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BDNF Val^{66}Met Polymorphism Is Related to Motor System Function After Stroke

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Abstract

Background

The val^{66}met polymorphism in brain-derived neurotrophic factor (BDNF) has been associated with poorer outcomes after stroke. The mechanism for this finding remains uncertain but might be related to the reduced motor system activation associated with this polymorphism in healthy people.

Objective

The current study examined whether the presence of the BDNF val^{66}met polymorphism is associated with reduced motor system activation after stroke.

Design and Methods

Forty-two patients with stroke who were enrolled in 1 of 2 studies of robot-assisted arm motor therapy participated in the study. All participants were tested for the BDNF val^{66}met polymorphism followed by functional magnetic resonance imaging during affected hand movement.

Results

Participants averaged 12 months poststroke and had wide-ranging motor deficits (Fugl-Meyer scale scores=14–60). Brain activation in participants without the BDNF val^{66}met polymorphism (n=26) spanned bilateral motor networks with a larger volume (total=334 cc) than that found in participants with this polymorphism (n=16) (97 cc). Regional analyses were consistent. Participants without this polymorphism showed larger ipsilesional primary sensorimotor cortex activation volume and magnitude compared with those in whom the polymorphism was present.

Limitations

The extent to which these findings generalize to other populations of people with stroke, such as those with stroke <7 days prior, remains uncertain.

Conclusions

Functional magnetic resonance imaging during affected hand movement showed decreased brain activation among participants with the BDNF val^{66}met polymorphism compared with those lacking this polymorphism, especially in the ipsilesional primary sensorimotor cortex contralateral to movement. These results echo findings in healthy people and suggest that genetic factors affecting the normal brain continue to be operative after stroke. The findings suggest a potential imaging-based endophenotype for the BDNF val^{66}met polymorphism's effect on the motor system that may be useful in a clinical trial setting.

Many interventions are under development to promote neural repair and improve behavioral outcomes after stroke, including growth factors, cellular therapies, small molecules, activity-based interventions, robotics, telerehabilitation, and electromagnetic devices.[1,2] A major limiting factor for restorative therapies, as with many interventions targeting patients with stroke, is the enormous heterogeneity of this population. A better understanding of the key factors behind such variability may be useful for identifying effective restorative therapies (eg, by generating improved methods for patient stratification, which would reduce variance and thereby increase study power).[3]

The basis for intersubject variability in spontaneous and treatment-induced behavioral recovery remains incompletely understood. A large number of molecular events contribute to the neural plasticity underlying behavioral recovery.[4,5] Direct measurement of the cellular events within the brain of a human patient recovering from stroke is rarely feasible. However, the study of genetic differences may provide a window for studying the molecular events underlying neural plasticity in humans.[6,7] One strategy in this regard is to define valid endophenotypes. An endophenotype can be defined as a measurement (eg, behavioral, imaging, biochemical) that is tightly linked to a particular genotype and is useful for distinguishing biological subgroups that look the same behaviorally.[8] An endophenotype is thus a component of a complex phenotype that is more directly related to the underlying genotype.[9] Examples include extent of obsessive compulsive symptoms in relation to autism spectrum disorder subgroups[10] and increased premotor cortex activation during motor-related functional magnetic resonance imaging (fMRI) in relation to selected Parkinson disease–related genotypes.[11] An endophenotype might be useful for understanding a biological system, defining treatment mechanisms, predicting risk of a particular outcome, or serving as an entry criterion in a clinical trial to help reduce enrollee heterogeneity.

Brain-derived neurotrophic factor (BDNF) is the most abundant neurotrophin in the brain and is important to many forms of learning and plasticity, including in the setting of neurological disease.[12] After stroke, BDNF levels increase, affecting neuronal survival, differentiation, and use-dependent plasticity.[13–15] A common single nucleotide polymorphism (SNP) for BDNF (BDNF val^{66}met polymorphism, also known as rs6265) has been identified at nucleotide 196, in which adenine is substituted for guanine, resulting in a single amino acid substitution at codon 66 (valine to methionine). This polymorphism is present in one or both alleles in approximately 30% of people in the United States,[16] and its frequency of occurrence may be higher elsewhere in the world (Tab. 1). An SNP is the most common type of genetic variation in humans, representing a change in a single nucleotide. Single nucleotide polymorphisms are common (approximately 1 in 300 nucleotides) and may result in an amino acid substitution[17] (as is the case for the BDNF val^{66}met SNP) or an alteration in mRNA stability.[18] Most often, an SNP has no discernible effect, although an otherwise silent SNP may affect a system when exposed to a challenge.[19] The BDNF val^{66}met polymorphism results in 18% to 30% less activity-dependent secretion of the BDNF protein.[17] Val^{66}met BDNF polymorphism has been associated with decreased learning and activity-related cortical plasticity in

