



The association of brain-derived neurotrophic factor Val66Met polymorphism with stroke outcomes: a cross-sectional pilot study

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Abstract

Aim: This study investigated the effect of brain-derived neurotrophic factor (*BDNF*) Val66Met polymorphism on post-stroke outcomes, including quality of life, physical fitness, cognitive function, depression, and overall disability.

Methods: The difference between Met carriers and non-Met carriers was analyzed for the entire sample and in pair-matched analysis, using age, sex, time since stroke, and race.

Results: We evaluated 89 stroke participants (mean age, 57 ± 10 years; 58% male; 54% White, and 49% Hispanic). Twelve participants (13%) had one copy of the *BDNF* Val66Met (Val/Met heterozygotes) and none had two copies (Met/Met homozygotes). Comparing Met ($n = 12$) and non-Met carriers ($n = 77$), no significant differences were observed in demographics or clinical characteristics, including motor or cognitive outcomes. In pair-matched analysis, a significant difference was observed for the Center for Epidemiological Studies Depression (CES-D) scale, where Met carriers had significantly greater CES-D scores than non-Met carriers (24 ± 16 vs. 9 ± 9 , $p = 0.011$). Regardless of the chosen CES-D cut-off scores (≥ 16 vs. ≥ 20), more cases of depressive symptomatology were observed among those with the *BDNF* Val66Met polymorphism than those without it (p values < 0.05).

Conclusions: The *BDNF* Val66Met polymorphism may be associated with post-stroke depression but not motor or cognitive recovery.

Keywords

stroke, recovery, genetic, polymorphism, *BDNF*



Introduction

Stroke represents the leading cause of long-term disability in the United States [1]. In the last few decades, our understanding of stroke pathophysiology, treatments, and long-term survival has profoundly improved, but stroke outcomes may still be less than optimal. Up to two-thirds of stroke survivors have residual physical or cognitive disabilities that can prevent them from living independently and vastly affect their quality of life [2]. Thus, a primary concern immediately after a stroke event is the evaluation of the individual's prospect for functional recovery. The capacity to recover after stroke, however, can be highly variable, in part due to different stroke subtypes and their impact on the distribution of risk factors, stroke severity, and outcomes. All of this highlights the need to elucidate the responsible mechanisms and develop more effective and individualized rehabilitation strategies for stroke treatment [3].

Recent findings have indicated an underlying deleterious effect of a brain-derived neurotrophic factor (*BDNF*) genetic polymorphism on outcomes and prognosis after stroke [4–6]. *BDNF* itself is the most abundant neurotrophin in the nervous system, involved in neurogenesis and neuroplasticity of the brain [7]. Single-nucleotide polymorphisms (SNPs) in the *BDNF* gene naturally occur in the form of Val66Met, in which methionine (Met) is substituted for valine (Val) at position 66 of the amino chain [8]. This altered pro-domain structure has been associated with a reduction of cerebral *BDNF* levels [8] and, accordingly, impaired brain structure and function [9].

Mechanistically, it is assumed that the Met allele results in a *BDNF* deficiency through the disruption of *BDNF* protein-protein interactions, protein stability, intracellular trafficking, and receptor binding affinities [6]. The *BDNF* Val66Met polymorphism has been associated with smaller hippocampal volume [10], greater susceptibility to migraines [11], psychiatric disorders (i.e., schizophrenia, major depression, anxiety [12, 13]), neurodegenerative disorders (i.e., Alzheimer's disease, multiple sclerosis, and Parkinson's disease [14]), and even fasting glucose in healthy adolescents [15]. Sex, age, ethnicity, and environmental factors may contribute to the discrepancy in the findings of *BDNF* Val66Met genetic studies [16]. Genetic studies have indicated that Val66Met is associated with a worse prognosis after stroke and an impaired response to rehabilitation therapies, independent of baseline deficits and traditional vascular risk factors [6, 17]. However, the role of the Val66Met polymorphism may diminish throughout the recovery process as other factors, such as the level of physical impairment, age, and depression, become more important [18]. In addition to potential functional deficits after stroke, the Val66Met polymorphism has been associated with poorer language outcome in the acute and chronic stages [19] and higher rates of depression in the acute stage of stroke [20].

