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ORIGINAL ARTICLE

Corticospinal excitability in the non-dominant hand is affected by BDNF genotype

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Abstract The objective of this study was to assess the functional state of corticospinal projections in the non-dominant hand according to brain-derived neurotrophic factor (BDNF) Val66Met polymorphisms. We investigated this in 34 healthy right-handed individuals (12 men, mean age 27.4 ± 3.4 years) who underwent two experimental sessions consisting of corticospinal excitability measurements with single-pulse transcranial magnetic stimulation (TMS) and hand motor function assessments with a sequential finger motor task of the non-dominant hand. Experimental sessions were separated by periods of at least 2 days to avoid carryover effects. Data were analyzed according to BDNF polymorphism (Val/Val vs. Val/Met vs. Met/Met group). Ten (29.4%), seventeen (50.0%), and seven (20.6%) participants were allocated to the Val/Val, Val/Met, and Met/Met groups, respectively. Motor thresholds to TMS did not differ among groups, but the amplitude of the motor-evoked potentials in the non-dominant hand induced by suprathreshold (120% of MT) TMS was significantly lower in the Met/Met group than in the other two groups ($p < 0.05$). Movement accuracy and reaction time in the sequential finger motor task showed no significant differences among groups. These results indicate that Met/Met BDNF homozygote status affects corticospinal excitability, and should be controlled for in studies of motor system function using brain stimulation. Our findings may have clinical implications regarding further investigation of the impact of BDNF genotype on the human motor system.

Keywords BDNF · Polymorphism · Transcranial magnetic stimulation · Corticospinal excitability

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Introduction

Genetic factors can impact the structure and function of the corticospinal system in three different contexts: development, neurodegeneration and aging, and learning and skill acquisition [1]. The regional expression of relevant gene products depends on movement-related activity within the maturing corticospinal circuits. This explains why motor experience and genetic factors interact during the maturation of the corticospinal system and the differentiation of motor representations subserving skilled limb movements [2].

Brain-derived neurotrophic factor (BDNF) is the most abundant neurotrophin in the brain and is highly expressed throughout the central nervous system. BDNF is also the most important mediator of synaptic efficacy, neuronal

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connectivity, and use-dependent plasticity [3]. A single nucleotide polymorphism has been identified in the human BDNF gene at codon 66 (Val66Met), and this replacement of Val66 with Met66 has been reported to disrupt cellular processing, trafficking, and the activity-dependent secretion of BDNF [4]. The BDNF Val66Met polymorphism impairs activity-dependent release of this growth factor, affects human brain motor system function and short-term motor system plasticity measured by fMRI, and is associated with errors in short-term learning as well as poorer retention [5–7]. Therefore, BDNF Val66Met polymorphisms may influence the functional state of corticospinal projections in a healthy population.

The functional state of corticospinal projections can be assessed by measuring the motor-evoked potentials (MEPs) elicited by transcranial magnetic stimulation (TMS) of the primary motor cortex [8]. This study was conducted to assess the functional state of corticospinal projections in the non-dominant hand according to BDNF Val66Met polymorphisms.

Materials and methods

Participants

Thirty-four young healthy volunteers (12 men, mean age 27.4 ± 3.4 years) were recruited from bulletin board advertisements and posters with institutional review board approval. All participants were Korean. Inclusion criteria were age (20–35 years), the absence of neurological and psychiatric diagnoses, and right handedness indicated by scores greater than 80 on the Edinburgh Handedness Inventory [9]. None of the participants had epilepsy, chronic illnesses, metallic intra-cranial implants, or any other contraindications or risk factors for TMS [10]. Our methods were approved by the Samsung Medical Center Institutional Review Board and this study conformed to the 2013 World Medical Association Declaration of Helsinki. All participants provided written informed consent prior to recruitment.

Experimental design

Each participant made three visits to the test facility, including one practice session and two experimental sessions; all sessions occurred at the same time of day. The participant began the experiment by practicing hand motor function assessments. Each experimental session included corticospinal excitability measurements and hand motor function assessments. Hand function assessments were conducted immediately after TMS measures. Experimental sessions were separated by periods of at least 2 days to avoid carryover effects.

