Genetic polymorphisms and post-stroke upper limb motor improvement – A systematic review and meta-analysis

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ABSTRACT

BACKGROUND: Post-stroke upper limb (UL) motor improvement is associated with adaptive neuroplasticity and motor learning. Both intervention-related (including provision of intensive, variable, and task-specific practice) and individual-specific factors (including the presence of genetic polymorphisms) influence improvement. In individuals with stroke, most commonly, polymorphisms are found in Brain Derived Neurotrophic Factor (BDNF), Apolipoprotein (APOE) and Catechol-O-Methyltransferase (COMT). These involve a replacement of cystine by arginine (APOEε4) or valines by 1 or 2 methionines (BDNF:val^{66}met, met^{66}met; COMT:val^{158}met; met^{158}met). However, the implications of these polymorphisms on post-stroke UL motor improvement specifically have not yet been elucidated.

OBJECTIVE: Examine the influence of genetic polymorphism on post-stroke UL motor improvement.

DESIGN: Systematic Review and Meta-Analysis.

METHODS: We conducted a systematic search of the literature published in English language. The modified Downs and Black checklist helped assess study quality. We compared change in UL motor impairment and activity scores between individuals with and without the polymorphisms. Meta-analyses helped assess change in motor impairment (Fugl Meyer Assessment) scores based upon a minimum of 2 studies/time point. Effect sizes (ES) were quantified based upon the Rehabilitation Treatment Specification System as follows: small (0.08-0.18), medium (0.19 -0.40) and large (≥0.41).

RESULTS: We retrieved 10 (4 good and 6 fair quality) studies. Compared to those with BDNF val^{66}met and met^{66}met polymorphism, meta-analyses revealed lower motor impairment (large ES) in those without the polymorphism at intervention completion (0.5, 95% CI: 0.11-0.88) and at retention (0.58, 95% CI:0.06-1.11). The presence of CoMT val^{158}met or met^{158}met polymorphism had similar results, with lower impairment (large ES ≥1.5) and higher activity scores (large ES ranging from 0.5-0.76) in those without the polymorphism. Presence of APOEε4 form did not influence UL motor improvement.

CONCLUSION: Polymorphisms with the presence of 1 or 2 met alleles in BDNF and COMT negatively influence UL motor improvement.

REGISTRATION: https://osf.io/wk9cf/.

PLAIN LANGUAGE SUMMARY

This research paper focuses on the impact of variations in DNA sequence in certain genes on improvement seen in the arms in people who have had a stroke. In this study, we studied the role of 3 genes previously identified as having variations in DNA sequence. The authors searched published research articles from 2000 onwards and selected articles that satisfied certain criteria. We then checked the quality of the selected papers. Next, we combined common data from same tests used to examine motor improvement in the arms to check if there was an overall effect. A total of 10 papers were found. The selected articles were either good or moderate in quality. Variations in DNA structure in 2 out of the 3 genes studied affected the ability to improve the use of the arms in daily life after a stroke. Such information can have important implications in the extent of recovery that is possible after a stroke. It can also be helpful to decide the best rehabilitation options that can be offered to help maximize their ability to use the arms after a stroke.

KEYWORDS: Arm, cerebrovascular accident, brain derived neurotrophic factor, Catechol-O-Methyltransferase, apolipoprotein, outcome, rehabilitation, genes

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Introduction

Stroke continues to be a leading cause of adult morbidity in the United States.[1] One of the most disabling aftereffects of a stroke is the presence of upper limb (UL) hemiparesis. A large proportion of stroke survivors present with UL sensorimotor impairments on the paretic side, reduced independence in performance of daily life activities (ADL) and restricted participation.[2] Along with spontaneous recovery mechanisms,[3] motor improvement of the paretic side enabling successful task-performance is attributable to adaptive neuroplasticity and motor learning.[4]

Successful task-performance entails an interaction of the individual, environment, and the task to be performed.[5] The role of the environment[6,7] and intervention-related factors influencing task-practice[8] have been extensively studied. Recently, there is a renewed focus on the role of individual-specific characteristics such as levels of motivation,[9,10] mood[10] and the role of biomarkers.[11] Bernhardt et al[12] defined biomarkers as "*indicators of disease state that can be used clinically as a measure reflecting underlying molecular and cellular processes that may be difficult to measure directly in humans and could be used to predict recovery or treatment response.*" Biomarker studies within the realm of neurorehabilitation include those based on biology (eg, genetics), structural and/or functional imaging[13] and neurophysiological markers[14] of central nervous system excitability and electrical activity.

The role of imaging-based biomarkers of structural and functional corticospinal tract connectivity alone[13] or in combination with neurophysiological markers (eg, motor evoked potential amplitude)[14] has been extensively studied. The role of genetics-based biomarkers is slowly gaining prominence,[15] with studies focusing on single nucleotide polymorphisms (SNPs).[11] These SNPs alter the basic functioning in cellular and molecular processes[16] and can influence functional improvement produced by (i) environmental interaction and (ii) in response to rehabilitation interventions.[17] Genetics-based biomarkers pertinent to stroke recovery include SNPs in Brain Derived Neurotrophic factor (BDNF), Catechol-o-Methyltransferase (COMT) and Apolipoprotein (APOE).[11]

An activity dependant[18] neurotrophin, BDNF is important for neuroplasticity and protection after injury. It facilitates synaptic transmission and long-term potentiation important for motor learning.[19] A common SNP that occurs in BDNF is substitution of 1 or 2 valines at codon 66 (rs6265) with methionine (val^{66}met or met^{66}met) due to substitution of adenine in place of guanine at nucleotide 196.[20] This polymorphism reduces activity-dependent BDNF release,[21] and results in altered learning and neuroplasticity in healthy controls[22] and after a stroke.[23,24]

The COMT enzyme helps degrade and thus influences the availability of Dopamine in the central nervous system.[25] Dopamine can influence post-stroke motor learning and improvement.[26,27] A commonly observed SNP (rs4680) results in a substitution from valine or methionine at codon 158 (in the membrane form) and codon 108 in the soluble form. This results in a 3-4-fold decrease in COMT activity.[28,29] The role of COMT polymorphism has primarily been assessed on motor learning in Parkinson's disease[30,31] and severe Schizophrenia.[32] Given that COMT is found in areas essential for motor learning,[33] such as striatum and motor cortex,[34] the effects of COMT polymorphism on post-stroke motor improvement need to be addressed.