Rates of *BDNF* Val66Met polymorphism vary by geographical region. In European populations, the prevalence of the *BDNF* Val66Met polymorphism ranges from 13% to 30% and among Asian populations from 39% to 46%. The overall prevalence of the Val66Met polymorphism in the United States ranges from 18% to 28%, suggesting that the Met allele—if associated with worse stroke outcomes—may affect a significant proportion of stroke survivors [21].

The aim of this pilot study was to investigate the effect of the Val66Met polymorphism on post-stroke outcomes, including quality of life, physical fitness, cognitive function, depression, and overall disability.

Materials and methods

Study participants

We included stroke participants enrolled in the Randomized Trial of Combined Aerobic, Resistance, and Cognitive Training who underwent a three-month exercise and cognitive training program. Details on the ascertainment of subjects, extensive assessments (including baseline), and exercise and cognitive training used in this clinical trial were described previously [22]. Briefly, inclusion criteria were a) ≥ 18 years old, b) stroke within one year, c) modified Rankin Scale (mRS) ≤ 3 , and d) less than ideal physical activity (defined as < 75 minutes of vigorous or < 150 minutes of moderate activity per week) for at least three months before enrollment. We excluded subjects with neurodegenerative diseases and those with unstable medical

and psychiatric conditions, which would preclude engaging in physical activity. Of 131 participants enrolled in the main trial, 89 participants (68%) had data available on the *BDNF* Val66Met polymorphism. The assessment of the Val66Met polymorphism was an ancillary study, which enrolled 89 consecutive patients, from the time the funding for this ancillary study was awarded until the completion of the main trial. Both main and ancillary studies were approved by the Institutional Review Board at the University of Miami Miller School of Medicine (IRB# 20140203), which ensures compliance with federal, state, and institutional regulations, based on ethical principles found in the Declaration of Helsinki (2013). All participants provided informed consent to participate in the study. The study was registered in the ClinicalTrials.gov (Unique Identifier: NCT02272426).

Baseline assessment

The outcomes assessed included an extensive evaluation of socio-economic status, vascular risk profile (e.g., self-reported presence of hypertension, diabetes mellitus, and dyslipidemia, or use of medications for those conditions), stroke characteristics, and relevant treatments (e.g., type of stroke, date of onset, and NIH stroke scale). Stroke-specific quality of life was evaluated with the Stroke Impact Scale (SIS). Functional status was assessed with the mRS, and motor impairment with the Motricity Index. Symptoms of depression were evaluated with the Center for Epidemiological Studies Depression (CES-D). A comprehensive neuropsychological evaluation included a global screening for mild cognitive impairment [Montreal Cognitive Assessment (MoCA)], and assessment of working memory (Digit Span Backwards and Letter-Number Sequencing), cognitive/motor processing speed (Digit Symbol Substitution Test and Grooved Pegboard), and executive function (Trail Making Test Part B and the Stroop Color Word Interference Test). Physical and functional fitness evaluation included gait performance [Timed Up and Go (TUG) and 15-Meter Walking Test], strength (Hand Grip and 30-Second Chair Stand), and endurance (6-Minute Walking Test).

