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Brain Stimulation

BRAIN STIMULATION

Efficacy and safety of multiple sessions of quadripulse stimulation in patients with stroke: A report of two cases

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Dear Editor

Quadripulse stimulation (QPS) is a new patterned repetitive transcranial magnetic stimulation (rTMS) protocol. In particular, QPS induces long-term effects [1], with low inter-individual variabilities, in healthy individuals [2,3]. Recently, various rTMS protocols have been used to improve motor function in patients with stroke [4]. However, there are no reports on the application of QPS in stroke patients. This study aimed to investigate how multiple sessions of QPS to the lesioned primary motor cortex (M1) combined with other therapies change motor function and electroencephalograms (EEGs) in stroke patients.

Two patients with chronic cerebral infarction were included in the trial after obtaining written informed consent (Table 1). The paretic finger functions as scored with the Stroke Impairment Assessment Set (SIAS) were 1C (partial individual movements, shown in the thumb and the index finger) in Case 1 and 1A (mass flexion) in Case 2. Both patients could not pick up the marble used in the Action Research Arm Test. The study was performed in accordance with the Declaration of Helsinki, was approved by the local Ethics Committee, and was registered to the UMIN Clinical Trial Registry (UMIN000032286).

The TMS was performed using four monophasic stimulators (Magstim 2002, The Magstim Company, Ltd., Whitland, Carmarthenshire, UK) integrated through a connecting module, and attached to a 70 mm figure-of-eight coil while subjects were seated comfortably. Motor evoked potentials (MEPs) were recorded from bilateral first dorsal interosseous muscle via surface electromyogram. Neuronavigation (Brainsight, Rogue Research, Inc., Montreal, Quebec, Canada) ensured a consistent coil position during all sessions. No MEPs were elicited from the affected hemisphere in both cases, and the active motor threshold (AMT) of the unaffected M1 was determined. The QPS protocol of four successive monophasic pulses delivered with an interstimulus interval of 5 milliseconds (QPS-5) was applied to a symmetric position (mirror region) of the unaffected M1 hotspot. One therapeutic session consisted of 360 trains of four pulses (total, 1440 pulses) at the intensity of 90% AMT and an intertrain interval of 5 seconds. To maximize clinical benefits, we used QPS for 30 minutes and kinesthetic illusion induced by visual stimulation [5] for 20 minutes (40 minutes including preparation), 5 times a week for 2 weeks. Task-oriented training for 60 minutes and Hybrid Assistive Neuromuscular Dynamic Stimulation therapy [6] was conducted once every day.

Resting-state EEGs were recorded before and after the intervention with subjects sitting relaxed in an armchair, while keeping their eyes open without blinking. The EEG data were acquired using Geodesic EEG system 400 MR (Electrical Geodesics Inc., Eugene, OR) and Net Station v5.2 recording software, and sampling at 1000 Hz. We used 128-channel high-impedance HydroCel Geodesic Sensor Nets, with an average of all channels as the reference. Nets were positioned on each participant by aligning the vertex (Cz) electrode with the vertex of the head. Electrode impedances were <50 kΩ, as recommended by the manufacturer. Analysis electrodes, C3 and C4, were selected according to the international 10–20 system. For offline analysis, we used a bandpass of 0.5–120 Hz, and a notch of 50 Hz, and removed noisy epochs manually. Data were segmented into epochs of 2 consecutive seconds (20 points). Power was calculated using MATLAB (MATLAB R2018a; The MathWorks Inc., Natick, MA, USA). Fast Fourier transformation (averaged window, 2 sec) was used to calculate power ($\mu V2$) for the following EEG bands and sub-bands: delta (1–3 Hz), theta (4–7 Hz), alpha (8–13 Hz), and beta (14–30 Hz), low alpha (8–10 Hz), high alpha (11–13 Hz), low beta (14–20 Hz), and high beta (21–30 Hz). Two-way repeated measures ANOVA and Bonferroni post hoc comparison was performed using IBM SPSS Statistics version 25 (IBM Corporation, Armonk, NY, USA) and the level of significance was set at 0.05 (0.003, after Bonferroni adjustments).

After a 20 min rest period following the first QPS session, Case 1 could move the middle finger individually and Case 2 could perform a mass finger extension (SIAS 1B) (Table 1). Restoration of paretic finger functions was accompanied by reduction of spasticity at the finger flexors (the examiner's subjective impression, not as measured with Modified Ashworth Scale), which made it possible for both patients to pick up and release the marble with their thumb and index finger. After the two-week intervention, the finger functions were SIAS 2 (able to move each finger but unable to extend and flex the fingers completely) in Case 1 and 1C (partial individual movements, shown in the thumb and middle finger) in Case 2. Both participants showed improved motor function with decreased spasticity of the paretic upper extremity. No definite MEPs were recorded in the affected hemisphere. There was no obvious adverse effect during the trial. Resting-state EEG analyses showed that time, bands, and the interaction effect between time and bands were significant, with significantly reduced powers in the beta band in both hemispheres (lesion side dominant) in Case 2, whereas no significant changes were seen in Case 1.

Ten sessions of QPS-5 to the lesioned M1 combined with other treatments achieved clinical improvements without any adverse effects. To our knowledge, this is the first report on multiple sessions of QPS applied to the stroke patients. In healthy volunteers, the after-effects of QPS-5 are longer (>75 minutes) [1] than those in the other rTMS protocols. Although it is unclear how QPS works

Table 1
Demographic data, QPS stimulation intensity, and Changes of Clinical evaluations and Electroencephalogram.