Although involved in lipid transport between cells, APOE helps modulate neuronal repair and regeneration of nervous tissue. One of the alleles of APOE is the Epsilon-4 form (ε4) with arginine at positions 112 and 158 in place of cystine (rs429358 and rs7412). Presence of APOE-ε4 can cause reduced hippocampal volume and cortical thickness, cognitive impairments[35] and lower recovery levels after traumatic brain[36] and spinal cord[37] injuries. After a stroke, previous meta-analyses[38,39] on the effects of APOE-ε4 revealed lower improvement after sub-arachnoid hemorrhage in those with, compared to those without the ε4 form. However, no association was reported with improvements noted after ischemic strokes. In both studies,[38,39] motor improvements were assessed using generic scales such as the modified Rankin Scale (mRS). Improved scores in assessments such as the mRS does not specifically represent UL motor improvement.[40] As presence of cognitive impairments influence UL motor improvement,[41] the effects of the APOE-ε4 form on post-stroke UL motor improvements needs to be systematically evaluated.

The influence of polymorphisms in BDNF and APOE on global stroke recovery has previously been reviewed.[11,16,24,39,42,43] These studies were either narrative reviews[11,16,24,43] or meta-analyses including global stroke outcomes like National Institutes of Health Stroke Scale and/or mRS.[39,42] Post-stroke UL motor improvement continues to remain variable and less than optimal in many cases.[44] Evaluation of whether and to what extent genetic polymorphisms influence the extent of improvement may help explain some of the observed variability. Using a systematic review and meta-analysis, we examined the influence of genetic polymorphisms on UL motor improvement. The question guiding our review was "*In individuals with post-stroke UL hemiparesis, does the presence, compared to the absence of genetic polymorphisms, influence motor improvement?*" Preliminary results have previously appeared as an abstract.[45]

Methods

This systematic review followed the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines. The protocol was registered on the Open Science Framework (https://osf.io/wk9cf/).

We searched the literature for studies involving human subjects published in English between the years 2000 and 2023. The last search was conducted in November 2023. Key search terms used included: stroke, cerebrovascular accident, upper

limb, arm, rehabilitation, impairment, activities of daily living, recovery, polymorphisms, gene*, neuroplasticity, and motor learning. The * sign after the word gene was used as a wildcard symbol which helped in searching for different words starting with gene including gene, genes, genetic and genetics. Databases searched included: PubMed and ISI Web of Science and the Google Scholar repository. We included studies that used clinical assessments of UL motor impairment and/or ADL and provided data for individuals with and without polymorphisms. We excluded studies focusing exclusively on lower limb or on only cognitive outcomes. We also excluded other reviews, although we searched the reference lists of these excluded reviews for pertinent citations. To identify additional relevant articles, we also searched reference lists of each retrieved study. The searches were initially conducted by 3 authors (RTM, CR and KMS). A separate search was run by the first author (SKS) at the same time, which was repeated again before the manuscript was submitted for publication. No major differences were found in these searches.

Data abstraction

We grouped the retrieved articles according to the polymorphism examined. We developed and used a data abstraction form to extract data from the selected articles. Data were initially extracted by RTM, CR and KMS. The first author (SKS) then verified that all relevant data were obtained from the selected articles. The extracted data included details about chronicity, distribution of sample based upon those with and without polymorphism, details about the intervention, outcomes used to assess change and the study results.

Study quality assessment

We assessed the quality of the selected articles using the modified version[46] of the reliable and valid Downs and Black (D&B) checklist.[47] The modified D&B checklist can be used to assess the quality of both randomized and non-randomized study designs. The total scores of this assessment and PEDro scale are highly correlated in studies involving post-stroke participants.[48] According to available guidelines,[49] we classified the scores as "excellent" (score 24-28), "good" (score 19-23), "fair" (score 14-18), or "poor" (score ≤13). The quality of each study was independently evaluated by RTM, CR and KMS, with discrepancies, if any, resolved by SKS and CLL.

Risk of bias

The risk of bias (ROB) was estimated using the Cochrane ROB tool[50] and ACROBAT-NRSI (A Cochrane Risk of Bias Assessment Tool: for Non-Randomized Studies of Interventions)[51] for randomized and non-randomized studies respectively. The Cochrane ROB tools assesses the following domains: sequence generation, allocation, concealment, blinding of participants, personnel and outcome assessors, incomplete outcome data, selective outcome reporting, and other sources of bias. For each domain, we assigned a judgment: Yes - indicating low ROB, No - indicating a high ROB, and Unclear - indicating unclear or unknown ROB where reported details were insufficient to reach a conclusion. The ACROBAT-NRSI tool assesses bias that can arise because of confounding, study participant selection, intervention measurement, departures from intended interventions, missing data, outcome measurement and reported result selection.

Statistical analyses

Descriptive statistics of the study populations were calculated as percentages of the total sample. When an article reported the effect of a particular polymorphism at both the motor impairment and activity limitation levels, they were considered separately. Meta-analyses (RevMan 5) examined differences in only Fugl-Meyer Assessment (FMA) scores in groups with and without BDNF polymorphism. Pooled effects of the BDNF polymorphism were quantified with standardized mean differences.[52] If at least 2 studies reported the effects of the BDNF polymorphism on change in FMA scores, we included them in the meta-analysis.[53,54] I^2 scores helped assess heterogeneity.[55]

Given that a variety of interventions were employed in the different studies, we used the random effects models (irrespective of I^2 values). Effect sizes were categorized as small (0.08 - 0.18), medium (0.19 - 0.40) and large (≥0.41), in accordance with the Rehabilitation Treatment Specification System recommendations.[56] Sensitivity analysis was carried out to assess the effect of provision of rehabilitation interventions. We conducted an additional analysis on the effects of the BDNF polymorphism excluding any study that did not report details of rehabilitation interventions provided.