Corticospinal excitability measurement

MEPs were evoked by single pulses of TMS at 120% of the resting motor threshold intensity (rMT) over the right (non-dominant) M1 using a 70-mm figure-of-eight coil. Participants sat comfortably in an armchair during experiments with their eyes open. A Synergy electromyography/evoked potentials system (Medelec Co., Ltd, Kingswood, Bristol, UK) was used to record and monitor the activity of the left (contralateral) first dorsal inter-osseus (FDI) muscle. Active and reference Ag/AgCl surface electrodes were attached to the skin overlying the belly of the FDI muscle and the metacarpophalangeal joint, respectively. A ground electrode was placed over either the ulnar styloid process or the ipsilateral forearm. EMG signals were filtered (20–2000 Hz), amplified, displayed, and stored for offline analysis. Relaxation of the measured muscle was controlled by continuous visual EMG monitoring. For single-pulse TMS, monophasic pulses with a posterior–anterior direction were delivered by a Magstim BiStim^2 (Magstim Co. Ltd, Spring Gardens, Whitland, Carmarthenshire, Wales, UK) equipped with a 70-mm figure-of-eight coil. The coil was held tangentially to the scalp, with the handle pointing backward and laterally at 45° from the mid-sagittal line. TMS was applied to the optimum scalp position for induction of MEPs in the FDI ("the hot spot") defined as the site where TMS induced MEPs of maximum peak-to-peak amplitude in the contralateral FDI muscle. rMT was defined as the lowest stimulus intensity able to evoke MEPs of at least 50-μV peak-to-peak amplitude in five of ten consecutive trials. Five sweeps of the MEPs at 120% of the rMT were collected, and the amplitude and latency of the MEPs were calculated [11].

Hand motor function assessment

Motor behavior was characterized using a sequential finger motor task that each participant completed using his or her left hand. The task was programmed using the SuperLabPro 2.0 software (Cedrus Co., Phoenix, AZ). Participants were seated comfortably in an upright position facing a computer monitor with the left hand placed palm down on a solid wooden board with five numbered buttons. Each number represented the finger to be used: No. 1 represented the thumb; No. 2, the index finger; No. 3, the middle finger; No. 4, the ring finger; and No. 5, the little finger [12]. A combination of the numbers 1, 2, 3, 4, and 5, in random order was presented in the center of the monitor for 3 s. Participants were asked to tap the corresponding fingers to the numbers that appeared on the screen as accurately and

rapidly as possible using the left hand, and to repeat the sequence over the following 40 s; this procedure is referred to as a task block. All participants were given the opportunity to practice the sequential finger motor task for approximately 15 min on a separate visit prior to any of the experimental sessions. During the experimental session, a total of 200 sequential numbers appeared on the screen during the motor task. Motor performance was assessed in terms of movement accuracy (MA, percent correct) and the reaction time of correct trials (RT) for each session.

BDNF genotyping technique

A sample of each participant's blood was genotyped for the BDNF Val66Met polymorphism. Whole blood was placed into EDTA tubes and DNA was extracted using the 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; five units of Taq polymerase, 0.25 µl; 10 × Taq buffer (20 mM Tris–HCl pH 8.0, 20 mM $MgCl_2$, 100 mM KCl), 5 µl; and each primer (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 was checked for success on 2% agarose gel. PCR product was then digested with the restriction enzyme pmlI. In the presence of the G allele (66Val), pmlI digestion produced two products, 180 and 120 bp, whereas the A allele (Met) was not digested and produced no products [5]. Participants were allocated to the Val/Val, Val/Met, and Met/Met groups according to BDNF genotype.

Data analysis

SPSS version 21.0 was used for statistical analyses. The Shapiro–Wilk test was used to determine the distribution normality of all continuous variables (all were found to be normally distributed; $p > 0.05$). Before comparisons, the test–retest reliability of parameters for the two experimental sessions was determined using intra-class correlation coefficients (ICCs). The mean value of the corticospinal excitability measurement and the hand motor function assessment for two experimental sessions were used for statistical analysis. One-way analysis of variance (ANOVA) for parametric variables and the Chi-square test for non-parametric variables were used for comparisons across the three study groups. For post hoc tests, Tukey's test was performed. Pearson correlation analysis was used to determine the relationship between corticospinal excitability and motor performance measures. Differences were regarded as significant when p values were <0.05.

