–90, and a moderate reduction by QPS50 in post-10–30 (post-10–30, $P = 0.093$,

$d' = –0.53$; post-40–60, $P = 0.030$, $d' = –0.90$; post-70–90, $P = 0.047$, $d' = –0.76$). In

terms of baseline physiological parameters, no significant differences were found in

AMT ($P = 0.73$), stimulus intensity for recording MEPs ($P = 0.49$), stimulus intensity

for recording QPS ($P = 0.68$) or mean baseline MEP amplitude ($P = 0.29$) (Fig. 1D)

between the QPS5 and QPS50 sessions. These findings confirm steady experimental

conditions across the sessions.

As expected from previous studies using the Magstim stimulator (The Magstim

Co. Ltd., Whitland, UK) [1,2,8], MEPs were bidirectionally modulated for over 60 min

by QPS when using the newly developed stimulator. In previous studies, the grand

mean normalized MEP was ~2.0 [1], 1.60 [8], and ~1.2 [2] in QPS5, *versus* ~0.5 [1],

0.67 [8], and ~0.8 [2] in QPS50. The grand means of normalized MEP measured in the

present study were comparable to those induced by the Magstim stimulator. These

effects induced by the newly developed stimulator are supported by previous

observations showing that short-interval intracortical inhibition is not sensitive to slight

differences in TMS pulse waveform [6]. In the present study, the effect sizes of MEP-

changes after QPS50 were found to be smaller than those measured after QPS5. A

similar trend was reported in previous studies [1,8,9].

Together, these findings reveal that the newly developed QPS stimulator is as

effective as the original QPS stimulator [1]. A promising approach to boost the after-

effect of QPS50 would be to combine QPS with afferent electric stimulation of the

peripheral nerves using paired-associative QPS [10].

References

[1]   Hamada M, Terao Y, Hanajima R, Shirota Y, Nakatani-Enomoto S, Furubayashi T,

et al. Bidirectional long-term motor cortical plasticity and metaplasticity induced by

quadripulse transcranial magnetic stimulation. J Physiol 2008;586:3927–47.

[2]   Tiksnadi A, Murakami T, Wiratman W, Matsumoto H, Ugawa Y. Direct comparison

of efficacy of the motor cortical plasticity induction and the interindividual

variability between TBS and QPS. Brain Stimul 2020;13:1824–33.

[3]   Nakamura K, Enomoto H, Hanajima R, Hamada M, Shimizu E, Kawamura Y, et al.

Quadri-pulse stimulation (QPS) induced LTP/LTD was not affected by Val66Met

polymorphism in the brain-derived neurotrophic factor (BDNF) gene. Neurosci Lett

2011;487:264–7.

[4]   Ridding MC, Ziemann U. Determinants of the induction of cortical plasticity by non-

invasive brain stimulation in healthy subjects: Induction of cortical plasticity by non-

invasive brain stimulation. J Physiol 2010;588:2291–304.

[5]   Matsumoto H, Ugawa Y. Quadripulse stimulation (QPS). Exp Brain Res

2020;238:1619–25.

[6]   Wessel MJ, Draaisma LR, Morishita T, Hummel FC. The effects of stimulator,

waveform, and current direction on intracortical inhibition and facilitation: A TMS

comparison study. Front Neurosci 2019;13:703.

[7] Hoddes E. Dement, WC. & Zarcone, V.(1972). The development and use of the Stanford Sleepiness Scale (SSS). Psychophysiology 1972;9:150.

[8] Nakamura K, Groiss SJ, Hamada M, Enomoto H, Kadowaki S, Abe M, et al. Variability in Response to Quadripulse Stimulation of the Motor Cortex. Brain Stimul 2016;9:859–66.

[9] Simeoni S, Hannah R, Sato D, Kawakami M, Rothwell J, Simeoni S, et al. Effects of Quadripulse Stimulation on Human Motor Cortex Excitability: A Replication Study. Brain Stimul 2016;9:148–50.

[10] Wiratman W, Murakmi T, Tiksnadi A, Kobayashi S, Hanajima R, Ugawa Y. Enhancement of LTD-like aftereffects by combining quadripulse stimulation for LTD with paired-associative peripheral nerve stimulation (paired-associative QPS). Clin Neurophysiol (in press)

Captions to figures

Figure 1. (A–C) Motor evoked potentials (MEPs) measured after QPS. (A) shows the grand average of the normalized MEP amplitudes, while (B) and (C) show the time courses of MEPs after QPS5 and QPS50, respectively. The vertical axis indicates the MEP amplitudes normalized by the baseline MEP amplitude in log scale, while the horizontal axes indicate QPS condition (A) or the time-block after QPS (B, C). (D) Comparison of baseline neurophysiological features between the QPS5 and QPS50 protocols. The active motor threshold (AMT) and stimulus intensity (SI) for recording MEPs, SI for recording QPS, and mean baseline MEP amplitude are shown. The vertical axis shows the percentage of maximum stimulator output (% MSO) in AMT and SI, while the vertical axis shows the mean baseline MEP amplitude (micro volt). The mean (black cross) and standard error (error bar) are also provided.

Supplementary Figure 1. Individual time courses of normalized MEP amplitude after QPS5 (A) and QPS50 (B). The vertical axis indicates the MEP amplitude normalized by the baseline MEP amplitude in log scale, while the horizontal axis indicates the time after QPS in minutes.