Results

The search and selection results are shown in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram. In total, 319 citations were identified through database and registry searches (Figure 1). After removing duplicates, 132 citations were screened, of which 16 were excluded. We sought 116 reports for retrieval and assessed 31 for full text eligibility, which were experimental studies including outcomes related to rehabilitation. We further excluded 21 studies, as they included lower limb and/or gait outcomes or used generic measures such as the mRS, NIHSS and Barthel Index. Ten articles assessing the effects of genetic polymorphisms on UL motor impairment and ADL performance were included in the qualitative synthesis (Figure 1). The reference lists of these ten articles did not yield any additional citations. These studies compared the differences between the dominant (BDNF: $val^{66}val$; COMT: $val^{158}val$; APOE: ε4 negative) and co-dominant (BDNF: $val^{66}met$; COMT:

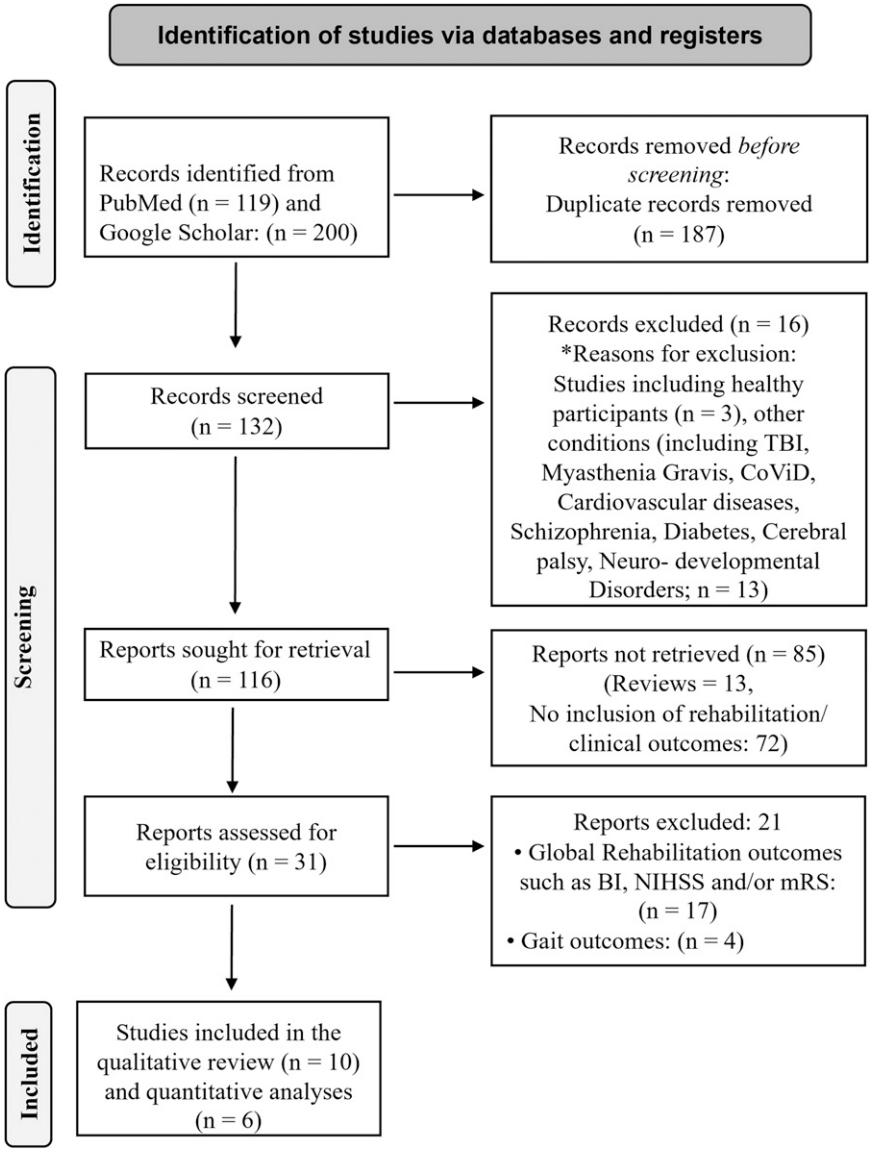

Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram.

val^{158}met; APOE: 1 ε4) or recessive (BDNF: met^{66}met, COMT: met^{158}met; APOE: both ε4 forms present) genotypes.

Out of the 10 studies, 8 examined the influence of the presence of 1 or both met alleles in BDNF and 2 addressed the effects of 1 or 2 met alleles in COMT. Two of the 8 studies assessing the effects of 1 or 2 met alleles in BDNF additionally examined effects of the presence of the APOE ε4 isoform. Six[23,57-61] of the 8 articles addressing effects of 1 or 2 met alleles in BDNF had available FMA scores assessed at the end of the intervention to be used for a meta-analysis. Two of these studies[59,60] also included a retention assessment, with that data being included for a second meta-analysis.

BDNF polymorphism (val^{66}met and/or met^{66}met)

In total, 598 individuals (59.2% men, 40.8% women) sustaining a stroke participated in the 8 studies included in the qualitative analysis. The average age of the participants (mean ± SD) was 58.4 ± 3.2 years. A greater proportion of participants had sustained ischemic strokes (79.7%) compared to hemorrhagic strokes (20.3%). The distribution of the more-affected side was almost equal (50.7% right, 49.3% left). Three[57,61,62] of the included studies were ranked as *'good'* and the remaining five[23,58-60,63] *'fair'* (Supplemental Table 1). Participants were either in the acute[57-60,63] or chronic[23,61,62] stage post-stroke. All participants had moderate-to-severe[64] UL motor impairment (FM score ≤49/66).

Table 1 presents a summary of studies evaluating the effects of BDNF val^{66}met and met^{66}met polymorphism with a focus on sample size, type and dose of rehabilitation provided (if any), main outcomes and results. The sample size used for the Meta-analysis was 295 (no polymorphism: 101, polymorphism: 194). Analysis revealed a *large* (0.50, 95% CI: 0.11 - 0.88, P = 0.01, I^2 = 54%, random effects model; Figure 2) effect size at the end

Table 1. Effect of BDNF val[66]met and/or met[66]met polymorphism.