Results

All participants successfully completed the experimental procedures without any complications or undesirable side-effects. Ten (29.4%), seventeen (50.0%), and seven (20.6%) participants were allocated to the Val/Val, Val/Met, and Met/Met groups, respectively. The Korean population showed a higher prevalence of Met alleles than Western population [13, 14]. These three groups were not significantly different with respect to age, gender, or handedness (Table 1).

Corticospinal excitability measurement

The test–retest reliability for the corticospinal excitability measurements is summarized in Table 2. ICCs demonstrated acceptable levels of test–retest reliability for all three parameters, ranging from 0.698 to 0.962 with narrow confidence intervals.

Figure 1 shows corticospinal excitability measurements for all three groups. One-way ANOVA showed a significant effect of genotype on the mean amplitude of the MEPs ($F_{2,31} = 4.733$, $p = 0.016$). Post hoc tests showed that the mean amplitude of the MEPs was significantly higher in the Val/Val and Val/Met groups than in the Met/Met group ($p = 0.045$, and $p = 0.013$, respectively). However, one-way ANOVA did not demonstrate any significant effect of genotype on the mean rMT or the latency of the MEPs ($F_{2,31} = 1.337$, $p = 0.277$, and $F_{2,31} = 2.758$, $p = 0.079$).

Hand motor function assessment

The test–retest reliability of the hand motor function assessment parameters is shown in Table 2. ICCs demonstrated acceptable levels of test–retest reliability for both parameters ranging from 0.737 to 0.799 with narrow confidence intervals.

Figure 2 shows results for the sequential finger motor task. There was no significant effect of genotype on the movement accuracy or reaction time in the sequential hand motor task (one-way ANOVA $F_{2,31} = 2.245$, $p = 0.123$, and $F_{2,31} = 0.380$, $p = 0.687$, respectively).

However, we did find movement accuracy in the sequential finger motor task to be significantly related to the mean amplitudes of MEPs across all study participants, with a Pearson correlation coefficient of 0.483 ($p < 0.05$, Fig. 3).

Table 1 General characteristics of participants

	Val/Val group ($n = 10$)	Val/Met group ($n = 17$)	Met/Met group ($n = 7$)	p value
Sex (M:F)	5:5	6:11	1:6	0.317
Age (years)	28.6 ± 4.0	27.3 ± 2.4	26.3 ± 4.3	0.362
EHI score	94.0 ± 7.4	93.8 ± 8.6	92.9 ± 3.6	0.958

EHI Edinburgh handedness inventory

Table 2 Inter-rater reliability for parameters analyzed with ICCs

	ICCs	95% CI	p value
Cortical excitability measurement			
Amplitude of the MEPs	0.698	0.396–0.849	<0.001
rMT of the MEPs	0.962	0.924–0.981	<0.001
Latency of the MEPs	0.920	0.840–0.960	<0.001
Hand motor function assessment			
MA of the sequential hand motor task	0.737	0.473–0.868	<0.001
RT of the sequential hand motor task	0.799	0.598–0.900	<0.001

ICC intra-class correlation coefficient, *MEPs* motor-evoked potentials, *rMT* resting motor threshold, *MA* movement accuracy, *RT* reaction time