healthy individuals[20–23] and slower or reduced behavioral recovery from stroke.[24–28] However, there has been limited study of the effects of this polymorphism on brain function in patients with stroke.

The current study aimed to better understand how variation in the gene for BDNF is related to the function of brain motor systems after stroke. Functional MRI was used to study a cohort of patients with residual arm weakness in the chronic phase poststroke. The primary hypothesis tested in the current study was that, as in a prior study of healthy individuals,[22] the presence of the BDNF val^{66}met polymorphism is associated with reduced brain activation during unilateral hand movement.

Method

Participants

The current analysis is of all patients who were enrolled in 1 of 2 studies of robot-assisted arm motor therapy.[29,30] Entry criteria included age >18 years, stroke ≥11 weeks prior, stable arm motor deficits (Fugl-Meyer scale [FM] score <60/66[31] or Action Research Arm Test score <52/57[32]) with preserved active range of motion of ≥5 degrees in the more affected index finger or wrist, stable examination (2 FM assessments taken 1–3 weeks apart could not vary by >3 points), and no contraindication to MRI. All participants provided written informed consent using procedures approved by the University of California, Irvine Institutional Review Board.

Study Design

Patient evaluation included the following measures: National Institutes of Health Stroke Scale (NIHSS),[33] Geriatric Depression Scale–short form,[34] Nottingham Sensory Assessment,[35] and the arm motor FM scale.[31] Patients returned 1 to 3 weeks later, the FM score was repeated, a blood sample was collected for genetic testing, and MRI data were obtained. Study therapy began <2 weeks later, during which all participants received 24 hours of robotic therapy over a 2- to 3-week period. Therapy consisted of repeated grasp-release movements of the affected hand and wrist using a pneumatically actuated robotic device that has been described previously.[29,36] The FM score was reassessed 1 month after end of therapy. All behavioral assessments were performed by a single rater.

Genotyping

Each participant's blood sample was genotyped for the BDNF val^{66}met polymorphism, as described previously.[22]

MRI Data Acquisition

Data were acquired using a Philips Achieva 3.0 T scanner (Philips Healthcare, Andover, Massachusetts). The participants' heads were restrained with a strap with padding placed on both sides to minimize head motion. Participants wore a plastic splint on the more affected forearm to help guide hand and wrist movements. Anatomical imaging included high-resolution T1-weighted images (3-dimensional MP-RAGE sequence, slice thickness=1 mm) and T2-fluid-attenuated inversion-recovery (FLAIR) images (slice thickness=4 mm). Three runs of blood oxygenation level–dependent (BOLD) images for fMRI (repetition time=2,000 milliseconds, echo time=30 milliseconds, 31 slices with 4-mm thickness and 1-mm interslice gap) were acquired. Each fMRI run had 48 brain volumes over 96 seconds, during which participants viewed a video that guided the stroke-affected hand and wrist to alternate between 24 seconds of 0.125-Hz grasp-release movements and 24 seconds of rest. An investigator observed movements during scanning to ensure adherence.

Data Analysis

Image preprocessing was performed blinded to genetic and clinical data. The fMRI data were analyzed using Statistical Parametric Mapping (SPM8, Wellcome Trust Center for Neuroimaging at UCL, London, United Kingdom). Each volume was realigned to the first volume, after which each participant's anatomical and fMRI data were coregistered and then spatially normalized into Montreal Neurological Institute (MNI) stereotaxic space. The fMRI data were then spatially smoothed (full width at half maximum=8 mm) and high-pass filtered. Statistical analyses were carried out using a general linear model and a standard hemodynamic response function, contrasting images acquired during rest with images acquired during movement. Data were visually inspected for artifact, and those with excessive head movement were removed. Images were flipped along the midline for participants with infarct on the right.

