

EFFECTIVE NEUROTROPHIC BIOMARKERS FOR MOTOR RECOVERY POST STROKE - A SYSTEMATIC REVIEW OF INTERVENTION STUDIES

Dr. Vishnu Priya T M^{1*}, Dr. P Senthil Selvam², Dr. P. Antony Leo Asseer³, Dr. S.S. Subramanian⁴

¹MPT Neurosciences, (PhD), PhD Scholar, School of Physiotherapy, Vels Institute of Science and Technology & Advanced Studies and Assistant Professor at Sathyabama Institute of Science and Technology, Chennai.

Email: priyavishnu835@gmail.com. ORCID ID: 0009000571749638 (Corresponding Author)

²MPT Orthopaedics, PhD, Professor & Head of the department, School of Physiotherapy, Vels Institute of Science and Technology & Advanced Studies, Chennai. Email: hodphysiotherapy@vistas.ac.in. ORCID ID: 0000-0002-1252-8342

³MPT Orthopaedics, PhD, Professor & Principal, Faculty of Physiotherapy, Sri Ramachandra Institute of Higher Education and Research, Porur, Chennai. Email: antonyleo@sriramachandra.edu.in. ORCID ID: <https://orcid.org/0000-0002-8489-7243>

⁴MPT Orthopaedics, PhD, Professor & Dean, Sree Balaji College of Physiotherapy, Pallikaranai, Chennai. Email: subramanian.podhigai1968@gmail.com. ORCID ID: 0000-0002-9944-6250

Received: 1st Apr, 2026 | Revised: 20th Apr, 2026 | Accepted: 21 Apr, 2026 | Available Online: 29th May, 2026

ABSTRACT

Background: Recovery after stroke relies on neuroplasticity, the brain's ability to reorganize neural networks. Rehabilitation interventions such as task-specific training, aerobic exercise, strength training and technology assisted therapies are designed to enhance this plastic potential. In recent years, attention has shifted toward identifying circulating biomarkers that reflect neuroplastic changes.

Aim: This review aims to assess and synthesize evidence on effective neurotrophic biomarkers associated with motor recovery following rehabilitation interventions in post-stroke individuals.

Methodology: Electronic databases PubMed, Cochrane Database of Systematic Reviews, PEDro, Google Scholar, Scopus, Web of science and direct web searches were utilized to do the search. The search terms used were 'stroke', 'post-stroke', 'neurotrophic', 'neuroplasticity', 'biomarkers', 'motor', 'training', 'rehabilitation' and 'recovery' either separately or in combination.

Results: A total of 133 articles via electronic databases and 12 articles through direct web search were obtained. After a thorough evaluation by reading the title and abstracts, upon removing the duplicates, 96 articles were excluded from the study due to variable reasons. A final of 12 articles were included in this review based on the inclusion criteria and relevance to the research question. All the included studies analyzed and correlated the expression of neurotrophic biomarkers in response to multiple rehabilitation intervention post stroke.

Conclusion: Within the limits of this review, it can be concluded that assessment of appropriate neurotrophic biomarkers gives a valuable insight about the progress of the rehabilitation intervention. The apt rehabilitation intervention subsequent to the biomarker analysis further elucidates motor recovery in individuals post stroke.

Keywords: Neurotrophic biomarkers; Motor recovery; Post stroke

How to cite this article: Vishnu Priya TM, Senthil Selvam P, Antony Leo Asseer P, Subramanian SS. Effective Neurotrophic Biomarkers for Motor Recovery Post Stroke - A Systematic Review of Intervention Studies. *Int J Drug Deliv Technol.* 2026;16(5): 1249. DOI: 10.25258/ijddt.16.5.11

Source of support: Nil.