The biomarkers included serum fasting glucose and BDNF levels, as well as the Val66Met polymorphism. Approximately 20 mL of blood was collected in three Sodium Citrate Vacutainer tubes for the BDNF sample, and one Sodium Fluoride or Na₂EDTA Vacutainer tube for the glucose. Blood samples were delivered on ice within two hours of collection, centrifuged, and stored at -80°C until processing. One aliquot of whole blood was then used for the *BDNF* Val66Met analysis using Applied Biosystems™ TaqMan™ 5'-nuclease assay chemistry. Each Applied Biosystems™ TaqMan™ SNP Genotyping Assay includes two allele-specific Applied Biosystems™ TaqMan™ MGB probes containing distinct fluorescent dyes and a PCR primer pair to detect specific SNP targets. These TaqMan probe and primer sets (assays) uniquely align with the genome to provide unmatched specificity for the allele of interest. Specifically, 10 ng of genomic DNA, extracted from whole blood, according to established protocols, was used in the amplification reaction. Cycling was performed on GeneAmp PCR Systems 9700 thermocyclers, with conditions recommended by Applied Biosystems. End-point fluorescence was measured on the QuantStudio™ 12K Flex Real-Time PCR System. Genotype discrimination of experimental results was then conducted using the QuantStudio™ 12K Flex Software. To ensure genotyping accuracy, 32 quality control samples per 384-well plate (8 per 96-well plate), matching within and across plates, were performed.

Statistical analysis

Met allele carriers vs. non-Met allele carriers were examined in relation to the outcomes of interest. Continuous variables were expressed as mean values $\pm$ SD, and categorical variables as counts and percentages. Normally distributed continuous variables were compared with mean and SD using independent sample *t*-tests, and non-normally distributed continuous variables with median and interquartile range using Wilcoxon signed-rank sum tests. Cohen's *d* (or "*r*" effect size for the Wilcoxon signed rank test) was used to estimate the standardized mean difference of an effect size with 95% confidence intervals. Categorical variables were assessed using chi-squared or Fisher's Exact tests.

A secondary confirmatory analysis was performed by matching the non-Met allele carriers with the carriers of one copy (Val/Met) of the *BDNF* polymorphism. The participants were matched by age ($\pm$ 5), sex,

time since stroke (categorized as less than 3 months, 3–6 months, and 6–12 months after a stroke), and race (categorized as White, Black, or other/unknown race). One Asian female Met carrier could not be sex- and race-matched to a non-Met carrier and was therefore excluded. Seven out of 11 pairs were matched within 2 years, the rest within 3 to 5 years. The pair matching was performed by an independent investigator blinded to non-matching outcomes. Independent *t*-tests were performed to compare differences between matching groups. Our post-hoc analysis included the cut-off for depression using two CES-D scores: ≥ 16 and ≥ 20 . Since this was an exploratory analysis, values of $p < 0.05$ were considered statistically significant without correction for multiple testing. A formal power analysis was not conducted for this study due to constraints on the available research funding, which limited the sample size to 89.

All statistical analyses were conducted using SPSS Statistics 25 (IBM Inc., Armonk, NY). Study data were collected and managed using REDCap electronic data capture tools.

Results

Of the total sample ($n = 89$), the mean age was 57 ± 10 years, 58% were male, 54% White, 39% African American, and 49% Hispanic. The average body mass index was 30 ± 5 kg/m². The prevalence of self-reported medication use for lipid disorders was 79%, for hypertension 74%, and for diabetes mellitus 29%. The prevalence of self-reported past smoking was 34% and current smoking was 12%. Time from stroke onset to study visit among all participants was < 3 months for 26%, 3–6 months for 22%, and > 6 months for 52%. Finally, 82% of participants had ischemic strokes and 18% had hemorrhagic strokes.

Overall, 12 participants (13%) had one copy of the *BDNF* Val66Met (Val/Met heterozygotes) and none had two copies (Met/Met homozygotes). Comparing Met and non-Met carriers demonstrated no statistically significant differences in any of the demographics or clinical characteristics (Tables 1, 2, and 3). Met carriers were less likely to be African American people ($p = 0.08$; Table 1), had lower National Institute of Health Stroke Scale (NIHSS) scores ($p = 0.08$; Table 1), and greater CES-D scores ($p = 0.08$; Table 3) than non-Met carriers.

