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Research article

BDNF genotype influence the efficacy of rTMS in stroke patients

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HIGHLIGHTS

- High-frequency rTMS facilitated cortical excitability regardless of BDNF genotype.
- Supra-threshold rTMS facilitated higher cortical excitability in Val/Val group.
- In Met allele group, cortical excitability showed no difference by rTMS intensity.
- BDNF polymorphism could influence neural response to rTMS in stroke patients.

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ABSTRACT

Brain-derived neurotrophic factor (BDNF) genotype can influence neural response to repetitive transcranial magnetic stimulation (rTMS) in normal individuals. In this study we established personalized stimulus intensity of facilitatory rTMS according to BDNF genotype in stroke patients. Twenty-two chronic stroke patients were enrolled. All patients underwent three different sessions of rTMS over the ipsilesional M1 in randomized order with a washout period exceeding 24 h: first condition, high-frequency rTMS with sub-threshold intensity; second condition, high-frequency rTMS with supra-threshold intensity; third condition, sham rTMS. Cortical excitability in the affected hemisphere was assessed with motor evoked potentials (MEPs) before and after stimulation. Data were analyzed according to BDNF genotype. Six [27.3%] and 16 [72.7%] participants were classified in the Val/Val group and Met allele group, respectively. In each group, significant increases were observed in the amplitude of MEPs after the stimulation in the first and second conditions ($p < 0.05$), but not in the third condition. However, a significantly higher increase of amplitude of MEPs was observed between the first and second conditions in only the Val/Val group ($p < 0.05$). BDNF genotype and stimulus intensity should be considered when high-frequency rTMS is used for the modulation of cortical excitability in patients with chronic stroke.

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1. Introduction

Brain-derived neurotrophic factor (BDNF) is the most abundant neurotrophin in the brain and is highly expressed throughout the central nervous system [21]. BDNF promotes neuronal survival, differentiation and synaptic function, and involves neurodegeneration [20]. BDNF has been reported to modulate *N*-methyl-D-aspartate receptor (NMDAR)-dependent long-term potentiation (LTP) and long-term depression (LTD)-related processes in the animal cortex [1,8,30]. A single nucleotide polymorphism has been identified in the human BDNF gene at codon 66 (Val66Met). The replacement of Val66 by Met66 disrupts cellular processing, trafficking, and activity-dependent secretion of BDNF [7]. In addition, the Met allele has been associated with poorer episodic memory as well as lower hippocampal [7] and prefrontal cortical activity [27]. In East Asian samples, especially Korean samples, the BDNF Val66Met polymorphism is more prevalent than in Western populations [24,26].

Repetitive transcranial magnetic stimulation (rTMS) appears to have inhibitory or facilitatory effects on cortical excitability and these modulatory effects are dependent on stimulation frequency

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[23]. High-frequency rTMS produces a local increase in cortical excitability in contrast to low-frequency rTMS which produces the opposite effect [2,3,6]. In clinical applications, meta-analyses support the efficacy of rTMS on motor recovery in patients with stroke [13,18]. Response to rTMS is highly variable between individuals, even among healthy subjects, and previous studies have suggested that the BDNF Val66Met polymorphism may influence short-term synaptic plasticity and incur no after-effects in several rTMS protocols [5,14,16]. In a recent study, the BDNF gene polymorphism negatively influenced the effect of rTMS on motor recovery of the upper extremity in stroke patients [4]. However, no study has examined the possibility of deriving personalized rTMS protocols in stroke patients according to BDNF genotype.

Development of effective rTMS protocols for stroke patients with the BDNF Val66Met polymorphism is especially important for East Asian patients. The effects of low-frequency rTMS on motor cortex excitability are dependent on stimulus intensity [9,17]. However, the influence of high-frequency stimulus intensity is not well known [22]. In this study, we aimed to establish personalized effective stimulus intensities of facilitatory rTMS according to BDNF genotype for stroke patients. We investigated whether the facilitatory effect of 10-Hz rTMS on cortical excitability is influenced by the intensity of rTMS and BDNF genotype.

2. Materials and methods

2.1. Participants

Twenty-two stroke patients (6 females) were enrolled after giving written informed consent. Inclusion criteria were age between 18 and 70 years, onset of stroke more than 6 months prior, presence of hemiparesis caused by stroke, and detectable motor evoked potentials (MEPs) in the affected first dorsal interosseus muscle (FDI). Exclusion criteria were a history of seizure, any metal components of the intracranial portion, accompanying neurological or psychiatric disorder, or any terminal illness. These methods were approved by the Samsung Medical Center Institutional Review Board (20110014021).