Conflict of interest: None

INTRODUCTION:

Stroke is a critical condition that occurs due to sudden decline of blood supply to a part of the brain. It is a very complex and dynamic process which can strike as either ischemic or hemorrhagic stroke. Ischemic strokes are caused by blocking the blood supply via blood clots whereas ruptures of blood vessels lead to hemorrhagic strokes [1]. The etiology of stroke can be polygenic such as high blood pressure, high cholesterol, uncontrolled diabetes, obesity, chronic deleterious habits, etc. The ultimate challenge is the recovery post stroke because there will be physical, cognitive and emotional impairments consequent to the occurrence of stroke which includes (i) motor defects - mobility, balance, coordination; (ii) sensory defects - numbing or tingling sensation; (iii) cognitive defects - memory loss, attention deficit, thinking & understanding deficit; (iv) communication defects - aphasia, dysarthria; (v) emotional defects - depression, anxiety and irritability [1–3]. Motor recovery after stroke is a tedious process as it requires the coordination of complex neural pathways that processes via various cellular and molecular conjunctions. Recovery after stroke necessitates intense neuroplastic changes that include synaptogenesis, axonal sprouting, cortical reorganization, neurogenesis, angiogenesis and long term potentiation. Stroke may be a momentary reaction to the body's chronic abnormal actions, but the recovery of it takes weeks to months and in severe cases it may even extend to years [4]. Neuroplasticity improves via therapeutic interventions that offer repeated neural stimulation. Over years physiotherapeutic interventions have progressed immensely facilitating recovery at a faster pace, especially therapy designed for individuals post stroke has drastically shifted from traditional to modern approaches. Also because of the affirmative efficacy, modern techniques have

been adopted in their standard protocol by many physiotherapists. Traditional rehabilitation therapy focuses on physical, occupational and speech therapy whereas modern rehabilitation therapy includes activity-based therapy such as constraint-induced movement therapy, high-dose activity-based rehabilitation, high doses of task-specific training, environmental enrichment, mirror therapy, robot assisted training, virtual reality, non-invasive brain stimulation [TMS/tDCS] and brain computer interface [5]. Apart from these aforementioned factors, recovery depends on age; stroke factors such as location, size & severity; phase of stroke; initiation of treatment; intensity of the treatment and precision rehabilitation [4]. The neuroplastic recovery were assessed via (i) neurophysiological tests - Transcranial Magnetic Stimulation (TMS), Motor Evoked Potentials (MEP), Somatosensory Evoked Potentials (SSEP), Electroencephalography (EEG), Electromyography (EMG), H-reflex testing & Event-Related Potentials (ERP); (ii) neuroimaging techniques - functional MRI (fMRI), diffusion tensor imaging (DTI) & PET scans and (iii) biological techniques - neurotrophic molecular biomarkers [6–8].

Neurotrophic biomarkers/ neurotrophins are either protein molecules or growth factors that modulate and promote neuroplasticity. They are the supreme coordinators of neuronal survival, growth, differentiation and synaptic plasticity. These neurotrophins can be an excellent & reliable indicator of neuroplasticity as their levels often change in accordance with the injury and rehabilitation of the neural network that are evaluated via blood (serum/plasma), CSF or neural tissues[6]. The common neurotrophic biomarkers are brain-derived neurotrophic factor (BDNF), nerve growth factor (NGF), neurotrophin-3 (NT-3), neurotrophin-4 (NT-4), Insulin like growth factor-1 (IGF-1), Vascular endothelial growth

