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The relationship between BDNF Val66Met polymorphism and functional mobility in chronic stroke survivors

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Abstract

Background—A single nucleotide polymorphism, Val66Met, in the Brain Derived Neurotrophic Factor (BDNF) gene has been studied for its role in recovery following stroke. Despite this work, the role of BDNF genotype on long-term recovery is unclear. Additionally, no study has examined its impact on functional mobility. As a result, the purpose of this study was to examine the relationship between BDNF genotype and functional mobility in chronic stroke survivors by first accounting for factors related to the Val66Met polymorphism and post-stroke recovery.

Methods—Participants 6 months post-stroke completed the Fugl-Meyer Lower Extremity Assessment (FMLE), Yesavage Geriatric Depression Scale (YGDS), 10 meter walk test (SSWS), and BDNF genotype testing. A regression model was used to determine if including genotype (Val or Met) and the genotype's interactions with age, gender, and depression increased the model fit in predicting functional mobility, as measured by SSWS, after accounting for physical impairment (FMLE) and personal information (age, gender, and YGDS).

Results—Sixty-three subjects, twenty-two percent of whom had at least one Met allele, were included. Impairment and personal information significantly predicted SSWS ($R^2=0.268$, $p<0.001$ and $R^2=0.158$, $p=0.002$, respectively). The addition of genotype and genotype's interactions did not significantly increase the variance accounted for in SSWS ($R^2=0.012$, $p=0.27$ and $R^2=0.006$, $p=0.723$, respectively).

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Conclusions—Our results suggest that the Val66Met polymorphism does not predict long-term, functional mobility following stroke. This difference may be due to differences in model variables or a reduced impact of the polymorphism as recovery progresses.

Keywords

stroke; genotype; recovery; function; brain-derived neurotrophic factor; prognosis

Introduction

Stroke is a leading cause of disability in the United States often resulting in deficits in functional mobility¹. Maximizing functional mobility and recovery following stroke is a primary goal of rehabilitation and is critical to reducing burden of care, decreasing risk of development of comorbidities, and improving quality of life^{1,2}. Despite interventions to improve functional mobility and recovery following stroke, long term outcomes vary greatly. As a result, factors that influence recovery after stroke have been explored. Physical impairments have been found to explain only a limited amount of the variance observed in functional mobility and recovery following stroke^{3–6}, suggesting that other factors, such as self-efficacy^{5,7}, comorbidities⁷, and fatigue^{5,7–10}, play an important role in recovery. Recently, advances in our understanding of genetics has led to research into their role in post stroke recovery^{11–14}.

Due to its role in neuroplasticity, Brain Derived Neurotrophic Factor (BDNF) has been one area of focus in stroke recovery¹⁴. Within the BDNF gene, there is a common single nucleotide polymorphism, Val66Met, which is found in about 30% of the population¹⁵. Evidence suggests that the presence of a Met allele in this polymorphism may negatively impact neuroplasticity; thus, slowing recovery following stroke. It is thought that this may be due to its impact on the secretion of the BDNF protein^{16,17} and changes to cortical activation¹⁸. Several studies have examined the role of BDNF genotype in acute recovery of stroke and found mixed results. Some studies have found that the Val66Met polymorphism negatively impacts recovery within the first 3 months of stroke^{19–22}. This has been found when measuring recovery with the Glasgow Outcome Scale (GOS)²¹, National Institutes of Health Stroke Scale (NIHSS), modified Rankin Scale (mRS)²², and Fugl-Meyer Upper Extremity Assessment²³. Other studies, however, have found that a Met allele does not impact outcomes in the acute and subacute phases of recovery^{24,25}. Specifically, Mirowska-Guzel et al found that the Val66Met polymorphism may impact the severity of the stroke on day 1 and 7, however, this impact was not present after 30 days²⁵.

Although it is important to understand factors impacting an individual's recovery acutely, it is also important to understand how BDNF genotype impacts long-term recovery. Few studies have examined this^{19,26,27}. Kim and colleagues (2012) found that at 1 year following stroke, individuals with the Met allele had poorer recovery as measured by the Barthel Index¹⁹. Conversely, Stanne et al (2014) found that a Met allele was not associated with long term recovery at 2 or 7 years post stroke as measured by the mRS²⁷. To further add to this uncertainty, Qin et al found that a Met allele resulted in improved recovery 6

months post stroke in a mouse model²⁶. Given these mixed results, the role of BDNF genotype on long-term recovery after stroke remains unclear.