Table 1. Socio-demographics, stroke characteristics, and clinical risk factors of non-Met and Met carriers.

Outcomes	Non-Met carriers ($n = 77$)	Met carriers ($n = 12$)	<i>P</i> values
Socio-demographics			
Age, mean (SD)	57.1 (9.7)	55.8 (15.1)	0.69
Women, n (%)	31 (40)	6 (50)	0.52
Race, n (%)			
African American	32 (42)	3 (25)	0.08
Caucasian	40 (52)	8 (67)	
Other/not reported	5 (6)	1 (8)	
Ethnicity, n (%)			
Hispanic or Latino	38 (49)	6 (50)	0.30
Not Hispanic or Latino	38 (49)	5 (42)	
Other/not reported	1 (1)	1 (8)	
Number of persons living within household, mean (SD)	2 (2)	2 (2)	0.26
Years of education, mean (SD)	13.2 (3.5)	12.7 (3.8)	0.62
Stroke characteristics			
NIHSS, mean (SD)	2.9 (2.2)	1.6 (1.3)	0.08
mRS, mean (SD)	2.1 (0.8)	2.0 (0.8)	0.58
SIS, mean (SD)	62.5 (12.5)	64.1 (11)	0.68
Time since stroke (< 3 months), n (%)	17 (22)	6 (50)	0.15
Clinical risk factors (yes)			
Past tobacco use, n (%)	27 (35)	3 (25)	0.41
Current tobacco use, n (%)	10 (13)	1 (8)	0.63
Hypertension, n (%)	57 (74)	9 (75)	0.94

Table 1. Socio-demographics, stroke characteristics, and clinical risk factors of non-Met and Met carriers. (continued)

Outcomes	Non-Met carriers (<i>n</i> = 77)	Met carriers (<i>n</i> = 12)	<i>P</i> values
Diabetes, <i>n</i> (%)	22 (29)	4 (33)	0.74
High cholesterol, <i>n</i> (%)	61 (79)	9 (75)	0.74
SBP (mmHg), mean (SD)	142.7 (23.8)	134.5 (17.3)	0.28
DBP (mmHg), mean (SD)	83.9 (12.7)	82.3 (14.7)	0.70
BMI (kg/m ²), mean (SD)	30.5 (4.5)	28.5 (5.1)	0.17

NIHSS: National Institute of Health Stroke Scale; mRS: modified Rankin Scale; SIS: Stroke Impact Scale; SBP: systolic blood pressure; DBP: diastolic blood pressure; BMI: body mass index.

Table 2. Functional fitness and biomarkers of non-Met and Met carriers.

Outcomes	Non-Met carriers (<i>n</i> = 77), mean (SD)	Met carriers (<i>n</i> = 12), mean (SD)	<i>P</i> values
Functional fitness			
Motricity U	99.4 (1.8)	99.7 (1.1)	0.58
Motricity A	85.2 (19.2)	91.3 (20.0)	0.31
Hand Grip U	31.9 (9.4)	29.2 (11.6)	0.39
Hand Grip A	16.8 (12.2)	20.4 (11.9)	0.36
6-Minute Walking (feet)	1,129.5 (495.1)	1,171.0 (701.9)	0.85
30-Second Chair Stand (sec)	8.6 (4.8)	9.9 (6.1)	0.42
TUG (sec)	21.9 (20.3)	18.1 (8.4)	0.55
15-Meter Walking Test (sec)	17.4 (15.1)	16.6 (9.9)	0.55
Biomarkers			
BDNF serum (pg/mL)	638.1 (844.8)	772.6 (851.1)	0.61
Glucose (mg/dL)	110.9 (37.6)	103.8 (19.7)	0.52

U: unaffected side; A: affected side; TUG: Timed Up and Go; BDNF: brain-derived neurotrophic factor; pg/mL: picograms/milliliter; mg/dL: milligram/deciliter.