factor (VEGF) and Glial Cell-Derived Neurotrophic Factor (GDNF) [9]. Among these, BDNF has emerged as an exclusive biomolecule in stroke rehabilitation because of its crucial role in synaptic plasticity, neuronal survival & long term potentiation promoting motor learning and cortical reorganization post stroke [10]. Similarly, IGF-1 and VEGF contribute to neurogenesis and angiogenesis, facilitating restoration of damaged neural networks and improving cerebral perfusion in ischemic regions [11,12]. Other neurotrophins such as NGF, NT-3, NT-4 and GDNF participate in neuronal maintenance, differentiation and synaptic remodeling, thereby supporting adaptive neuroplastic mechanisms during the recovery process [9]. These therapeutic approaches enhance the neurotrophin signalling pathways promoting functional reorganization of the brain. Consequently, monitoring upregulation/downregulation of neurotrophic biomarkers from baseline following rehabilitation provides valuable insight into the biological mechanisms underlying motor recovery. Previous literature evidence has proved that neurotrophic biomarkers can be used as a standard when assessing the neuroplastic changes pertaining to motor rehabilitation post stroke irrespective of the factors compromising rehabilitation outcomes. Chen T et al. evaluated BDNF and NGF biomarkers to analyze the efficacy of the intervention and its ability for motor recovery in stroke patients. They found a significant upregulation of both the markers indicating motor recovery [13]. Gorna S et al. analyzed the expression of BDNF, IGF-1, GDNF and VEGF and found significant upregulation for BDNF at week 3 but with the duration the other markers showed uncertain upregulation making it difficult to conclude except for GDNF which neither upregulated or downregulated [14]. Wang Y et al. evaluated NT-3 and found a constant increase post intervention pertaining to motor recovery [15]. Though there is proven evidence of association between neurotrophic biomarkers and motor recovery post stroke, the extent to which biomarkers respond to rehabilitation interventions remains a gap. The upregulation/downregulation of the neurotrophic biomarkers across the trials indicate the association but the difference in intervention protocols and heterogeneity of

stroke population makes it unclear about the assessment of neurotrophic biomarkers. To identify the reliability of the different neurotrophic biomarkers, there is need for associating of expression of these markers with the neuroplasticity and the factors that influence rehabilitation outcomes. Therefore, this systematic review is performed to comprehensively analyze the intervention based evidence on the expression of the neurotrophic biomarkers for motor recovery post stroke.

MATERIALS & METHODS:

This systematic review was done in accordance with Systematic review & Meta analysis [PRISMA] guidelines 2020 with a structured research question “Does rehabilitation interventions associated with motor recovery post stroke alter the expression of neurotrophic biomarkers?”. The PICO for this research question are as follows: P- Post stroke; I- Rehabilitation interventions; C-NA & O- Neurotrophic biomarker expression in response to motor recovery. This review is registered in PROSPERO before the commencement of the study (ID 1330793).

Search strategy:

A literature search was done with relevant electronic databases that include PubMed/MEDLINE, PEDro, Google scholar, Scopus, Web of science and Cochrane Central Register of Controlled Trials (CENTRAL). Further search was made via google search & cross references to eliminate missing literature evidence. The search terms used were ‘stroke’, ‘post-stroke’, ‘neurotrophic’, ‘neuroplasticity’, ‘biomarkers’, ‘motor’, ‘training’, ‘rehabilitation’ and ‘recovery’ either separately or in combination.

Search combinations according to the databases:

PubMed/MEDLINE& COCHRANE: (stroke OR post stroke) AND (neurotrophic OR neuroplasticity) AND biomarkers AND motor AND (training OR rehabilitation OR recovery)

Google scholar, PEDro, Scopus & WOS: Post-stroke AND neurotrophic biomarkers AND motor recovery.

Inclusion & Exclusion criteria:

Inclusion criteria:

- Age - Adult population >18 years of age
- Acute, sub acute or chronic phases post stroke
- Rehabilitation intervention studies (RCTs, quasi-experimental, controlled trials, comparative trials, prospective observational intervention trials)
- Measurement of serum or plasma neurotrophic biomarkers
- Pre-post biomarker assessment
- Reported motor/functional outcomes [e.g.,Fugl Meyer assessment(FMA), Action Research Arm test (ARAT), gait, Stroke Rehabilitation Assessment of movement (STREAM), Modified Barthel Index(MBI)]
- Human trials
- Last 10 years

Exclusion criteria:

- Non- stroke neurological conditions
- Animal studies
- Retrospective observational/cross-sectional studies without intervention
- Studies measuring only salivary or CSF biomarkers
- Non-motor outcome studies

Data collection & analysis:

After a thorough search of electronic databases based on the predefined inclusion & exclusion criteria, duplicates and irrelevant studies were removed. All the selected studies were screened independently by 2 researchers and the discrepancies were discussed & sorted. The abstracts were studied to identify the final studies. Full text articles were evaluated when the abstracts did not provide adequate information. The data extracted and analyzed were: Author, year, study design, sample size, age, stroke phase, intervention, type of sample, biomarkers analyzed, time point of measurement, motor outcome, follow-up, key findings [with respect to biomarkers], conclusion and limitations.

Quality assessment:

PEDro scale [16] for randomized trials and Newcastle–Ottawa Scale (NOS) [17] for comparative/ cohort/ prospective observational studies were utilized to assess the quality of methodology and to eliminate the risk of bias.

RESULTS:

Study selection: The systematic search from the electronic databases retrieved 133 studies in total. After removal of duplicates 96 studies were identified. A total of 79 studies were further eliminated after reading titles and abstracts. On thorough evaluation, 9 studies were excluded as they did not meet the inclusion criteria. The manual web search yielded another 12 studies, but after reading the abstracts, only 4 articles were selected. Thus, a total of 12 studies were finally included [13–15, 18–26]. The study selection process is depicted in the form of PRISMA flowchart [2020] in figure 1. Though this review primarily focuses on intervention studies, 2 prospective observational studies were included in the final list of 12 articles since their findings were aligning with the review objective.