Brain activation was first characterized for each of the 2 genotype groups (BDNF val^{66}met polymorphism absent and BDNF val^{66}met polymorphism present) using separate 1-sample *t* tests. The 2 genotype groups were then directly contrasted using a 2-sample *t* test. Statistical testing used random effects methods, with significance set at $P<.001$ uncorrected for multiple comparisons and ethnicity included as a covariate.

Regional analyses also were performed on each participant's activation map. Two motor system regions of interest (hand area of primary sensorimotor cortex and dorsal premotor cortex) were generated on each brain side using a 12-mm-diameter sphere centered at coordinates derived from a meta-analysis of prior motor activation studies.[37] Activation volume and activation magnitude (% signal change) were then extracted from each region of interest.

Statistical analysis (JMP 8.0.2, SAS Institute Inc, Cary, North Carolina) used 2-tailed testing with alpha=.05. Parametric statistics were used, as all data were normally distributed or could be transformed to a normal distribution, except for the NIHSS, for which nonparametric statistical testing (Wilcoxon rank sum test) was used. Given the exploratory nature of this investigation, no correction was made for multiple comparisons. All analyses controlled for ethnicity.

Role of the Funding Source

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Results

Of the 48 patients with stroke studied, 6 had excessive head motion during scanning and were removed from further analysis, leaving 42 participants, who are the focus of this report. Overall, participants had wide-ranging motor deficits (mean FM score=37, standard error of the mean [SEM]=2, range=14–60) and neural injury (mean infarct volume=59 cc, SEM=14, range=0.5–361) and were a mean of 12 months poststroke (SD=3, range=3–124). Of these 42 participants, 26 lacked the BDNF val^{66}met polymorphism and 16 had the polymorphism (13 with a single copy and 3 with 2 copies). The polymorphism was in Hardy-Weinberg equilibrium. Clinical and radiological characteristics are presented in Table 2 and did not differ between the 2 genotype groups except for ethnicity, where presence of the polymorphism was associated with a difference in ethnicity ($P=.055$), driven by a higher proportion of Asian participants having the polymorphism compared with non-Asian participants (70% versus 28%, respectively; $P=.027$), as expected.[16]

Functional MRI Analyses

Among the 26 patients with the BDNF val^{66}met polymorphism absent, significant ($P<.001$) activation was present that spanned a large (total=334 cc) area distributed across bilateral motor networks, including peri-Rolandic cortex, supplementary motor area, thalamus, basal ganglia, and cerebellum (Figure, image A). Among the 16 patients with the polymorphism present, the pattern of activation ($P<.001$) was similar overall but much smaller in volume (total=97 cc; Figure, image B). However, these differences did not reach significance when total brain activation was directly compared between the 2 genotype groups, even in a

secondary analysis using a threshold of $P<.01$. Removing the 3 participants having 2 copies of the polymorphism had a negligible effect on the results.

Significant differences between the 2 BDNF val^{66}met genotype groups were found when examining regional metrics of fMRI activation. Participants who lacked the BDNF val^{66}met polymorphism, as compared with patients who had the polymorphism, showed larger ipsilesional primary sensorimotor cortex activation volume ($P=.03$) and ipsilesional primary sensorimotor cortex activation magnitude (% signal change, $P=.037$, Tab. 3). Removing the 3 participants having 2 copies of the polymorphism tended to amplify group differences, with participants who lacked the BDNF val^{66}met polymorphism showing larger ipsilesional primary sensorimotor cortex activation volume ($P=.036$), ipsilesional primary sensorimotor cortex activation magnitude ($P=.01$), and contralesional primary sensorimotor cortex activation magnitude ($P=.056$).

Discussion

The current study examined brain function in relation to BDNF genotype in patients with wide-ranging degrees of hemiparesis after stroke. Functional MRI during affected hand movement showed decreased brain activation among patients with the BDNF val^{66}met polymorphism compared with those lacking this polymorphism, especially in the primary sensorimotor cortex contralateral to movement. These results echo findings in a prior study of healthy individuals[22] and suggest that genetic factors that affect the normal brain continue to be important after stroke. These findings suggest a potential imaging-based endophenotype for the BDNF val^{66}met polymorphism in the motor system, which may be useful in a clinical trial setting.