Table 3. Depression and cognition of non-Met and Met carriers.

Outcomes	Non-Met carriers (<i>n</i> = 77), mean (SD)	Met carriers (<i>n</i> = 12), mean (SD)	<i>P</i> values
Depression			
CES-D	16.9 (12.6)	24.2 (14.8)	0.08
Cognition			
MoCA	20.7 (5.2)	19.8 (7.5)	0.60
HVLT (verbal learning and memory)			
Total recall	19.9 (5.9)	18.2 (5.5)	0.38
Delayed	6.5 (3.4)	5.1 (3.5)	0.22
Retention %	75.2 (26.7)	61.6 (32.9)	0.15
WAIS-R digit (processing speed)	35.7 (16.4)	30.7 (21.3)	0.39
D-KEFS (executive function)			
Color naming			
Time	40.2 (17.2)	52.1 (17.4)	0.28
Uncorrected	0.7 (1.7)	3.2 (6.4)	0.23
Self-corrected	0.9 (1.2)	1.6 (1.8)	0.29
Word reading			
Time	34.6 (16.8)	43.2 (20.5)	0.12
Uncorrected	0.2 (0.9)	0.9 (2.8)	0.43
Self-corrected	0.3 (0.7)	0.5 (1.0)	0.40
Inhibition			
Time	90.4 (39.8)	101.6 (45.9)	0.41
Uncorrected	3.3 (6.0)	4.5 (5.8)	0.54
Self-corrected	2.3 (2.5)	2.4 (3.7)	0.90

Table 3. Depression and cognition of non-Met and Met carriers. (*continued*)

Outcomes	Non-Met carriers (<i>n</i> = 77), mean (SD)	Met carriers (<i>n</i> = 12), mean (SD)	<i>P</i> values
Inhibition switching			
Time	104.1 (40.5)	113.7 (55.3)	0.52
Uncorrected	5.7 (6.6)	5.0 (7.0)	0.76
Self-corrected	1.6 (1.6)	2.6 (3.5)	0.46

CES-D: Center for Epidemiological Studies Depression; MoCA: Montreal Cognitive Assessment; HVL: Hopkins Verbal Learning Test; WAIS-R: Wechsler Adult Intelligence Scale; D-KEFS: Delis-Kaplan Executive Function Test.

Using the pair-matched analysis with the *BDNF* Val66Met polymorphism and controls, the average age for 11 Met carriers and 11 non-Met carriers was the same (58 ± 14 years). The only significant difference was observed for CES-D scores. Met carriers had significantly greater CES-D scores than non-carriers (24 ± 16 vs. 9 ± 9 , $p = 0.011$).

When analyzing the entire sample and proportion of participants with CES-D scores above the standard cut-off ≥ 16 [23], 67% of Met carriers ($n = 8$; mean $\pm$ SD = 30 ± 11) were classified as having depressive symptoms, compared to 40% of non-Met carriers ($n = 31$; mean $\pm$ SD = 29 ± 10), which was significant [χ^2 (1, $N = 89$) = 3.7, $p < 0.05$].

When analyzing the entire sample and proportion of participants with a more conservative cut-off ≥ 20 [24], 63% of Met carriers and 32% of non-Met carriers were classified as having depressive symptoms, and the difference between carriers and non-carriers remained statistically significant ($p = 0.04$).

Discussion

In this racially and ethnically diverse sample of stroke survivors, the *BDNF* Val66Met polymorphism was not associated with motor and cognitive outcomes and was associated with worse depressive symptoms up to one year after stroke.

Depression is a common complication after stroke [25] and is associated with worse functional outcomes [26] and higher mortality [27]. A systematic review of observational studies [28] found that one-third of all stroke survivors experience depression up to five years after stroke. In the present study, one-third of the participants had depressive symptoms, which is comparable to the systematic review (36%) when also using a CES-D cut-off of ≥ 20 , as an accepted threshold score with high sensitivity and specificity in the general [24] and stroke populations [29].

