Brain Stimulation 7 (2014) 553–558

Contents lists available at ScienceDirect

Brain Stimulation

journal homepage: www.brainstimjrnl.com

BDNF Polymorphism and Differential rTMS Effects on Motor Recovery of Stroke Patients

Won Hyuk Chang [a], Oh Young Bang [b], Yong-Il Shin [c], Ahee Lee [e], Alvaro Pascual-Leone [d], Yun-Hee Kim [a,e,*]

[a] Department of Physical and Rehabilitation Medicine, Center for Prevention and Rehabilitation, Heart Vascular and Stroke Institute, Samsung Medical Center, Sungkyunkwan University School of Medicine, Korea
[b] Department of Neurology, Samsung Medical Center, Sungkyunkwan University School of Medicine, Korea
[c] Department of Rehabilitation Medicine, Pusan National University College of Medicine, Pusan National University Yangsan Hospital, Pusan, Korea
[d] Berenson-Allen Center for Noninvasive Brain Stimulation, Department of Neurology, Harvard Medical School and Beth Israel Deaconess Medical Center, 330 Brookline Avenue, Kirstein Building, Room KS158, Boston, MA 02215, USA
[e] Samsung Advanced Institute for Health Science and Technology, Sungkyunkwan University School of Medicine, Seoul, Korea

ARTICLE INFO

Article history:
Received 17 December 2013
Received in revised form
16 March 2014
Accepted 18 March 2014
Available online 21 April 2014

Keywords:
Stroke
Motor recovery
rTMS
BDNF
Single nucleotide polymorphism

ABSTRACT

Background: The brain-derived neurotrophic factor (BDNF) gene often shows a single nucleotide polymorphism that is thought to influence synaptic plasticity. It also affects the modulatory effects of repetitive transcranial magnetic stimulation (rTMS) on motor cortex excitability.
Objective: This study investigated whether BDNF polymorphism influences the effect of rTMS on the motor recovery of patients with stroke.
Methods: Forty-four patients (mean age 53.8 years) experiencing unilateral motor weakness after stroke were recruited. rTMS was applied over the primary motor cortex of the affected hemisphere at 10 Hz with 1000 pulses/day for 10 days. Each patient's motor functions were assessed using the Fugl-Meyer assessment (FMA) and the box and block test (BBT) before, immediately after and 2 months after the intervention. BDNF genotyping was performed via PCR assays of whole blood samples. The patients' data were grouped and analysed into Val/Val and Met allele groups according to the presence or absence of the BDNF polymorphism.
Results: Nine patients (20.5%) were classified into the Val/Val group, and thirty-seven patients (79.5%) were classified into the Met allele group. The patients' baseline motor functions did not differ between the two groups. The FMA and BBT scores showed significant improvement immediately after and 2 months after rTMS in both groups. In addition, the time and groups were found to interact significantly, with the Val/Val group improving to a greater extent than the Met allele group in terms of their FMA and BBT scores.
Conclusions: The findings suggest that the BDNF gene polymorphism negatively influences the effect of rTMS on the motor recovery of upper extremities in stroke patients.

Contributorship statement: I (Y–H Kim) contributed to the study concepts and design, interpretation of the results, manuscript editing, and approval of final version of submitted manuscript. Dr. Chang contributed to the design of the study, operationalizing the experimental procedure, data acquisition and analysis, and manuscript drafting. Dr. Bang contributed to patient selection and assessment, manuscript editing. Dr. Shin contributed to patient selection and manuscript editing. Dr. Lee contributed to patient assessment and data collection. Dr. Pascual-Leone contributed to study concept development, interpretation of the results, and manuscript editing.