The current functional imaging results in patients with stroke regarding the influence of the BDNF val^{66}met polymorphism on brain function are consistent with findings in a prior study of healthy individuals.[22] In the current study, total brain activation in patients with the polymorphism absent was 3.4-fold larger compared with those with the polymorphism present, similar to the 2.8-fold difference found in healthy individuals.[22] In patients with stroke, the greatest difference between genotype groups was found in the primary sensorimotor cortex contralateral to hand movements (Tab. 3), also as described in healthy individuals.[22] The absence of correction for multiple comparisons suggests the potential for type I error; however, the convergence of regional activation findings and the similarity with prior findings in healthy people mitigate this concern. The current study design does not permit disentangling of polymorphism effects during the lifetime of activity preceding the stroke[38] from polymorphism effects during the months following the stroke. However, current results do underscore that many principles of brain organization present before a stroke remain in effect after a stroke. The current example pertains to a reduction in brain activation associated with hand movement among people with the BDNF val^{66}met polymorphism, and prior studies have emphasized this finding in relation to hand dominance[39] and somatotopic organization.[40]

The current findings do not indicate that the BDNF val^{66}met polymorphism has a major impact on motor outcomes after stroke; however, the study was likely underpowered to detect such an effect. The BDNF val^{66}met polymorphism has been associated with decreased learning and activity-related cortical plasticity in the motor system of healthy individuals.[20–23] In addition, a number of studies suggest that the BDNF val^{66}met polymorphism may be associated with poorer recovery and functional outcome after stroke. For example, among 105 patients with subarachnoid hemorrhage, those with the BDNF val^{66}met polymorphism present had poorer outcome[24] and in the presence of an infarct performed worse on tests of learning and memory.[25] Among 341 patients with an unruptured arteriovenous malformation undergoing surgery, those with the BDNF val^{66}met polymorphism present had poorer functional outcomes.[27] Across 286 patients with stroke, those with the BDNF val^{66}met polymorphism had poorer functional outcomes at 1 year poststroke.[28] Among 255 patients with stroke enrolled in the Glycine Antagonist In Neuroprotection (GAIN) clinical trials, those with the BDNF val^{66}met polymorphism had poorer recovery of body function and structure

(change in NIHSS score) at 1 month but not 3 months poststroke.[26] In the current study, this polymorphism was not associated with a difference in baseline behavioral status or with treatment-related change in motor status (Tab. 2). This finding may reflect a type II error, as the current study was not sufficiently powered to detect a genotype-related difference across a population of patients with wide-ranging motor deficits after stroke. Regardless, if the BDNF val^{66}met polymorphism is indeed associated with poorer outcomes, it does not suggest nihilism or futility with respect to treatment planning for this patient subgroup but rather that different approaches may be needed to foster optimal recovery in this population.

What is the significance of a polymorphism-related difference in brain function that is not accompanied by a difference in behavioral course? The convergence of findings in analysis of regional activation (Tab. 3) and the strong overlap with findings in healthy people[22] support the validity of the current fMRI results that brain activation differs after stroke in relation to BDNF val^{66}met polymorphism status; furthermore, these effects are not rare in humans and may vary according to ethnicity[16] (Tab. 1). The absence of a behavioral counterpart is reminiscent of studies of the epsilon4 allele of the apolipoprotein E (ApoE) gene.[41] In individuals who are neurologically normal, the presence of the ApoE epsilon4 polymorphism is associated with abnormal activation patterns in memory-related brain regions.[41] Brain mapping provides an endophenotype of polymorphism effects. In the case of the ApoE epsilon4 polymorphism, this endophenotype predicts subsequent memory decline in these individuals.[41] Potentially, the same may be true for the BDNF val^{66}met polymorphism, which one report found to be associated with functional decline during the year following stroke onset.[28] An endophenotype is useful to identify biologically distinct subpopulations.[42] Genetically mediated alterations in brain function are not always manifest at the level of behavior[43] but may be important to understanding treatment response. Imaging measures may serve as endophenotypes and thereby be particularly useful in phase 2 trials of various interventions such as drugs or devices to help define a target population[44,45] or to stratify patients.[3] The current findings suggest that functional imaging, using fMRI or perhaps other techniques,[22,46,47] provides a molecular window into stroke recovery[6] that could potentially inform issues such as patient selection or dose planning.