Additionally, while studies assessing both short and long-term recovery after stroke have used well established measures to track patient outcomes, the measures used in past studies evaluate general recovery rather than functional mobility²⁸. Functional mobility is particularly important when evaluating long term recovery due to its linkages with the development of comorbidities, depression, and quality of life following stroke^{1,2,29}. To date, no studies have examined the impact of the BDNF genotype on functional mobility. As a result, studies evaluating the long-term impact of BDNF genotype on recovery post stroke using measures of *functional mobility* are needed. Self-selected walking speed (SSWS) is a commonly used measure of functional mobility that has been found to predict community participation, quality of life, and physical activity after stroke^{4,30-35} and therefore, could be readily used in a model exploring the relationship between the polymorphism and functional mobility after stroke.

Past research has also explored personal factors that impact the effect of the Val66Met polymorphism in numerous conditions. Through this work it is apparent that the impact of a Met allele has complicated interactions with age, gender, and depression³⁶⁻⁴¹. Several studies suggest that age and the Val66Met polymorphism may interact to reduce the negative impacts of a Met allele^{39,40}. A similar interaction between gender and the Val66Met polymorphism has been observed in the development of Alzheimer's Disease³⁶ and the performance of motor learning tasks⁴¹. In each of these studies, the negative impact of a Met allele is reduced or negated in females. Lastly, the presence of a Met allele has been found to increase the risk of and persistence of depressive symptoms in individuals^{37,38}. Based on these complex interactions, it is important that models assessing the role of the Val66Met polymorphism in stroke recovery account for these personal factors and their potential interaction with genotype. While older age, female gender, and the presence of depression have been associated with poorer recovery in the subacute phase of stroke⁴², their interaction with the BDNF polymorphism in stroke has been minimally explored. In a study by Mirawska-Guzel et al (2014), the negative impact of a Met allele was found only in older females (>55 years old)⁴². This study, however, is one of the few that have examined the impact of these personal factors *with* the BDNF polymorphism on stroke recovery.

As a result, the purpose of this study was to examine the relationship between BDNF genotype and functional mobility in *chronic* stroke survivors by examining a model that accounts for physical impairment and significant personal factors and then BDNF genotype and possible interactions. We hypothesized that individuals with the Met allele would demonstrate poorer recovery of functional mobility after stroke, but that this would be impacted by the interaction of the presence of the Met allele and age, gender, and depression.

Methods

Subjects

Participants were recruited from local physical therapy practices, physicians, support groups, and advertisements. To be included, individuals needed to be at least 21 years of age, have had a stroke at least 6 months prior to evaluation, be able to walk at least 10 meters without physical assistance, and not currently be enrolled in physical therapy services. Individuals were excluded if they had had a cardiac event, such as myocardial infarction or a cardiac medical procedure, within the past 3 months or subjective reports of unexplained dizziness within the past 6 months. All participants signed an informed consent approved by the Human Subjects Review Board at the University of Delaware prior to participation. This study was a secondary analysis of a larger study; thus, sample size was determined based on the primary study. Additionally, this manuscript conforms to “Strengthening the Reporting of Observational Studies in Epidemiology” (STROBE) Guidelines.

Clinical Assessments

Participants completed a clinical assessment by a licensed physical therapist. The clinical assessment included completion of Lower Extremity Fugl Meyer Score (FMLE)⁴³, the Yesavage Geriatric Depression Scale (YGDS)⁴⁴, and the 10 meter walk test³⁴. SSWS was calculated from the 10 meter walk test. During this test, participants were allowed to use the assistive device that they use during community ambulation. In addition, personal information including age, gender, and time since stroke was recorded.

Genetic Analysis

Each subject provided 2 mL saliva sample in a DNA Self-Collection Kit (DNA Genotek, Kanata, Canada) containing a DNA stabilizing buffer. The samples were sent to DNA Genotek (GenoFIND Services, Salt Lake City, UT) for processing. Genotek created a set of primers to amplify the region surrounding the Val66Met polymorphism of the BDNF gene and then examined the sample for the presence of the Val66Met polymorphism. Extracted DNA results of genotyping were sent to the primary investigator with remaining saliva samples destroyed following analysis.