STUDY; SAMPLE SIZE (N); VAL/VAL AND MET ALLELE DISTRIBUTION AND DOWN'S AND BLACK SCORE	INTERVENTION	REHABILITATION PROVIDED/ DOSE	OUTCOMES AND TIMING OF ASSESSMENT	RESULTS
Chang et al, 2014; n = 44; Val/Val: n = 9; Met allele: n = 35 DBS: 19 (good)	10 sessions of rTMS over 2 weeks. Each session had 50 trains of 10 Hz frequency for 5 seconds at 90% RMT	Each train of rTMS was followed by 50 seconds of reaching and grasping exercises.	• Upper and lower limb Fugl-Meyer Assessment (FMA) scores • Box and Blocks Test (BBT). Assessments conducted at baseline, end of the intervention and 2-month retention.	*FMA*
		Active and active assisted exercises consisting of range of motion exercises, moving, and grasping and releasing cups and cubes.		• Upper limb: Greater change seen in *Val*/*Val* group at post (10 points) and retention (23 points) compared to Met alleles (4 and 11 points) respectively ($P < 0.05$).
		All participants also received conventional Physical (PT) and Occupational Therapy (OT) sessions, involving gait, fitness, and ADL training for 3 hours each day.		• Lower limb: Both groups improved at both assessments with no between group difference.
				BBT:
				• Greater change seen in *Val*/*Val* group (16 blocks) compared to Met alleles (6 blocks; $P < 0.05$) at retention.
Chang et al, 2016; n = 62; Val/Val: n = 12 Met allele; n = 50 DBS: 18 (fair)	10 sessions of rTMS over 2 weeks. Each session had 20 trains of 50 stimuli of 10 Hz frequency at 90% RMT	Each train of rTMS was followed by 50 seconds of reaching and grasping exercises.	• Upper and lower limb and total FMA scores	• 20 participants were good responders and 42 were poor responders.
		All participants also received conventional PT and OT sessions, involving gait, fitness, and ADL training for 3 hours each day.	• Degree of preserved Corticospinal Tract (CST) integrity quantified by diffusion tensor imaging and presence/absence of MEP in the FDI muscle.	• Greater proportion of good responders had *Val*/*Val* genotype (35%) compared to poor responders (11%).
			Assessments conducted at baseline and end of the intervention.	• Those with *Val*/*Val* genotype had significantly higher change in upper limb FMA scores (13.7 points) compared to Met alleles (1 point)
			Patients classified as good or poor responders depending upon the amount of change in UL FMA scores: Good responders (≥5 points); poor responders (≤4 points)	• Individuals with *Val*/*Val* genotype almost twice more likely to have better improvement than those with Met alleles.

(Continued)

Table 1. Continued.

STUDY; SAMPLE SIZE (N); VAL/VAL AND MET ALLELE DISTRIBUTION AND DOWN'S AND BLACK SCORE	INTERVENTION	REHABILITATION PROVIDED/ DOSE	OUTCOMES AND TIMING OF ASSESSMENT	RESULTS
Kim et al, 2016a n = 35; Val/Val: n = 10 Met allele; n = 25 DBS: 17 (fair)	No details provided	No information provided	• Upper limb FMA scores	*UL FMA scores*
			• Values of fractional anisotropy (FA), axial diffusivity (AD) and radial diffusivity (RD) for CST.	• Greater change in the *Val/Val* group at T2 (7 points) and T3 (17 points) compared to the Met group (4 and 12 points respectively).
			Assessments conducted at baseline, T1 (1 month after baseline) and T3 (3 months after baseline)	• Moderate positive correlation with FA values at T1 (r = 0.78) and T2 (r = 0.72) for the *Val/Val* group and at T3 (r = 0.59) for the Met group
				• Moderate positive correlation with AD scores at T1 (r = 0.78) and T2 (r = 0.72) for the *Val/Val* group.
				• Moderate negative correlation with RD values scores at T3 (r = −0.59) for the Met group.
Kim et al, 2016b n = 42; Val/Val: n = 26 Met allele; n = 16 DBS: 16 (fair)	Robotic therapy spread over 2-3 weeks.	Therapy consisted of repeated grasp and release movements of the affected hand and wrist.	• Upper limb FMA scores	• No difference in change in upper limb FMA scores between the *Val/Val* group at T2 (2.1 points) and the Met group (3.2 points) at the end of therapy.
		Participants wore a Hand Wrist assistive rehabilitation device and practiced tasks with real objects as well as virtual reality games (eg, squeezing lemons, moving jewels into a safe, etc.)	• Values of percentage change on fMRI signals and activation volume obtained from the ipsi- and contralesional primary sensorimotor cortex and dorsal premotor cortex using fMRI.	• However, the *Val/Val* group had greater percentage signal change (P = 0.037) and activation volume (P = 0.03) in the ipsilesional primary sensorimotor cortex compared to the those in the Met group.
		Tasks focusing on speed, reaction time, force, and range of motion were also practiced.	Assessments conducted at baseline, T1 (end of therapy)	

(Continued)

Table 1. Continued.

