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Somatosensory-evoked potential modulation by quadripulse transcranial magnetic stimulation in patients with benign myoclonus epilepsy

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HIGHLIGHTS

- In healthy subjects, quadripulse transcranial magnetic stimulation (QPS) over the primary motor cortex (M1) induces bidirectional heterotopic plasticity in the somatosensory cortex (S1), following the Bienenstock–Cooper–Munro (BCM)-like theory.
- In patients with benign myoclonus epilepsy (ME patients), QPS over M1 induces long-term potentiation (LTP) but no long-term depression (LTD) in S1.
- QPS is not applicable to the treatment for ME patients because the frequency dependency may be completely different between the healthy subjects and the patients.

ABSTRACT

Objective: In patients with benign myoclonus epilepsy (ME), giant sensory-evoked potential (SEP) reflects the hyperexcitability of the sensory cortex. The aim of this study was to compare the effect of quadripulse transcranial magnetic stimulation (QPS) on the median nerve SEP between ME patients and healthy subjects.
Methods: Ten healthy volunteers and six ME patients with giant SEP participated in this study. QPSs at interpulse intervals (IPIs) of 5, 30, 50, 100, 500 and 1250 ms were applied over the left primary motor cortex (M1) for 30 min. The peak-to-peak amplitudes of N20 to P25 (N20–P25) and P25 to N33 (P25–N33) components were measured at the left somatosensory cortex.
Results: In healthy participants, the P25–N33 was bidirectionally modulated by QPS over M1, following the Bienenstock–Cooper–Munro (BCM) theory. The N20–P25 was not affected by any QPSs. In ME patients, the giant P25–N33 was potentiated after any QPSs. Furthermore, the N20–P25 was also

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potentiated after QPS at IPIs of 5, 30, 50 100 or 500 ms.
Conclusions: In ME patients, the cascade for long-term depression-like effects may be impaired.
Significance: The giant SEP was furthermore enhanced by QPS.
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1. Introduction

In patients with cortical myoclonus, both the sensory cortex (Shibasaki et al., 1985) and the motor cortex (Manganotti et al., 2001; Hanajima et al., 2008, 2011) are hyperexcitable. Previous magnetoencephalographic studies demonstrated that the sensory or motor cortices contribute differently to the generation of myoclonus (Ugawa et al., 1995; Mima et al., 1998). Some anticonvulsants suppressed giant somatosensory-evoked potential (SEP) and decreased myoclonic jerks (Shibasaki et al., 1985; Kanazawa and Nagafuji, 1997). Based on these findings, the giant SEP suppression may have a therapeutic potential for myoclonic patients. This hypothesis leads us to find out some physiological methods that suppress the cortical hyperexcitability in the patients.

Several conventional repetitive transcranial magnetic stimulation (rTMS) techniques such as theta burst stimulation (TBS) or paired associative stimulation (PAS) over the primary motor cortex (M1) altered ipsilateral sensory cortical functions. They induced changes in the main components (Enomoto et al., 2001; Kodama et al., 2009; Ragert et al., 2004; Wolters et al., 2005), high-frequency oscillations (HFOs) of SEP (Murakami et al., 2008) or tactile perceptions (Satow et al., 2003). Quadripulse stimulation (QPS) over M1 also elicited bidirectional modulation of the somatosensory cortex (heterotopic effect) (Nakatani-Enomoto et al., 2012). One aim of this research was to study the QPS effect in patients with benign myoclonus epilepsy (ME patients) in order to evaluate the applicability of QPS as treatment for ME patients.

The direction of the long-term effect induced by repetitive stimulation usually depends on the stimulation frequency used for the induction procedure. The same frequency dependency was present in human motor cortical experiments (Pascual-Leone et al., 1994; Jennum et al., 1995; Chen et al., 1997; Muellbacher et al., 2000). The effects of QPS over the motor cortex were consistent with this theory on both MEPs (Hamada et al., 2007, 2008, 2009) and SEPs (Nakatani-Enomoto et al., 2012). Furthermore, the modulation of M1 after QPS with different interpulse intervals over M1 (homotopic effect) followed Bienenstock–Cooper–Munro (BCM)-like curve (Bienenstock et al., 1982; Hamada et al., 2008). However, it is not known whether the effect by QPS over M1 on SEPs (heterotopic effect) follows this rule. The other aim of this study was to investigate the stimulation frequency dependency of the sensory cortical heterotopic effect by QPS over M1 in healthy subjects.

Table 1
Clinical summary of the benign myoclonus patients. Basic data of the benign myoclonus patients are summarized. PHT, phenytoin sodium; VPA, valproic acid; CZP, clonazepam; GTC, generalized tonic clonic seizure; N, no seizure experience.

Case	Age	Sex	Medication	Seizure attack
1	74	M	PHT 225 mg	N
2	61	M	VPA 300 mg, CZP 6 mg	GTC (three times in life)
3	59	F	VPA 300 mg	N
4	55	M	VPA 300 mg	N
5	51	F	VPA 100 mg, CZP 1.5 mg	N
6	51	F	PHT 200 mg, CZP 6 mg	N

2. Methods

2.1. Subjects

Subjects included six ME patients with giant SEP aged 51–74 years (Table 1) and 10 healthy volunteers aged 32–55 years. One patient totally fitted to the clinical criteria of benign adult familial myoclonus epilepsy (BAFME). Five other patients lacked seizure episodes, but they all had cortical reflex myoclonus and autosomal dominant inheritance (Hitomi et al., 2011). The P25–N33 component of the median nerve SEP was between 22.3 and 67.1 μV in amplitude (giant SEP). The cortical long-loop reflexes were abnormally exaggerated in all the patients. The jerk-locked

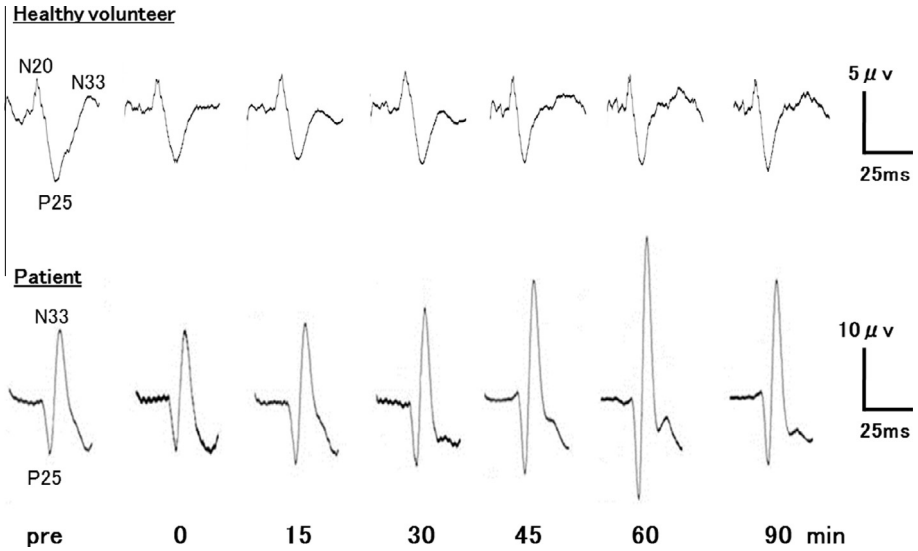

Fig. 1. Typical SEP waveforms before and after QPS-50 in healthy subject and benign myoclonus epilepsy (ME) patient.

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