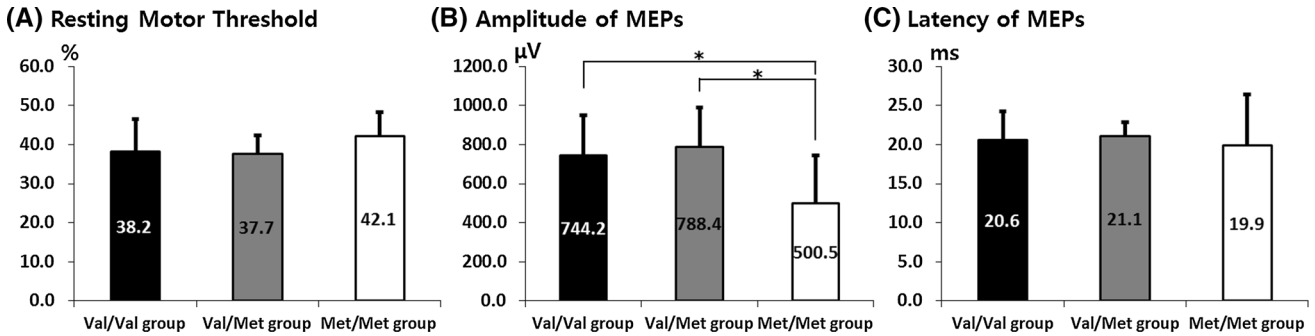
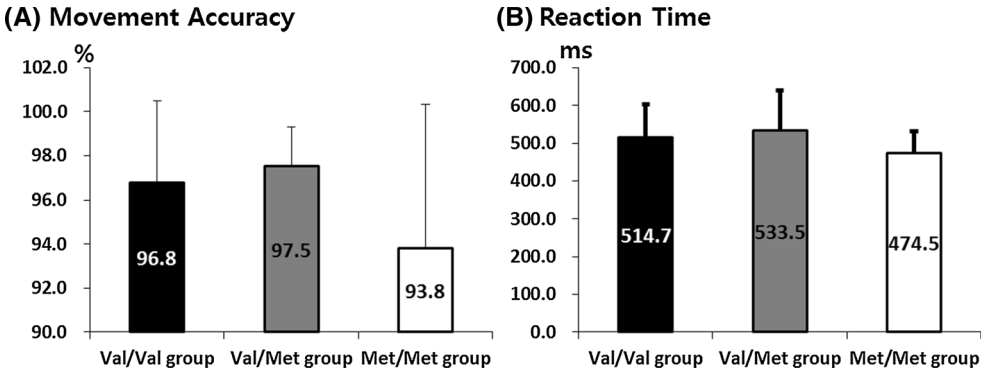


Fig. 1 Corticospinal excitability measurements by group. *MEPs* motor-evoked potentials. *Error bars* represent standard deviation

Fig. 2 Sequential finger motor tasks by group. *Error bars* represent standard deviation



Discussion

This study aimed to characterize the effect of BDNF genotype on corticospinal excitability. We focused on the non-dominant hand as a more sensitive measure, given the overlearned effect of hand dominance. We found that while rMT were not different, the amplitudes of MEPs evoked by TMS at 120% of rMT were significantly larger in Val/Val and Val/Met participants than in Met homozygotes. Therefore, these results might suggest that the consideration of BDNF genotype is needed in studies addressing corticospinal excitability.

Many previous reports [5, 13, 15–18] have not found significant differences of motor cortex excitability

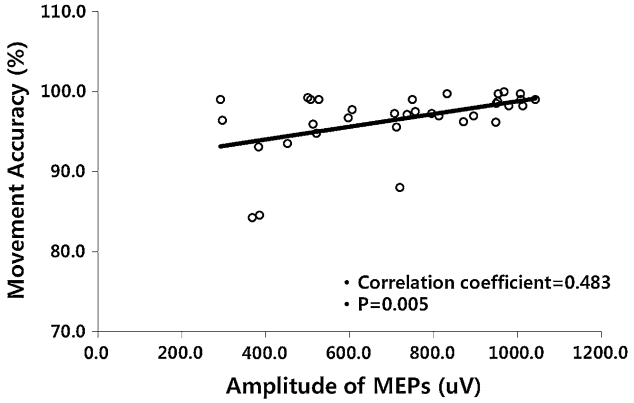


Fig. 3 Correlation between the amplitude of motor-evoked potentials and the movement accuracy of the sequential finger motor task