Previous stroke and non-stroke studies have shown an inconsistent association between the *BDNF* Val66Met polymorphism and depression spectrum. A significant association between the polymorphism and post-stroke depression (PSD) was found in a South Korean study ($n = 286$) one year post-stroke [20], where depression was diagnosed using the Mini International Neuropsychiatric Interview and applying DSM-IV criteria two weeks after stroke. Similar findings were observed in a Chinese stroke cohort ($n = 254$) [30], indicating that a cluster of polymorphisms, including *BDNF* Val66Met, may play a central role in regulating the underlying mechanisms of PSD. The same authors concluded that PSD may be caused by many collaborative polymorphisms and that each polymorphism had a weak or moderate risk for the occurrence of PSD—in this study assessed by the 17-item Hamilton Depression rating scale, an instrument designed not to diagnose but to monitor depression.

In the non-stroke literature, a meta-analysis of case-controlled studies [31] revealed that the *BDNF* Val66Met polymorphism was not significantly associated with major depressive disorder, but was present in a sex-stratified analysis, where the same association was significant for men and not women. The *BDNF* Val66Met polymorphism was independently associated with depression in type 2 diabetes after adjusting for gender, hemoglobin A1C, and BMI [32]. The same polymorphism was the only SNP (rs6265; the other two common ones are rs7103411 and rs71224442) associated with the severity of depressive symptoms on the CES-D scale in older adults [33].

No association between the *BDNF* Val66Met polymorphism and depression was found in several other studies [34, 35], and no major effect was found when the same polymorphism was analyzed as a moderator between physical activity [36] or antidepressant treatment response [37] and depression.

In the current study, we observed significant differences in depressive symptomatology rates based on polymorphism status. Regardless of the chosen CES-D cut-off score (≥ 16 vs. ≥ 20), 27% more cases of depressive symptomatology were observed among those with the *BDNF* Val66Met polymorphism than those without it. In the matching analysis, that difference was even greater, and slightly over 40%. Also in the matching analysis, those with the polymorphism—and worse depression scores—had 42% greater *BDNF* serum levels than those without the polymorphism. The same trend contradicts the theory that low serum *BDNF* is a state of abnormality and that patients with the clinical diagnosis of depression have significantly lower levels of *BDNF* than non-depressed patients [38]. This paradoxical effect, observed in our study, may be explained in several ways. Elevated *BDNF* in preclinical models, associated with improved learning, may at the same time have pro-depressive effects [39]. The underlying theory is that elevated *BDNF* levels have dichotomous effects on parts of the mesolimbic reward circuit: negative effects on the ventral tegmental area and nucleus accumbens pathway, and positive effects on hippocampal circuits [39, 40]. Furthermore, the Met variant has been hypothesized to decrease the activity of *BDNF* [41], so it is possible to have elevated *BDNF* levels but with reduced activity with the Val/Met genotype compared to the Val/Val genotype [42]. Individuals with depression may also have elevated *BDNF* levels because of higher use of pharmacological antidepressant treatment (not assessed in our study), which has been shown to restore and elevate *BDNF* levels [43]. Lastly, an inverse association between *BDNF* levels and inattentive problems and executive function has been documented, suggesting that brain damage can induce an increase in *BDNF* to promote neuronal survival and reverse brain damage [44].

We found no differences in gait speed as a marker of functional mobility between Met carriers and non-Met carriers. Prior studies of stroke survivors [18, 45] similarly found no association between the presence of the same Val66Met *BDNF* polymorphism and gait speed. It has been suggested that Met carriers do not have worse recovery than Val carriers but may recover through different mechanisms, relying more on subcortical rather than intracortical plasticity [46]. Conversely, more than 800 patients with the first ischemic stroke had worse disability, assessed with the mRS, in the presence of the Met allele [17]. A recent systematic review and meta-analysis suggested that the Val66Met polymorphism may be associated with worse functional outcomes after stroke [47]. In our analysis, we did not observe any significant differences in various stroke-specific scales, including the mRS, between Met carriers and non-Met carriers.