Statistical Analysis

A regression model was used to determine how well BDNF genotype predicts recovery of functional mobility following stroke as measured by SSWS. This measure was selected to represent functional mobility because it provides insight into the functional health of an individual and community participation^{4,30,32–35}. It has been correlated with functional status^{34,45}, fall risk⁴⁶, quality of life⁶, and ability to navigate the community³⁴; thus, providing a robust measure of functional mobility. The model included four constructs which were added sequentially as follows: physical impairment (block 1 contained: FMLE), personal information (block 2 contained: age, gender, YDGS), BDNF polymorphism (block 3 contained: a dichotomous indicator for Met or no Met), and potential interactions (block 4 contained: polymorphism’s interaction with age, gender, and depression). The FMLE, a measure of impairment, was added to the model first due to its ability to predict SSWS after

stroke^{47,48}. The selected personal information was included due to past research suggesting these factors can impact stroke recovery^{32,33} and the role of the Val66Met polymorphism³⁶⁻⁴¹. Lastly, the interaction of BDNF genotype with age, gender, and depression was included since previous literature suggests such interactions exist in other populations^{36,39-41}. There was no missing data. All assumptions for regression were tested and met. The change in R^2 was used to determine if a given block was significantly related to SSWS. All analyses were performed using SPSS (Version 24.0; Chicago, Illinois).

Results

Sixty-three subjects (42 males, 61.1 ± 12.0 years) participated in this study. Twenty-two percent of the participants had at least one Met allele in the BDNF gene. Forty-seven of these subjects had an ischemic stroke, while the remaining 16 subjects had a hemorrhagic stroke. Complete demographics are presented in Table 1 with a description of clinical measures in Table 2. The initial block, physical impairment (FMLE), was significant ($R^2=0.268$, $p<0.001$). The second block containing age, gender, and depression was also significant ($R^2=0.158$, $p=0.002$), indicating that these factors predicted SSWS above and beyond physical impairment. The addition of the third block (BDNF genotype) to the model was not significant ($R^2=0.012$, $p=0.27$). Similarly, the addition of the final block containing interactions was not significant ($R^2=0.013$, $p=0.74$). The results of the regression model are presented in Table 3.

Discussion

The results of this study support previous work finding that physical impairment^{3,4,6,49} and personal information^{7,32} can significantly predict a proportion of long term functional mobility following stroke; however, contrary to our hypotheses, this study suggests that neither BDNF genotype or the interactions accounts for additional variability in long term functional mobility recovery. In order to detect a significant impact of BDNF genotype, given the effect size we observed with a power of 0.8, 649 subjects would be needed. These results are consistent with work suggesting that BDNF genotype does not predict short^{24,25} and long term^{19,27} general recovery post stroke. Our results are also supported by work suggesting that Met carriers do not recover to a different extent than Val carriers, but rather recover through a different mechanism⁵⁰. These results are in contrast to previous work suggesting that genotype predicts acute¹⁹⁻²² and long term¹⁹ post stroke general recovery. It is possible that our results differ from the previous work supporting the role of the Val66Met polymorphism due to differences in our model's independent and dependent variables, a reduced importance of the polymorphism as recovery progresses, or sample size limitations.

Past studies investigating the role of the Val66Met polymorphism on recovery after stroke have used dependent variables, such as the Barthel Index, GOS, and mRS, that do not examine functional mobility and provide minimal insight into activity level and participation within the community⁵¹. SSWS, on the other hand, is known to be related to level of disability³⁴, quality of life⁶, mortality⁵², and fall risk⁴⁶ in addition to walking function in the community^{4,30-35}. Given these differences, it is reasonable to expect that using a measure of *functional mobility* as a proxy for recovery rather than one of the measures previously used

could yield different results. Due to the importance of functional mobility in post stroke recovery, understanding how the BDNF genotype impacts this specific aspect of recovery is important when considering long term outcomes.

The independent variables in our model may also explain our differing results. In our model, we specifically examined whether the BDNF genotype explains variation in long-term recovery of functional mobility after stroke *above and beyond* factors that we know help predict recovery and that can be measured more easily. As a result, physical impairment and personal factors, which are known to predict a portion of recovery following stroke^{3,7,9}, were added to our model prior to including genotype. Our results suggest that knowing an individual's genotype does not provide additional information about an individual's functional mobility recovery above what can be gained through a physical assessment and demographic information. Although the personal factors that were included in our model were included in other studies that found BDNF genotype to predict short term stroke recovery⁴², the impact of BDNF genotype *above* what can be easily assessed (i.e. age, gender, and physical impairment) was not examined. However, due to past work, we believe including these factors is necessary to provide a complete picture of BDNF genotype's impact on post-stroke functional mobility.