2.2. Experimental design

All patients underwent three different sessions of rTMS over the ipsilesional M1 in randomized order with a washout period exceeding 24 h: first condition, 10 Hz high-frequency rTMS with sub-threshold intensity (90% of the resting motor threshold (rMT)); second condition, 10-Hz high-frequency rTMS with suprathreshold intensity (110% of rMT); third condition, sham rTMS. Cortical excitability with MEPs was assessed before and after stimulation in each condition.

2.3. Cortical excitability measurement

MEPs were assessed using a single magnetic stimulation at 120% of rMT over the ipsilesional M1 using a 70 mm figure-of-eight coil. During the interventions, patients were seated comfortably in an armchair with their eyes open. A Synergy electromyography/evoked potentials system (Medelec, Kingswood, Bristol, UK) was used for recording and monitoring the activity of the contralateral FDI muscle. Single-pulse transcranial magnetic stimulation (TMS) was applied over the ipsilesional M1 with a Magstim Rapid2® stimulator (Magstim, Spring Gardens, Wales, UK). The coil was held tangentially to the scalp, with the handle pointing backward and laterally at 45° from the mid-sagittal line. Using TMS, the optimum position ("hot spot") was defined as the site where TMS induced MEPs of maximum peak-to-peak amplitude in the contralesional FDI muscle. The hot spot was marked with a skin pen to ensure that the coil was held in the correct position throughout the experiment. rMT was defined as the lowest stimulus intensity able to evoke MEPs of at least 50 μV peak-to-peak amplitude in five out of 10 consecutive trials. Five sweeps of the MEPs at 120% of the rMT were collected and the mean amplitude and latency of the MEPs were calculated [25]. All MEP assessments were independently performed by a rater blinded to the rTMS condition.

2.4. rTMS interventions

rTMS was delivered on the scalp over the ipsilesional M1 in accordance with safety recommendations [29] using a figure-of-eight shaped coil connected to a Magstim Rapid® stimulator with two Booster Modules (Magstim, Spring Gardens, Wales, UK). The coil was held tangentially to the scalp with the handle pointing backward and laterally at 45° from the mid-sagittal line to stimulate the motor cortex. Three conditions of rTMS composed of 20 trains of rTMS of 5 s stimulation and 55 s intertrain interval during the 20 min. Sham rTMS was performed with the coil held at an angle of 90° to the scalp using the same stimulation parameters (noise, time, frequency) as with real sub-threshold rTMS [15]. After rTMS, we assessed each participant for known side effects of rTMS [29].

2.5. BDNF genotyping technique

Blood samples from each patient were genotyped for the BDNF Val66Met polymorphism. Whole blood was collected into EDTA tubes and DNA was extracted using standard procedures. Polymerase chain reaction (PCR) amplifications were set up with the following oligonucleotide primers. Amplification reactions were performed in a total volume of 50 μl, containing approximately 50 ng of genomic template, 2.5 mM deoxyribonucleotide triphosphate (dNTP) mixture 4 μl, 5 units of Taq olymerase 0.25 μl, 10× Taq buffer (20 mM Tris–HCl pH 8.0, 20 mM MgCl2, 100 mM KCl) 5 μl, and each of the primers (10 pmol/μl). The PCR cycling conditions consisted of an initial denaturation for 5 min at 94 °C, followed by 33 cycles of 94 °C for 30 s, 60 °C for 30 s, and 72 °C for 30 s, and a final extension at 72 °C for 5 min. PCR success was assessed using 2% agarose gel electrophoresis. The PCR product was digested with the restriction enzyme *pmlI*. In the presence of the G allele (Val), *pmlI* digestion produced two products of 180 and 120 bp, whereas, the A allele (Met) was not digested and produced no products. All patients were successfully genotyped [5]. BDNF genotyping was performed after completing all three different conditions of rTMS. Patients were classified into the Val/Val group and Met allele group according to BDNF genotype.

2.6. Statistical analysis

SPSS version 21.0 (SPSS, Chicago, IL, USA) was used for statistical analyses. We compared the values in both groups according to BDNF genotype. The increment ratio of amplitude of MEPs was defined as: (post-stimulation amplitude of MEPs – pre-stimulation amplitude of MEPs)/pre-stimulation amplitude of MEPs. The Kolmogorov–Smirnov test was used for all continuous variables to determine whether or not the distribution was normal, and the results showed no normal distributions ($p < 0.05$). The Kruskal–Wallis test was used to compare differences among the conditions in each group. Post hoc analysis was performed using the Mann–Whitney test with Bonferroni's correction. The Wilcoxon signed rank test was used to compare the difference between pre- and post-stimulation in each condition. The Mann–Whitney test and Chi-square test were used to compare the general characteristics or values between the two groups. Differences were regarded as significant when the p-value was < 0.05.

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