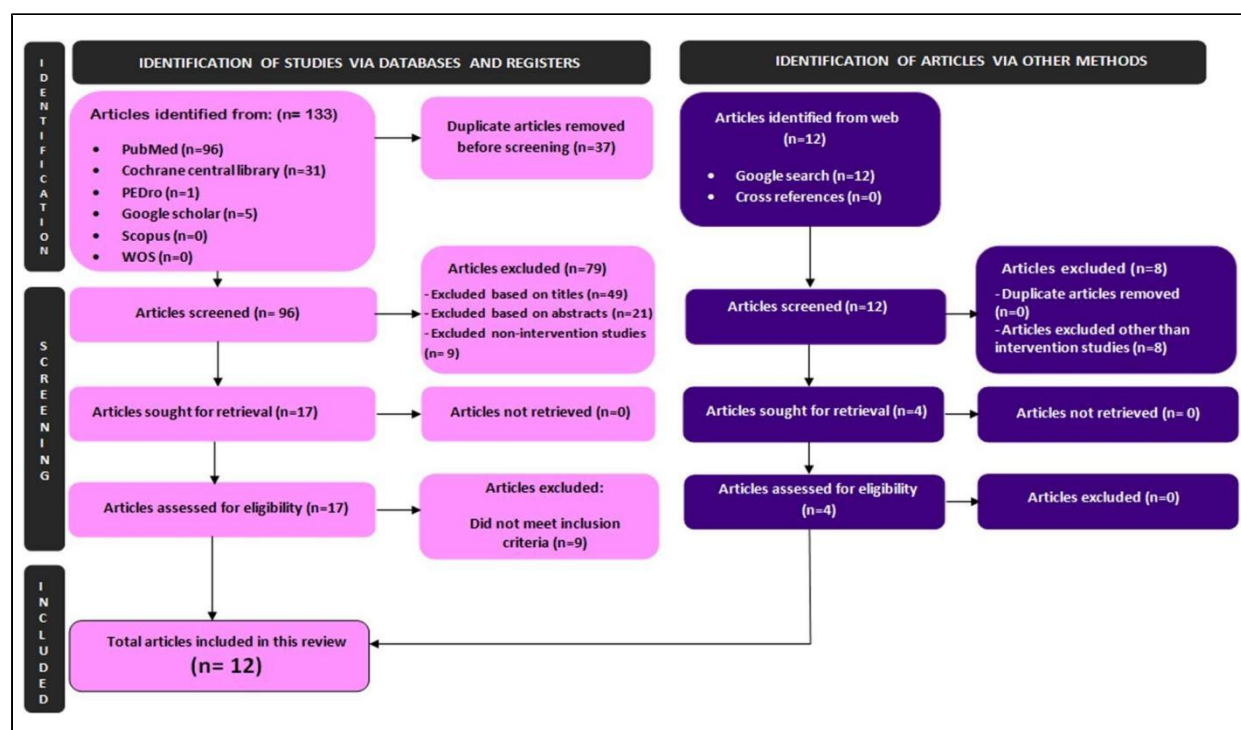


Figure 1: The PRISMA flowchart depicting the study selection process for this systematic review. A final of twelve studies were included based on the criteria and research

question of this review.

Study Characteristics: A brief summary of the final selected articles according to the review requirement is tabulated in Table 1.

Neurotrophic Biomarkers Investigated: Of the 12 included studies, 7 neuronal markers were analyzed: BDNF, NGF, GDNF, VEGF, IGF-1, Irisin & NT-3; 4 neuronal injury markers were investigated: NSE, NfL, A β 42/A β 40 & Total Tau and 6 non-neuronal markers were analyzed as a supporting evidence for motor recovery post stroke: IL-6, IL-10, TNF- α , cortisol, MMP-9 & MMP-2.

- **Neuronal markers:** 11 among the 12 studies included investigated BDNF. 8 studies reported a constant upregulation in the BDNF levels following post-stroke rehabilitation interventions [4,13–15,20,22,23,25]. 3 studies reported no change in BDNF levels [19,21], despite the intervention period being twelve weeks in 1 of the 3 studies, they identified nil change indicating

variability depending on the factors influencing the intervention & its outcomes [24]. NGF was consistently upregulated in pre & post intervention which were reported by 2 studies [13, 15]. NT-3 also had shown a raise in levels in 1 study [15]. GDNF showed no significant change [14]. 2 studies have evaluated VEGF and found a significant increase in the levels [14,26]. IGF-1 showed uncertainty as 2 studies reported no change in the expression levels [14, 20] whereas 1 study mentioned an upregulation [26]. Irisin expression was mostly uncertain or unchanged across 2 studies [14], [19].

- **Neuronal injury markers:** 1 study had investigated NSE, NfL, A β 42/A β 40 ratio & Total Tau and identified no significant change pertaining to neuroplastic changes or motor recovery except for upregulated NSE [21].

Phase of stroke & Neurotrophic biomarker expression: The expressions of the neuronal markers were greatly influenced by the phase of stroke as well. Rehabilitation interventions after a short or medium term intervention conducted at **acute phase** [**<1 month**] [13,21,25] reported variable BDNF expressions with 2 studies establishing upregulation and downregulation in 1 study. NSE was found to be upregulated but other neuronal injury markers NfL, total Tau, or A β 42/A β 40 showed no change. Individuals with **subacute stroke** [**<6 months**] [23, 26] reported increased expression of BDNF, VEGF & IGF-1 after a short or medium rehabilitation intervention. In the **chronic phase** [**>6 months**] [18–20,22,24], a robust increase in BDNF, NGF, NT-3 & IGF-1 were noticed irrespective of the intervention or follow-up duration. Some moderate intensity or low specificity interventions also exhibited no BDNF change indicating that intervention intensity and type is also important during chronic phase of stroke. 2 studies have not specified the phase of stroke and evaluated a random expression of neuronal markers to estimate only the neuroplasticity [14,15].