STUDY; SAMPLE SIZE (N); VAL/VAL AND MET ALLELE DISTRIBUTION AND DOWN'S AND BLACK SCORE	INTERVENTION	REHABILITATION PROVIDED/ DOSE	OUTCOMES AND TIMING OF ASSESSMENT	RESULTS
Shiner et al, 2016 n = 54; • Val/Val: n = 27 • Met allele: n = 27 DBS: 19 (good)	Wii based movement therapy (n = 40) or modified constraint induced movement therapy (mCIMT, n = 14).	10 one-hour long sessions on consecutive weekdays.	• Upper limb FMA • Wolf Motor Function Test - timed task (WMFT- tt) • Motor Activity Log Quality of Movement (MAL-QoM) scores. Assessments conducted at baseline and at the end of the intervention.	• All participants improved on FMA, WMFT -TT and MALQoM scores at the end of the interventions.
		Sessions targeted movements of the more-affected hand and arm.		• Overall, no difference in amount of change in FMA, WMFT-tt and MAL-QoM scores between those with *Val/Val* and Met alleles.
		The Wii group played golf, bowling, baseball, boxing, and tennis using the controller in the more-affected arm. mCIMT group received task-based training on object manipulation focusing on movement speed.		• However, subgroup analysis revealed less change in those with Met alleles and moderate (8.9%) or high (13.8%) functional ability on WMFT-tt scores compared to those with *Val/Val* (25.2% and 37.3% respectively).
		Individuals classified into those with low (inability to move >1 block on BBT), moderate (inability to complete Perdue Pegboard test) and high (ability to complete Perdue Pegboard test) functional ability.		• Similar results were seen on FMA values with less change in those with Met alleles and moderate (7%) or high (2%) functional ability compared to those with *Val/Val* (10% and 4% respectively).
Chang et al, 2017; n = 97; Val/Val: n = 21 Met allele: n = 76 DBS: 14 (fair)	Traditional inpatient rehabilitation	Traditional inpatient (2 hrs PT, 1 hr OT) followed by outpatient rehab (1 hr PT, 30 mins OT) or home exs.	• Upper limb FMA scores.	*Individuals with normal FMA scores or mild and moderate impairment*
			Assessments conducted at baseline and T1 (after 3 months).	• Baseline FMA scores explained 47% of variance in FMA scores at T1
			Participants classified into 4 categories based upon FMA scores at T1: Normal: 66, mild impairment (41-65), moderate impairment (25-40), and severe 0-24).	*Individuals with severe motor impairment*
				• A combination of presence of Met alleles, baseline FMA scores and age explained 59.5% of the variance in FMA scores at T1. Individuals with Met alleles were 1.48 times less likely to have better scores on the upper limb FMA.
				• Smaller proportion of individuals with two (10%) or one Met allele (31%) recovered significantly at T1compared to those with *Val/Val* genotype (42.9%).
				• Significant correlation between number of Met alleles and FMA score at T1 (rho = −0.248, $P < 0.05$).

(Continued)

Table 1. Continued.

STUDY; SAMPLE SIZE (N); VAL/VAL AND MET ALLELE DISTRIBUTION AND DOWN'S AND BLACK SCORE	INTERVENTION	REHABILITATION PROVIDED/ DOSE	OUTCOMES AND TIMING OF ASSESSMENT	RESULTS
Park et al, 2020; DBS: n = 58; Val/Val: n = 17 Met allele: n = 41 17 (fair)	Traditional inpatient rehabilitation	All participants received the same dose of PT and OT (3-week intensive inpatient rehabilitation).	• Upper limb FMA scores.	*Upper limb FMA scores*
			• FA values for CST, intrahemispheric connection from M1 to the ventral premotor cortex and corpus callosum (CC).	• Similar mean change seen in upper limb FMA scores in those with *Val/Val* (12.6 points) and Met alleles (13.8 points) at T2.
			Assessments conducted at baseline and T2 (after 3 months).	• *In the Val/Val group*, moderate negative correlation with FA in contralesional intrahemispheric connection from M1 to the ventral premotor cortex at T2 (r = −0.60; *P* = 0.024).
				• *In those with Met alleles*, moderate positive correlation with FA in the in the ipsilesional CST (r = 0.47; *P* = 0.003) and FA in the CC (r = 0.41, P = 0.011).
Cramer et al, 2022; n = 206; Val/Val: n = 166; Met allele: n = 40 DBS: 21 (good)	Task oriented upper extremity training or OT	Participants were randomized to 30 hrs each of task-oriented upper extremity training (Accelerated skill acquisition program), dose-equivalent occupational therapy, or standard of care.	• Change in Log WMFT-tt. • Cerebral atrophy measured using ventricular brain ratio. Assessments carried out at baseline and at end of 12 months	• Overall, no difference in amount of change in Log WMFT-tt scores between individuals with Met alleles compared to those with *Val/Val* genotype.
				• Greater cerebral atrophy (*P* < 0.01) seen in individuals with Met alleles compared to those with *Val/Val* genotype.
				• This enlargement was caused primarily by an enlargement in ventricular volume (*P* = 0.0098).

ADL: Activities of Daily Living;DBS: Downs and Black Checklist Score; FDI: Flexor Digitorum Indicis; fMRI: Functional Magnetic Resonance Imaging; MEP: Motor Evoked Potential; rTMS: Repetitive Transcranial Magnetic Stimulation; RMT: Resting Motor Threshold.

of the intervention period for improvement in UL FMA scores in those without compared to those with the polymorphism. At retention testing, the sample size used was 79 (no polymorphism: 19, polymorphism: 60). We found a similar large effect size (0.58, 95% CI: 0.06 - 1.11, P = 0.03, I^2 = 0%, random effects model; Figure 3).

In addition to UL FMA scores, other assessments at the body structure and function level included use of functional magnetic resonance imaging (fMRI), diffusion tensor imaging (DTI) and MRI. In terms of fMRI outcomes, lower ipsilesional activation volume and percentage signal change were noted in individuals with the Met alleles as compared to the Val homozygous individuals.[23] Use of DTI revealed differences in radial and axial diffusion[59] and fractional anisotropy[60] between individuals with and without Met alleles. Individuals with Met alleles also had greater cerebral atrophy on MRI.[62]

Sensitivity analysis included an additional meta-analysis being conducted with data from 5 studies included in this analysis. The only excluded[59] study provided no details on whether and if so, how many sessions of any form of rehabilitation were provided to the participants. The sample size used for this meta-analysis was 260 (no polymorphism: 91, polymorphism:169). Analysis revealed a large (0.43, 95% CI: 0.01 - 0.86, P = 0.046, I^2 = 57%, random effects model;

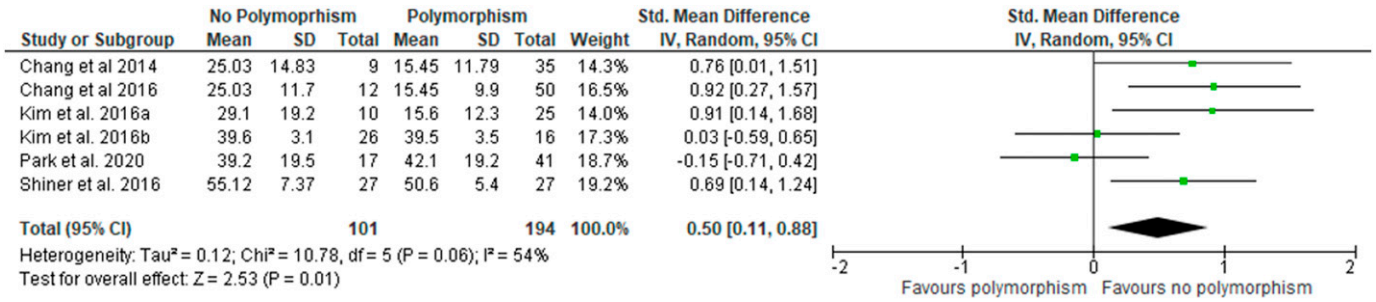

Figure 2. Results of meta-analyses examining influence of genetic polymorphisms on upper limb motor impairment quantified using the Fugl-Meyer Assessment, at the end of the intervention period. Larger squares indicate bigger study effect sizes. The diamonds represent pooled effects of results of individual studies. The location of the diamond indicates the estimated effect size and precision of the estimate is indicated by the width of the diamond.