according to BDNF genotype. However, these studies assessed baseline MEPs of the dominant hand in healthy participants. In addition, the characteristics of MEPs in Met homozygotes were analyzed separately in only one report by Lee et al. [13], while other previous studies only compared motor cortex excitability between Val homozygotes and Met carriers [5, 15–17]. Learning and skill acquisition may be influenced by genetic factors [1]. BDNF polymorphisms have particular impacts not on long-term cortical plasticity, but on short-term cortical plasticity [6]. Training of sufficient intensity and duration can overcome the effect of BDNF polymorphisms on short-term cortical plasticity [6]. A previous report [19] observed associations between handedness and morphological features of human motor system and demonstrated significant hemispheric asymmetry in the corticospinal tract in right-handers that were reduced in left-handers. Right-handers also demonstrated increased inhibitory processing that favored control of the left hemisphere, whereas both motor cortices exhibited equal capability in left-handers [20]. These results reflected the smaller degree of asymmetry in left-handers compared with right-handers at both behavioral and functional levels [21, 22]. Because the baseline non-dominant motor system was investigated in healthy young strong right-handed individuals, this study differed from the previous reports [5, 13, 15–18]. Di Lazzaro et al. [23] reported no differences in baseline MEPs according to BDNF genotype when the right hemisphere was probed in a sample consisting predominantly of right-handers. However, this report did not compare baseline MEPs between Val homozygotes and Met carriers, and only 2 of 29 participants were Met homozygotes. In this study, there was no significant difference in MEPs between Val/Val and Val/Met groups. Therefore, the proportion of Met homozygotes in this study could have led to the variation in results between it and the previous report [23].

In this study, we found no significant difference among the three groups in the performance of the motor sequence task, despite the significant relationship between corticospinal excitability and hand motor function. The change in corticospinal excitability measured by MEP amplitude was positively associated with enhanced motor performance accuracy in stroke patients [24]. However, no previous reports have documented the relationship between corticospinal excitability and motor function in a healthy population. Further studies with larger samples will be needed to investigate behavioral motor function according to BDNF genotype.

A few previous studies reported the influence of double copies of BDNF polymorphisms with rare Met homozygotes (Met/Met) [4, 25]. In assessments of episodic memory, Met homozygotes exhibited lower scores compared with the other two genotype groups [4]. In addition, Met homozygotes showed no changes after paired associative stimulation and a reduction in MEPs after complex visuomotor tracking compared with the other two genotype groups [25]. Population differences in BDNF Val66Met polymorphism frequencies have been identified in the previous reports [26]. The proportion of Met homozygotes was only 3.4% in a sample of European descent, but was 23.4% in an East Asian sample [14]. In this study of Koreans, 20.6% of participants were Met homozygotes. The influence of BDNF Met homozygotes will, therefore, have greater impact in the Asian population.

A unilateral assessment of baseline corticospinal excitability in the non-dominant hand does not provide information about the influence of the BDNF genotype on baseline corticospinal excitability in the dominant hand. Although the previous studies have addressed the latter question, we did not compare the characteristics of baseline corticospinal excitability between the dominant and non-dominant hand in this study. There was variability in the amplitude of MEPs within and between subjects [27]. In addition, a number of factors have already been described that contribute to this variability, such as the menstrual cycle [28], subjects' age [29], and the time of day [30]. We could not control all of these influencing factors in this study. It has been suggested that neuronavigation might increase the consistency of MEPs [31]. The neuronavigation system could yield more accurate results in this study. Although all parameters in this study represented the mean of two different experimental sessions to reduce this variability, the relatively small number of TMS pulses without the neuronavigation system used to obtain MEPs was one of limitations of this study. We also did not measure intracortical circuits of the motor cortex using paired-pulse TMS [32]. These are limitations of this study. There were only seven Met/Met participants, because the sample size of this study was relatively small. Although the inclusion

criteria in this study were narrow, the small size of the study population could act as a potential statistical bias, which is one of limitations of this study. To explore these limitations, further studies will be needed.

Conclusions

In summary, we found that BDNF genotype, especially Met homozygotes, might influence the human motor system. Our findings may have clinical implications regarding further investigation of the impact of BDNF genotype on the human motor system.

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Compliance with ethical standards

Conflict of interest Dr. A. Pascual-Leone serves on the scientific advisory boards for Nexstim, Neuronix, Starlab Neuroscience, Neuroelectrics, Axilum Robotics, Magstim Inc., and Neosync; and is listed as an inventor on several issued and pending patents on the real-time integration of transcranial magnetic stimulation with electroencephalography and magnetic resonance imaging. The other authors have no conflicts of interest to declare. The authors declare no competing interests.

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