It is also possible that the role of the Val66Met polymorphism, diminishes as other factors become more important throughout the recovery process. During the chronic phase of stroke, self-efficacy and the number of comorbidities have been shown to be significantly related to recovery of functional mobility^{3,5,7,29,32,49}. It is possible that, while BDNF genotype may impact acute general recovery from stroke, the impact of genotype may be reduced as factors such as these become more relevant during the chronic phase of post-stroke recovery. Given this possibility, longitudinal studies evaluating the role of BDNF genotype on functional mobility throughout stroke recovery would be valuable.

Despite our findings, our study is not without limitations. The primary limitation of this study is the small sample size. The size of our sample limits our ability to do further analysis including examining the impact that the type of stroke (i.e. ischemic vs hemorrhagic) may have on this relationship. Siironen et al (2007) found that in individuals with hemorrhagic stroke, there is an association of BDNF genotype and outcome after 3 months²¹; however, in studies looking at the impact of BDNF genotype individuals with ischemic stroke during acute and subacute general recovery, the results are mixed^{22,24,25}. Thus, future work should examine the long-term relationship between type of stroke, BDNF genotype, and general recovery and *functional* mobility. Other potential work with larger sample sizes should evaluate the potential impact of ethnicity on this relationship, as the prevalence of the BDNF polymorphism varies with ethnicity¹⁵. Another limitation is that our sample only included individuals who could walk at least 10 meters without assistance. Although this includes a large portion of individuals following stroke, it does not include individuals with more severe deficits following stroke. Despite this, the portion of our sample with a Met allele (n=14 or 22%) is similar to that which is reported in the population; thus, our findings are likely still representative of stroke survivors. A final limitation is that our subjects were evaluated at various time points in the chronic phase of stroke recovery. Despite this, it is widely accepted that spontaneous recovery no longer occurs 6 months after stroke⁵³; thus, it

is unlikely that participants in this study would make significant gains in recovery during the time of assessment. Future work standardizing the time at which evaluation is performed would be useful.

Conclusions

BDNF has been related to neuroplasticity and acute recovery following stroke; however, our results suggest that in chronic stroke, the impact of BDNF genotype on functional mobility recovery appears limited, when other factors, such as impairment level and personal factors are known. As such, long term prognoses related to functional mobility after stroke should not be based solely on BDNF genotype.

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Table 1

Demographic Information

Characteristic	Subject Information
Total Sample Size (n)	63
Age	
Mean± SD (yrs)	61.1± 12.0
Range (Min-Max; yrs)	25–86
Gender	
Male (n)	42
Female (n)	21
Side of Hemiparesis	
Right (n)	37
Left (n)	26
Type of Stroke	
Ischemic (n)	47
Hemorrhagic (n)	16
Time Since Stroke	
Mean± SD (months)	29.2 ± 44.8
Range (Min-Max; months)	6–300
Genotype	
Valine (n)	49
Met (n)	14

Abbreviations: SD=Standard Deviation, n=number, Min=minimum, Max=maximum

Table 2

Clinical Characteristics

Characteristic	Subjects
FMLE (mean± SD)	22.9 ± 5.9
YGDS (mean± SD)	3.4 ±3.1
SSWS (mean± SD; m/s)	0.71 ± 0.28
Assistive Device (n)	
None	42
Straight Point Cane	10
Small Based Quad Cane	4
Large Base Quad Cane	2
Hemi-Walker	1
Rollator	4
Orthotic Device(n)	
None	49
Articulating AFO	9
Solid AFO	5

Abbreviations: SD=Standard Deviation, FMLE= Fugl Meyer Lower Extremity, YDGS= Yesavage Geriatric Depression Scale, SSWS= Self-selected walking speed AFO= Ankle Foot Orthosis

Table 3

Regression Results

Block	Predictor	R ²	R ²	p
1	Physical Impairment	0.280	0.280	p<0.001
2	Personal Information	0.438	0.158	0.002
3	Genotype	0.450	0.012	0.27
4	Genotype Interactions	0.462	0.013	0.74

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