Our study did not observe significant differences between the two *BDNF* genotypes on tests of cognition. These findings conflict with another study [48] reporting that Met allele carrier status was associated with worse cognitive outcomes after stroke. It should be noted, however, that this study used the cognitive subscale from the Functional Independence Measure instrument—primarily a measure of disability—whereas our study utilized a broader and more sensitive neuropsychological battery.

Lastly, the prevalence of the *BDNF* Val66Met polymorphism (Met/Met and Val/Met genotypes) in our study cohort was 13%. This rate is lower than previously reported among the American, European, and Asian cohorts of healthy individuals, where the rates ranged from 18% to 28% for studies from the United States [8, 49] to 39% to 46% for those from Asia [50, 51].

Strengths of the current study include the extensive assessment of demographics, physical characteristics, and physical and cognitive status of the study participants. Our limitations are a small sample size and a cross-sectional design that precludes the determination of causality between risk factors and the outcomes of interest. It needs to be mentioned that the CES-D is a self-reported measure rather than a clinically administered diagnostic tool that may not only report depressive symptoms but also general psychological distress. We did not collect outpatient rehabilitation information, where different rates and types of rehabilitation programs between the groups could have existed and affected the outcomes. We also did not collect the use of the recombinant form of tissue plasminogen activator, which, potentially by increasing *BDNF* expression, could play a role in stroke recovery [52]. Besides assessing the

number of people our stroke participants lived with in their household (not significantly different between the groups) and matching for sex, our study did not assess other depression-specific risk factors, such as the extent of perceived social support, family and personal history of depression, and anti-depression treatments. Due to the small sample size, our matching approach was limited; for example, our participants were age-matched for up to five years vs. the traditional one to two years. A small sample size also precluded us from running a subgroup analysis to examine sex- and age-dependent effects of the *BDNF* Val66Met polymorphism on stroke outcomes.

This study suggests that the *BDNF* Val66Met polymorphism may be associated with PSD but not motor or cognitive recovery. Future prospective studies with larger sample sizes, with the capacity to account for potential confounding variables observed in this study, should continue to explore the role of the *BDNF* Val66Met polymorphism in stroke recovery. In relation to depression outcomes, future research should incorporate clinical diagnostic assessment. Lastly, future studies could build upon our work by examining the differences in the same outcomes between stroke subtypes, such as lacunar and non-lacunar ischemic strokes [53].

Abbreviations

BDNF: brain-derived neurotrophic factor

CES-D: Center for Epidemiological Studies Depression

Met: methionine

mRS: modified Rankin Scale

PSD: post-stroke depression

SNPs: single-nucleotide polymorphisms

Val: valine

Declarations

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Author contributions

ET: Conceptualization, Formal analysis, Investigation, Writing—original draft. GJF: Conceptualization, Formal analysis, Investigation, Writing—review & editing. LTS: Methodology, Formal analysis, Investigation, Data curation, Writing—review & editing. LJC: Formal analysis, Investigation, Data curation, Writing—review & editing. SK: Formal analysis, Investigation, Writing—review & editing. CBW: Formal analysis, Investigation, Writing—review & editing. DL: Formal analysis, Investigation, Writing—review & editing. TR: Visualization, Supervision, Project administration, Funding acquisition, Writing—review & editing. All authors read and approved the submitted version.

Conflicts of interest

The authors declare that there are no conflicts of interest.

Ethical approval

Both main and ancillary studies were approved by the Institutional Review Board at the University of Miami Miller School of Medicine (IRB# 20140203). The study was registered in the ClinicalTrials.gov (Unique Identifier: NCT02272426).

Consent to participate

All participants provided informed consent to participate in the study.

Consent to publication

Not applicable.

Availability of data and materials

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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