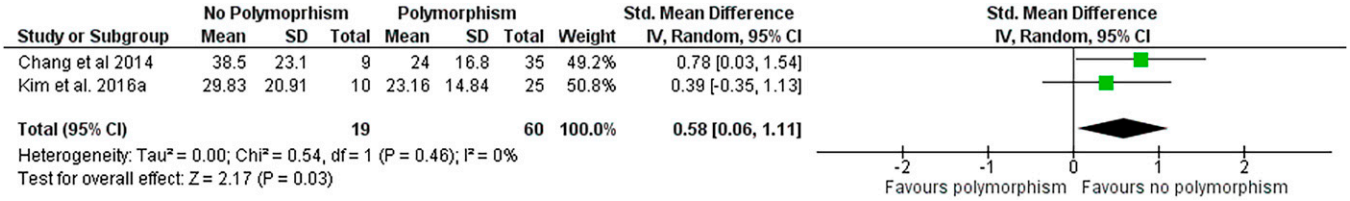

Figure 3. Results of meta-analyses examining influence of genetic polymorphisms on upper limb motor impairment quantified using the Fugl-Meyer Assessment, at retention testing. Larger squares indicate bigger study effect sizes. The diamonds represent pooled effects of results of individual studies. The location of the diamond indicates the estimated effect size and precision of the estimate is indicated by the width of the diamond.

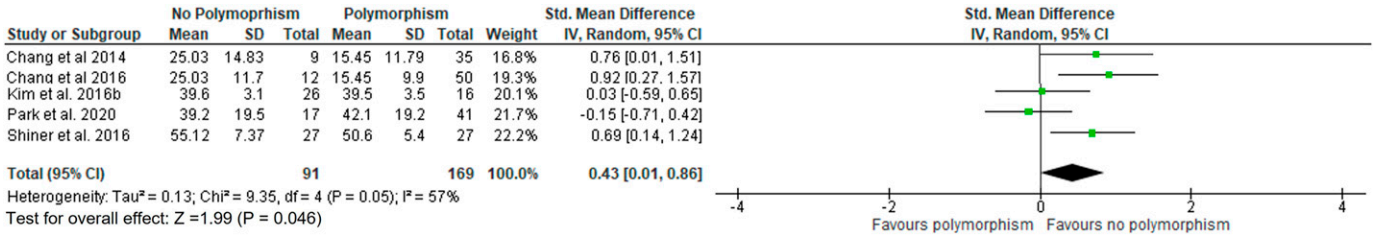

Figure 4. Results of sensitivity analysis (meta-analyses) examining influence of genetic polymorphisms on upper limb motor impairment quantified using the Fugl-Meyer Assessment, at the end of the intervention. Larger squares indicate bigger study effect sizes. The diamonds represent pooled effects of results of individual studies. The location of the diamond indicates the estimated effect size and precision of the estimate is indicated by the width of the diamond.

Figure 4) effect size at the end of the intervention period for improvement in UL FMA scores in those without compared to those with the polymorphism.

APOE ε4 polymorphism. Table 2 presents a summary of studies evaluating the effects of APOE ε4 and COMT val[158]met or met[158]met polymorphism. Two (good quality[61,62]) of the 8 studies examining the effects of BDNF polymorphism also assessed the effects of APOE ε4 polymorphism. These 2 studies included a total of 260 participants (61.5% men, 38.5% women). A greater proportion of participants had sustained ischemic strokes (83.4%) compared to hemorrhagic strokes (16.7%). The distribution of the more-affected side was equal (50 % right, 50% left).

Both studies used the Wolf Motor Function Test - timed test (WMFT-tt) as the primary outcome. No differences were noted between individuals with and without the APOE ε4 forms on WMFT-tt scores (Table 2A). In addition, groups did not differ on the amount of change seen in UL FMA scores and self-reported levels of UL quality (assessed using the Motor Activity Log)[61] or in the amount of cerebral atrophy noted between groups.[62]

COMT polymorphism (val^{158}met and/or met^{158}met). Two studies (1 good[65] and 1 fair[66] quality) including 157 participants (59.7% men, 40.3% women) examined the influence of COMT val^{158}met or met^{158}met polymorphism (53: no polymorphism, 104: polymorphism). A greater proportion of participants had sustained ischemic strokes (83.8%) compared to hemorrhagic strokes (16.2%). The distribution of the more-affected side was 46.8% right side, 51.9 %, left side and 1.3% of the participants had bilateral strokes. The studies used either the UL section of the Rivermead Motor Assessment (RMA)[65] or the FMA.[66]

Compared to those with met^{158}met, participants with val^{158}met allele (ES = 0.51) or val^{158}val (ES = 0.76) distribution had greater recovery with large effect sizes on the UL section of the RMA, at the end of the intervention period.[65] Individuals with val^{158}val distribution had greater recovery on the total FMA at the end of the intervention period (ES = 2.69), and at 3 (ES = 1.51) and 6 months (ES = 1.98) retention testing.[66] In addition, participants without the polymorphism improved more on other components of the RMA scores[65] including gross function, leg, and trunk function and higher Functional Independence Measure (FIM) scores.[66] Lack of available data from 2 or more studies using the same outcome measures precluded us from conducting a meta-analysis on the effects of APOE ε4 and COMT (val^{158}met, met^{158}met) polymorphisms.