Demographic Data	Case 1			Case 2		
Age, sex	64 y/o, male			67 y/o, female		
Stroke	Right corona radiata infarct			Left corona radiata infarct		
Time from onset	5 months			4 years		
EHI	+100			+56		
QPS stimulation intensity	40%			52%		
Clinical Evaluations	Pre intervention	After the first QPS	Post intervention	Pre intervention	After the first QPS	Post intervention
MMSE	28	–	30	30	–	30
SIAS finger function	1C (I-II)	1C (I-III)	2	1A	1B	1C (I, III)
FMA U/E motor	12	–	15	22	–	31
FMA U/E sensory	12	–	12	12	–	12
ARAT	13	–	35	9	–	15
Marble with I&II	0	–	2	0	–	2
Pick up and release Marble with I&II*	Impossible	Possible	–	Impossible	Possible	–
BBT	2	–	16	0	–	1
MAS wrist extension	1+	–	1+	3	–	1
MAS finger extension	1+	–	0	3	–	1

EEG powers at rest		Pre	Post	P value	Pre	Post	P value
C3	Delta	0.002 ± 0.001	0.002 ± 0.001	0.139	0.004 ± 0.002	0.006 ± 0.004	0.065
	Theta	0.136 ± 0.073	0.158 ± 0.081	0.389	0.204 ± 0.086	0.217 ± 0.082	0.621
	Alpha	0.472 ± 0.196	0.571 ± 0.292	0.224	0.536 ± 0.122	0.436 ± 0.218	0.089
	Low alpha	0.206 ± 0.100	0.328 ± 0.238	0.047	0.243 ± 0.082	0.200 ± 0.094	0.140
	High alpha	0.266 ± 0.174	0.244 ± 0.105	0.639	0.293 ± 0.106	0.236 ± 0.150	0.179
	Beta	0.599 ± 0.151	0.719 ± 0.322	0.154	2.402 ± 0.653	1.073 ± 0.268	**0.000**
	Low beta	0.297 ± 0.071	0.381 ± 0.139	0.025	0.989 ± 0.319	0.534 ± 0.174	**0.000**
	High beta	0.303 ± 0.104	0.338 ± 0.116	0.540	1.413 ± 0.529	0.539 ± 0.152	**0.000**
C4	Delta	0.002 ± 0.002	0.002 ± 0.001	0.772	0.006 ± 0.004	0.011 ± 0.008	0.033
	Theta	0.137 ± 0.061	0.117 ± 0.052	0.291	0.317 ± 0.118	0.340 ± 0.126	0.560
	Alpha	0.519 ± 0.190	0.548 ± 0.143	0.590	0.808 ± 0.221	0.772 ± 0.289	0.664
	Low alpha	0.265 ± 0.146	0.303 ± 0.110	0.369	0.430 ± 0.177	0.380 ± 0.136	0.340
	High alpha	0.254 ± 0.095	0.245 ± 0.085	0.771	0.379 ± 0.141	0.392 ± 0.202	0.818
	Beta	0.604 ± 0.138	0.711 ± 0.212	0.071	2.628 ± 0.572	1.995 ± 0.553	**0.001**
	Low beta	0.279 ± 0.093	0.385 ± 0.137	0.009	1.443 ± 0.467	0.957 ± 0.259	**0.000**
	High beta	0.324 ± 0.087	0.327 ± 0.125	0.949	1.185 ± 0.338	1.039 ± 0.356	0.203

EHI, Edinburgh Handedness Inventory; QPS, Quadripulse stimulation; MMSE, Mini-Mental State Examination; SIAS, Stroke Impairment Assessment Set; FMA, Fugl-Meyer Assessment; ARAT, Action Research Arm Test; BBT, Box and Block Test; MAS, Modified Ashworth Scale. Values are given as mean $\pm$ standard deviation. BOLD indicates P-value less than 0.003 (0.05/16, Bonferroni adjustments). * This test examines an ability to pick up and release the marble with thumb and index finger.

in stroke patients, this study found the acute clinical effects of one QPS session. Besides, QPS before other treatments is expected to raise the overall therapeutic effects. To what extent each treatment contributed to the results, however, is unclear.

The results of resting-state EEG provided some evidence of the safety of multiple sessions of QPS-5 applied to stroke patients. One session of QPS-5 applied to the left M1 did not induce any changes in the power-spectrum of the resting-state EEG in both C3 and C4 in healthy subjects [7]. No significant changes in EEGs in Case 1 supports the safety of QPS applied to stroke patients. On the other hand, decreased power in the beta band was shown in Case 2. Higher beta activity is related to motor tasks requiring higher efforts. The increased high-beta band during resting-state EEGs in the affected hemisphere after stroke is associated with poor motor function and reflects a compensation or maladaptive plasticity state [8]. The Case 2 showed compensative movements accompanied with high spasticity during admission, hence the intervention could favorably improve plasticity resulting in clinical improvements and reduced spasticity.

There are some limitations to this study. First, the stimulation intensity based on the AMT of the unaffected hemisphere should be lower than that of the affected hemisphere, which influences the effects of QPS-5. The acute effects of QPS-5 were clinically beneficial in both the cases, however, inter-individual variability of QPS must be considered to tailor individual treatments targeting recovery from paresis [9]. The other limitations include the small sample size and no comparison with sham stimulation. Further research will be needed under the safety guidelines [10].

Declarations of interest

None.

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