Acknowledgments and sources of funding: This research was supported by the Samsung Medical Center Clinical Research Development Program (#CRDP CRS-110-05-1), the Samsung Biomedical Research Institute (#SBRI C-B0-214), a grant from the National Research Foundation of Korea (No. 2011–0016960) and a KOSEF grant (M10644000022-06N4400-02210). APL was supported in part by Harvard Catalyst, the Harvard Clinical and Translational Science Center (the National Center for Research Resources, the National Center for Advancing Translational Sciences, National Institutes of Health Award 8UL1TR000170-05 and financial contributions from Harvard University and its affiliated academic health care centres). The content is solely the responsibility of the authors and does not necessarily represent the official views of Harvard Catalyst at Harvard University, its affiliated academic health care centres or the National Institutes of Health.

Financial disclosures: The authors state that there are no conflicts of interest to declare.

* Corresponding author. Department of Physical Medicine and Rehabilitation, Heart Vascular and Stroke Institute, Samsung Medical Center, Samsung Advanced Institute of Health Science and Technology, Sungkyunkwan University School of Medicine, 50 Irwon-dong, Gangnam-gu, Seoul, 135-710, Korea. Tel.: +82 2 3410 2824, 2818; fax: +82 2 3410 0388.
E-mail addresses: yunkim@skku.edu, yun1225.kim@samsung.com, yunkim1225@empal.com (Y.-H. Kim).

1935-861X/$ – see front matter © 2014 Elsevier Inc. All rights reserved.
http://dx.doi.org/10.1016/j.brs.2014.03.008

Introduction

Repeated transcranial magnetic stimulation (rTMS) reportedly has a beneficial effect on the motor functions of patients with stroke [1–3]. In a previous study, it was found that a single session of 10 Hz rTMS facilitated practice-dependent plasticity and improved motor learning in patients with chronic stroke [4]. In addition, consecutive multi-session rTMS applied during the subacute period of stroke has had positive long-term effects on motor recovery [5–7]. However, even among healthy patients, the inter-individual response to rTMS is highly variable [8], and a number of factors contribute to this variability, such as the patient's age [9], the time of day [10] and the patient's menstrual cycle [11].

Brain-derived neurotrophic factor (BDNF) is a member of the neurotrophin family of growth factors and plays a major role in neuronal survival, synaptic plasticity and learning and memory [12]. A single nucleotide polymorphism (SNP) of the BDNF gene significantly impairs the intracellular trafficking and activity-dependent release of the BDNF [13,14]. Considering that one of the possible mechanisms of rTMS in facilitating motor function is the promotion of plastic changes in synaptic efficacy [8], BDNF polymorphism may affect the synaptic plasticity induced by rTMS in the human brain. Consistent with such notions, a previous study reported decreased or absent after-effects of theta burst stimulations in healthy patients carrying the Met allele of the BDNF gene [15]. However, no reports have considered the influence of BDNF polymorphism on the rTMS effects in stroke patients. Thus, this study investigated whether BDNF polymorphism significantly influences the beneficial effects of rTMS on the motor functions and recovery of patients with stroke.

Materials and methods

Study patients

Subacute stroke patients with unilateral motor weakness were recruited according to the following inclusion criteria: (1) had suffered their first-ever stroke, whether ischemic or hemorrhagic; (2) were within a post-stroke onset time of less than 2 weeks; and (3) had suffered moderate to severe motor impairment in their affected upper extremities (an upper limb score of less than 40 according to the Fugl-Meyer assessment (FMA-UL)) [16]. Patients were excluded if they had (1) suffered any clinically significant or unstable medical disorder, (2) experienced any neuropsychiatric comorbidity, (3) suffered direct injury to the primary motor cortex, (4) suffered complete internal carotid artery occlusion, (5) a history of seizure disorder or post-stroke seizure or (6) an intracranial metallic implant.

Forty-seven stroke patients with hemiparesis were recruited in accordance with these inclusion criteria. Three patients dropped out during the experimental procedure for various personal reasons, leaving forty-four patients in the final analysis (Fig. 1A). The study protocol was approved by the Institutional Review Board of Samsung Medical Center (CRS110051), and written informed consent was obtained from all of the patients.