Risk of bias

Overall, the risk of bias was low for all studies (Supplemental Figure 1, Supplemental Table 2), except one.[59] The ROB for this 1 study could not be ascertained for the domains of measurement of interventions and departures from intended interventions, as information on whether the participants received any intervention or not was missing.

Discussion

Results from this systematic review and meta-analysis (on the effects of BDNF val^{66}met and met^{66}met polymorphism) indicated that the presence of some genetic polymorphisms negatively influence post-stroke UL motor improvement. The meta-analyses revealed that presence of BDNF val^{66}met and met^{66}met polymorphism negatively impacted UL motor improvement assessed using the FMA, immediately after the end of the intervention period as well as at retention testing. Overall, majority of the studies had low risk of bias, which lends further credence to these results. Sensitivity analyses revealed that results continued to remain significant even with the exclusion of the study where information on some domains of bias was not available.

These results are in agreement to those found previously,[42] and extend those findings more specifically to UL motor improvement and not just general recovery from a stroke. We also found that while APOE ε4 polymorphism does not influence UL motor improvement, presence of COMT val^{158}met and/or met^{158}met polymorphism has a negative impact. Our results for APOE ε4 agree partially with those found previously,[39] and go beyond those results by focusing on UL motor improvement. To our knowledge, this is the first review which has systematically investigated the effects of COMT polymorphism on post-stroke UL motor improvement.

Study quality assessment

Of the ten articles included in the review, four[57,61,62,65] were ranked as *'good'* and the remaining six[23,58-60,63,66] *'fair'*. None of the articles were categorized as being of *'poor' or 'excellent'* in quality. We used the modified D&B checklist in this review, as both randomized and non-randomized study designs were included. The modified D&B checklist score includes an assessment of internal and external validity, reporting standards and sample size. Commonly non-reported details across studies in this review include information on external validity (3 questions) and on power/sample size analysis. Inherent word limitations in manuscript length may often preclude exclusion of such information in the main text. It is suggested that such information be reported at least as supplemental material to provide a better overview of the rationale behind participant selection in the studies.

Interventions used and number of sessions

A variety of interventions were used amongst the various studies included in the review. The interventions used included the use of rTMS along with traditional physical (PT) and occupational therapy (OT) sessions,[57,58] provision of traditional PT and OT sessions alone,[60,63,65] virtual reality platform along with robotic assistive devices,[23] commercial gaming solution (ie, Nintendo Wii),[61] modified constraint induced movement therapy,[61] and task-oriented UL training.[62] No details were provided for 2 studies.[59,66] The above-mentioned interventions were delivered at different intensities. Time spent in therapy was the most common metric used to denote intensity in the included studies. Time spent in therapy was either 60 minutes/day,[61,62] 90 minutes/day (outpatient rehabilitation phase)[63] or 3 hours/day.[57,58,63] Therapy was provided for 10 sessions over 2 weeks,[57,58,61] 2 - 3 weeks[23,60] or 30 sessions.[62] Information on exact number of sessions was not provided for the other studies.

Although time spent in therapy is 1 metric of intensity,[67] other metrics include numbers of repetitions[68] as well as "*amount of physical and/or mental work put forth by the client*".[69] Previous work involving healthy controls with BDNF polymorphism has shown that employing a high number of repetitions (about 800 repetitions/session) for about 5 days can cause significant changes in short-term plasticity even in those with the polymorphism.[70] The minimal number of repetitions/session in individuals with BDNF and other polymorphisms that have also sustained a stroke are currently unknown.

Table 2. Effect of APOE and COMT polymorphism.

STUDY; SAMPLE SIZE (N); DISTRIBUTION AND DOWN'S AND BLACK SCORE	INTERVENTION	REHABILITATION PROVIDED/ DOSE	OUTCOMES AND TIMING OF ASSESSMENT	RESULTS
A. Effects of APOE ε4 polymorphism				
Shiner et al., 2016; n = 54; ε4: n = 9; non ε4: n = 45 DBS: 19 (good)	Wii based movement therapy (n = 40) or modified constraint induced movement therapy (mCIMT, n = 14).	10 one-hour long sessions on consecutive weekdays.	• Upper limb FMA • Wolf motor function test - timed task (WMFT- tt) • Motor activity Log quality of movement (MAL-QoM) scores. Assessments conducted at baseline and post-intervention.	• All participants improved on FMA, WMFT-TT and MALQoM scores at the end of the interventions.
		Sessions targeted movements of the more-affected hand and arm.		• Overall, no difference in amount of change in FMA and MAL-QoM scores between ε4 carriers and those with non ε4 genotype.
		The Wii group played golf, bowling, baseball, boxing, and tennis using the controller in the more-affected arm. mCIMT group received task-based training on object manipulation focusing on movement speed.		• ε4 carriers tended to take longer to complete ADL activities (WMFT-tt, P = 0.057) compared to those with non ε4 genotype.
		Individuals classified into those with low (inability to move >1 block on BBT), moderate (inability to complete Perdue Pegboard test) and high (ability to complete Perdue Pegboard test) functional ability.		
Cramer et al, 2022; n = 206; ε4: n = 61; non ε4: n = 145 DBS: 21 (good)	Task oriented upper extremity training or occupational therapy	Patients were randomized to 30 h each of task-oriented upper extremity training (Accelerated skill acquisition program), dose-equivalent occupational therapy, or standard of care.	• Change in Log WMFT-tt. • Cerebral atrophy measured using ventricular brain ratio. Assessments carried out at baseline and at end of 12 months.	• Overall, no difference in amount of change in Log WMFT-tt scores between ε4 carriers and those with non ε4 genotype.
				• No differences seen in cerebral atrophy between individuals with and without the polymorphism.
B. Effects of COMT polymorphism (val^{158}met and/or met^{158}met)				
Liepert et al, 2013; n = 83, Val/val = 12 met allele: 71 DBS: 19 (good)	Traditional rehabilitation	Rehabilitation program included PT, OT, endurance, and strength training. Program was adapted to individual needs of the patient. Details unavailable on total duration of therapy.	• Rivermead motor assessment (RMA) and Barthel Index (BI) scores. RMA scores divided into gross function, leg and trunk and upper limb function.	RMA scores • Individuals with 2 met alleles showed less improvement in gross function (P = 0.003), leg and trunk function (P = 0.022) as well as upper limb function (P = 0.047). • Significant correlation with BI scores at all time points (P < 0.001).
			Assessments carried out at baseline,4 weeks later and at the end of 6 months.	