The results of the current study suggest that genetic factors that affect the healthy brain remain operative after stroke. The effect of the BDNF val^{66}met polymorphism on the motor system in the current cohort of people with hemiparetic stroke is similar to that found previously in healthy people[22] (ie, reduced brain activation, particularly the in primary sensorimotor cortex contralateral to movement). Although this polymorphism has previously been associated with poorer poststroke recovery by several measures, its behavioral significance in the current cohort is uncertain. Further studies might explore whether the current findings represent an endophenotype useful for stratifying patients with stroke in a clinical trial setting. Variance in outcome measures is substantial in many types of rehabilitation trials, including those that use activity-based, robotic, or pharmacological interventions. Increasing evidence suggests that endophenotypes may be useful in defining patient subgroups in a number of disorders.[8,9,11,48] The current results suggest that this approach also may be useful in the setting of stroke rehabilitation.

Footnotes

Dr Cramer provided concept/idea/research design, project management, fund procurement, participants, facilities/equipment, and institutional liaisons. Dr Kim, Mr Gramer, and Dr Cramer provided writing. Dr Quinlan, Mr Gramer, and Dr Cramer provided data collection. All authors provided data analysis. Dr Kim provided consultation (including review of manuscript before submission).

This study was approved by the University of California, Irvine Institutional Review Board.

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Figures and Tables

Table 1.

Variable	Japan	Italy	United States
BDNF allele frequency			
Allele A (met)	41.1%	29.7%	18.0%
Allele G (val)	58.9%	70.3%	82.0%
BDNF genotype			
A/A (met/met)	15.9%	8.1%	4.5%
G/A (val/met)	50.3%	43.2%	27.1%
G/G (val/val)	33.8%	48.7%	68.4%

Allele and Genotype Frequencies for Brain-Derived Neurotrophic Factor (BDNF) Val^{66}Met Polymorphism in 3 Countries[a]

[a]Data are from a meta-analysis by Shimizu et al,[16] who found these ethnic differences across the 3 countries to be significant.

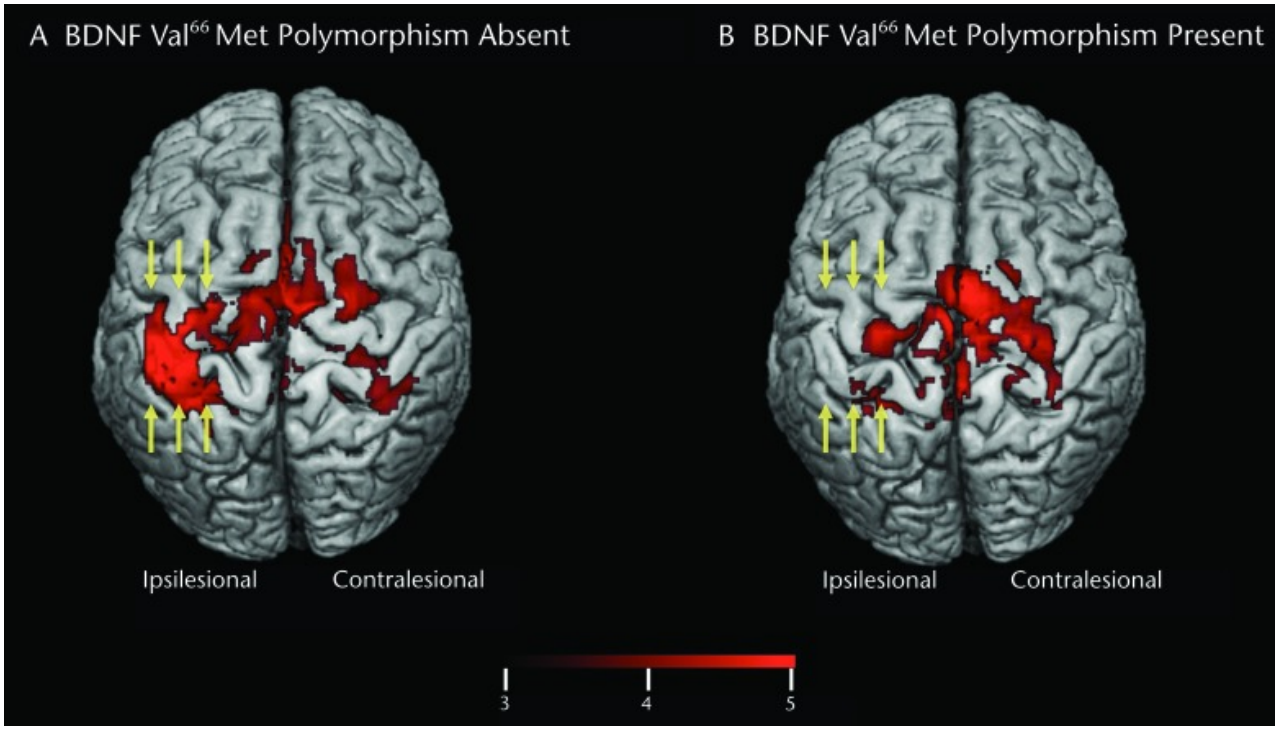
Table 2.