Experimental design

The study was designed as a parallel-group double-blind clinical analysis. The patients' motor functions were assessed prior to (Pre-rTMS), immediately after (Post-rTMS) and 2 months after (Follow-up) rTMS intervention (Fig. 1B).

Motor cortex mapping for determining the resting motor threshold

To determine the optimal scalp location and rTMS intensity, single-pulse TMS was administered to each patient using a TMS system (Magstim Rapid2® stimulator, Magstim Ltd., UK) and a 70 mm figure-eight coil before the 10-day rTMS intervention and according to our previously reported protocol [7]. Once a hotspot was identified, a single-pulse stimulus was delivered to the site to determine the resting motor threshold (RMT), defined as the lowest stimulus intensity necessary to produce motor-evoked potentials (MEPs) of a peak-to-peak amplitude $\geq$ 50 μV in 5 of 10 subsequent trials.

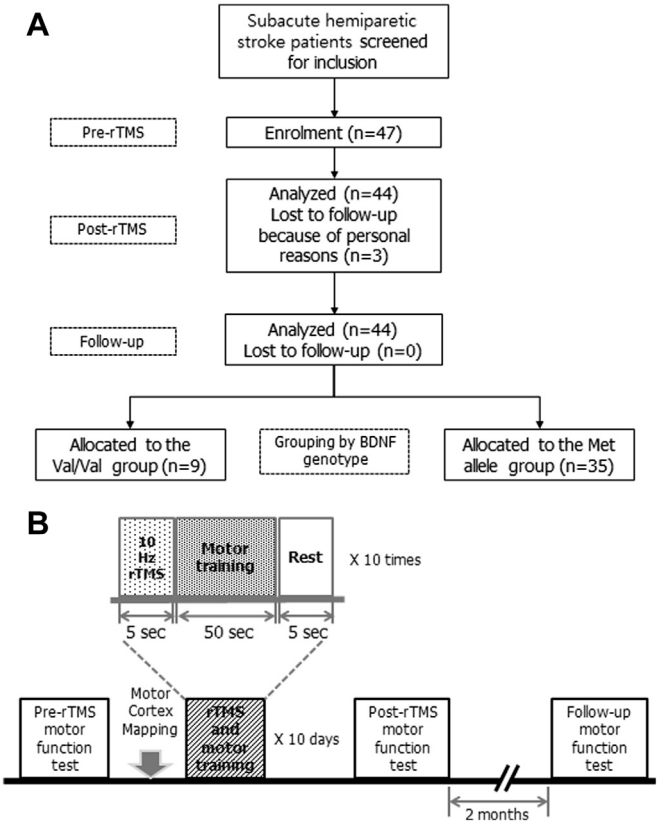

Figure 1. Experimental design. (A) Study flow chart. (B) rTMS and motor training paradigm.

Repetitive transcranial magnetic stimulation

Over a 2-week period, the patients underwent 10 sessions of rTMS to the primary motor cortex of the affected hemisphere. A Magstim Rapid2® stimulator with two booster modules was used to administer the therapeutic rTMS. Fifty trains were applied at 10 Hz for 5 s, and the coil over the target motor cortex area was applied at 90% RMT in correspondence with the paretic hand. For patients with no apparent MEPs on the affected hemisphere, the hotspot and intensity were determined using the mirror image of the unaffected hemisphere [7]. One thousand pulses were delivered with a 55 s inter-train interval consisting of 50 s of motor training and 5 s of rest. The motor cortex was stimulated by holding the figure-eight coil tangentially to the skull at an approximate 45° angle to the midsagittal plane with the handle pointing posteriorly. The rTMS protocols used in the study followed those used in previous reports [4,7,17] and rTMS application safety guidelines [18]. The motor practice consisted of 50 s of reaching and grasping exercises, which were conducted after each rTMS train by the same licensed physical therapist, who did not participate in the patients' function evaluations. The motor training protocol included active and active-assistive ranges of motion exercise of the affected