Duration of intervention & Neurotrophic biomarker expression: The follow-ups after the rehabilitation intervention is equally important as that of the expression of the neuronal biomarkers. 12 studies were categorized into short term intervention [**<2 weeks**], medium term intervention [**3-8 weeks**] and long term intervention [**>12 weeks**]. 4 studies had performed **short term rehabilitation intervention** with the duration ranging from 7 days to 2 weeks [19,20,23,25]. BDNF was found to be increased in 3 studies and 1 study showed no change in the expression levels. Irisin and IGF-1 showed no change. 5 studies had performed **medium term rehabilitation intervention** with the duration ranging from 3 to 8 weeks [13,14,18,21,26]. BDNF was increased in 3 studies but no change in 1 study. IGF-1 showed inconsistency as it was upregulated in 1 study and downregulated in another. NSE, NGF & VEGF were noticed to be upregulated across the studies. Irisin & GDNF showed uncertain results. 3 studies performed a **long term rehabilitation intervention** with duration ranging from 12 weeks to 6 months [15,22,24].

BDNF was persistently increased in 2 studies but showed no change even when the intervention was carried out for 12 weeks. Other biomarkers NT-3 & NGF showed upregulation pertaining to the rehabilitation intervention.

Type/ intensity of intervention & Neurotrophic biomarker expression: 2 studies have utilized **neuromodulation assisted rehabilitation:** Real vs trans-auricular vagus nerve stimulation [taVNS] with physical therapy and tDCS + Foot Drop Stimulator [FDS] + gait training vs sham tDCS + FDS + gait training [18,20]. Both the studies reported upregulation of BDNF even in the chronic phase of stroke. However, IGF-1 remained unchanged. 4 studies have adapted **exercise based rehabilitation:** Moderate-Intensity Continuous Training [MICT] + standard neurorehabilitation vs LICT, High-intensity aerobic exercise prior to modified constraint-induced movement therapy [mCIMT], Moderate-Intensity Cycle Ergometer Training + Robotic Training vs Low-Intensity Circuit Training and High-Intensity Interval Training [HIIT] vs Moderate-Intensity Continuous Training [MICT] [14,19,22,24]. Exercise based rehabilitation depends upon the intensity and duration of exercise hence the expression of BDNF was variable. Also GDNF, IGF-1, Irisin & VEGF exhibited no change. 2 studies utilized **task specific/ motor skill training:** Distributed practice vs massed practice using Accelerated Skill Acquisition Program [ASAP] and Biofeedback electrical stimulation + early intensive rehabilitation training among acute stroke population and found a constant upregulation of BDNF & NGF biomarkers [13,25]. 4 studies utilized **multimodal/ conventional rehabilitation:** Extensive multimodal cognitive and motor rehabilitation, Internet-based remote rehabilitation guidance + wearable device training, Standard post-stroke rehabilitation during hospitalization and Neurorestoration physiotherapy protocol vs conventional physiotherapy [15,21,23,26]. Multimodal rehabilitation during the acute phase demonstrated NSE upregulation but inconsistent expression of other neuronal markers. In contrast, after a 12 weeks rehabilitation program BDNF, NGF & NT-3 showed upregulation indicating neurotrophic support with prolonged

therapy. Also upregulation of VEGF & IGF-1 were noticed.

Quality assessment [Risk of Bias and Applicability Concern]: PEDro scale (0-10) was utilized to evaluate the quality of methodology of randomized trials of included studies. 8

studies were assessed and scored based on the PEDro scale [14,15,18–20,22–24]. NOS scale (0-9) was utilized to analyze the quality of the non randomized intervention studies. 4 studies were assessed and scored accordingly [13,21,25,26]. Further the scoring according to the respective scales is depicted in figure 2.