Variable	Polymorphism Absent	Polymorphism Present	*P*
n	26	16	
Age (y)	57.6±3.1	58.5±2.8	.85
Sex (M/F)	17/9	10/6	.85
Diabetes (Y/N)	6/20	3/13	1.00
Hypercholesterolemia (Y/N)	14/12	8/8	.81
Race			.055
Asian	3	7	
Caucasian	15	9	
Hispanic	2	0	
Black	4	0	
Other	2	0	
Time poststroke (mo)	11.9±4.8	13.3±5.0	.43
Side of infarct (L/R)	16/10	10/6	.95
Handedness (L/R)	2/24	0/16	.52
Volume of infarct (cc)	48.1±13.1	78.0±32.2	.79
NIH Stroke Scale	4 (3–5.25)	4 (3.25–5.75)	.97
Geriatric Depression Scale	3.4±0.4	3.3±0.9	.52
Nottingham Sensory Assessment	13.5±0.8	13.2±1.0	.80
FM score	36.4±3.1	37.4±3.5	.84
Treatment-related change in FM score	2.1±0.5	3.2±0.7	.20

Participant Characteristics in Relation to Brain-Derived Neurotrophic Factor Val^{66}Met Polymorphism[a]

[a]Values are mean±standard error of the mean, except for the National Institutes of Health Stroke Scale, for which values are median (interquartile range). Scores on the arm motor Fugl-Meyer scale (FM) reflect moderate-to-severe arm motor deficits (maximum score=66; higher is better). Scores on the Nottingham Sensory Assessment reflect overall mild sensory deficits (maximum score=17; higher is better). Scores on the Geriatric Depression Scale reflect overall mild depression symptoms (higher is worse; scores >10 generally consistent with depression). M=male, F=female, Y=yes, N=no, L=left, R=right.

Figure.



Brain activation in each genotype group, contrasting paretic hand movement with rest. During movement of the paretic hand, larger brain activation (measured using a significance threshold of $P<.001$, which is approximately $Z>3$ in the figure) was seen among (A) the 26 patients with stroke who lacked the brain-derived neurotrophic factor (BDNF) val^{66}met polymorphism compared with (B) the 16 patients with stroke who had the polymorphism. This finding was particularly true in the primary sensorimotor cortex contralateral to the moving hand (indicated by yellow arrows), which, in each case, was the *ipsilesional* primary sensorimotor cortex. The color bar at bottom indicates significance of activation.

Table 3.

Variable	BDNF Val^{66}Met Polymorphism		*P*
	Absent	Present	
% signal change			
Ipsilesional primary sensorimotor cortex	0.88±0.17	0.66±0.20	.037
Contralesional primary sensorimotor cortex	0.21±0.35	0.42±0.14	.17
Ipsilesional dorsal premotor cortex	0.58±0.14	0.41±0.09	.27
Contralesional dorsal premotor cortex	0.61±0.12	0.50±0.09	.41
Activation volume (cc)			
Ipsilesional primary sensorimotor cortex	1.8±0.45	1.23±0.45	.03
Contralesional primary sensorimotor cortex	1.0±0.25	0.94±0.30	.22
Ipsilesional dorsal premotor cortex	1.3±0.27	1.57±0.38	.65
Contralesional dorsal premotor cortex	1.4±0.23	1.51±0.35	.53

Regional Brain Activation During Paretic Hand Movement According to Brain-Derived Neurotrophic Factor (BDNF) Val^{66}Met Polymorphism Status[a]

[a]Values are mean±standard error of the mean.