(Continued)

Table 2. Continued.

STUDY; SAMPLE SIZE (N); DISTRIBUTION AND DOWN'S AND BLACK SCORE	INTERVENTION	REHABILITATION PROVIDED/ DOSE	OUTCOMES AND TIMING OF ASSESSMENT	RESULTS
Kim et al, 2016 n = 74, Val/val = 41 met allele = 33 DBS = 15 (fair)	No details provided	No details provided.	• Total Fugl-Meyer assessment (FMA) and functional independence measure (FIM) total scores. Assessments carried out at hospital admission, discharge 3- and 6-mos Post- discharge.	FMA scores • Lower scores at discharge, 3-mos and 6 mos post discharge assessments in those with met alleles (P < 0.01) compared to the val heterozygous group. FIM scores • Lower scores at discharge (P < 0.01), 3-mos and 6 mons post discharge (P < 0.05) assessments in those with met alleles compared to the val heterozygous group.

DBS: Downs and Black Checklist Score; OT: Occupational Therapy; PT: Physical Therapy.

Approaches similar to those used previously could be employed to estimate the minimal number of repetitions to achieve a plateau in motor performance in a single session.[71,72] Whether using a fixed number of repetitions results in better UL motor improvement in post-stroke individuals with polymorphisms remains to be estimated.

Outcomes used to assess improvement

A variety of outcomes were used to assess the effects of the different polymorphisms. At the body structure and function level, in addition to the FMA, the RMA, MRI, fMRI and DTI were used. Only the FMA scores were used for the meta-analysis. At the activity level, Box and Blocks Test, WMFT and Motor Activity Log helped specifically assess UL activity performance, while outcomes including Barthel Index and FIM helped assess general activity performance. All the selected outcomes have well established psychometric properties.[73] However, no study used any assessment at the participation level. Hence the effects of the polymorphism at the participation level remain unknown.

There is preliminary evidence that better UL FMA and total FMA scores are associated with higher participation levels (measured using Stroke Impact Scale; SIS).[74] Similarly, preliminary evidence is also available that better mRS scores at discharge are linked to greater autonomy and family role performance domains of another measure of participation (Impact on Participation and Autonomy-English version).[75] Given that val[66] met and/or met[66] met polymorphisms negatively influence recovery of FMA and mRS[39] scores, it can be speculated that it could also negatively impact participation. However, this will have to be separately verified in future studies.

The outcome of choice would be the SIS, which is recommended as a measure of choice by previous consensus papers. If select core measures such as those recommended by previous publications[76-78] are used, the effects across the different levels of the ICF could be better understood. These measures include the FMA at the impairment level, WMFT or Action Research Arm Test at the activity level and SIS at the participation level. In addition, the UL part of the FMA does not account for the use of altered movement patterns.[64] It is currently unknown whether individuals with genetic polymorphisms use compensatory movement patterns for task completion.

Influence of ethnicity

Majority of the studies in this review emerged from Asia, particularly from Southeast Asia, with only 4 studies[23,61,62,65] being conducted outside Asia. Amongst these 4 studies, three[23,61,62] had detailed demographics available on ethnicity of the participants. Individuals belonging to Asian ethnicity have poor outcomes after a stroke.[77] There are some reports that individuals of Asian ethnicity tend to receive less rehabilitation services compared to individuals from a Caucasian ethnicity and have higher rates of hospital readmission.[78-80] In addition, in all the 3 biomarkers examined in this meta-analysis, individuals with Asian ethnicity have higher rates of polymorphisms.[81-83] The presence of high rates of the polymorphisms can be an additional factor explaining the lower rates of post-stroke motor improvement seen in this population. This information can likely play an important role in prediction of prognosis after a stroke. Furthermore, it can also help make decisions as to whether and if so, the extent to which

provision of rehabilitation interventions need to differ for this population.

Limitations

We only included studies involving adult participants published in English (since no one in the team was proficient in other languages). It might be possible that we missed studies published in other languages. None of the studies had an explicit sample size calculation. Information on baseline levels of depression and/or intake of antidepression medication was available in only 2 studies.[23,65] Information on the presence of depression is essential, as the presence of genetic polymorphisms is an additional risk factor[84–86] for post-stroke depression and can influence the extent of UL motor improvement.[10] None of the 4 studies[23,61,62,65] published from outside Asia conducted an analysis on the rates of recovery assessed using clinical and/or radiological outcome measures between different ethnicities. Future studies will also need to address the effects of ethnicity on stroke rehabilitation outcomes.

Conclusion

Results of our review suggest that presence of genetic polymorphisms in BDNF (val^{66}met and met^{66}met) and COMT (val^{158}met and/or met^{158}met) negatively impact post-stroke motor improvement. This was confirmed at the body-structure and function domain of the ICF for the UL using the meta-analysis on the effects of BDNF val^{66}met and met^{66}met polymorphism. Our findings may contribute to the understanding of 1 of the underlying mechanisms to help explain some variability in post-stroke UL motor improvement. This is valuable information for the means of tailoring a plan of care, creating realistic goals, and providing relevant, individualized rehabilitation to every patient. In addition, new questions have been identified including does the (i) use of a fixed number of repetitions result in similar or better levels of UL motor improvement in individuals with genetic polymorphisms; (ii) presence of COMT val^{158}met and/or met^{158}met continue to influence motor improvement at retention testing; (iii) presence of genetic polymorphisms influence participation levels and (iv) do individuals with genetic polymorphisms use altered movement patterns and if so, to what extent. Answers to these emergent questions can help better understand the influence of genetic polymorphisms on post-stroke upper limb motor improvement.

Ethical statement

Ethical approval

Ethics approval was obtained from all particpants for all the included studies.

Author contributions

Sandeep K Subramanian: Conceptualization; Funding acquisition; Methodology; Project administration; Formal Analysis, Supervision; Writing – review & editing.

Riley T Morgan: Investigation, Formal Analysis, Data Curation, Writing – Original draft.

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Kayla M Shepherd: Investigation, Formal Analysis, Data Curation, Writing – Original draft.

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