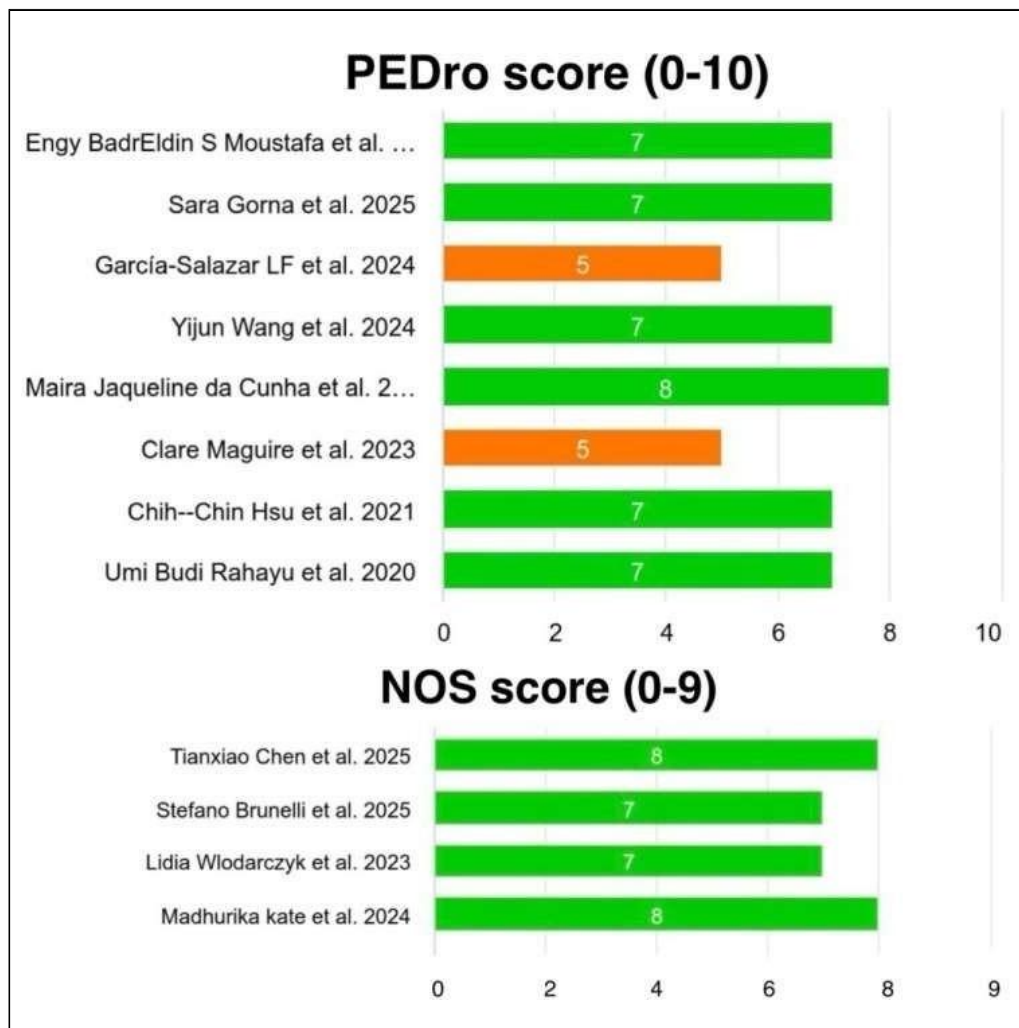


Figure 2: The PEDro score [0-10] for 8 studies and NOS score [0-9] for 4 studies are depicted in the form of a bar chart. The green bar depicts good methodological quality of the articles with the score >7 for both PEDro and NOS scale whereas the orange bar depicts moderate methodological quality of the included articles with a PEDro score of 4-6.

The risks of bias of the included studies were visualized using the ROBVIS tool [RoB 2.0 visualization]. The detailed domain oriented risk of bias is illustrated using the ROVIS traffic light plots for randomized trials [figure 3] & non

randomized intervention trials [figure 4] separately. Overall, for randomized trials the risk of bias ranged from low to high whereas for non randomized intervention trials, all the four studies demonstrated low risk.

	Risk of bias domains						
	D1	D1b	D2	D3	D4	D5	Overall
Study Engy BadrEldin S Moustafa et al. 2025							
García-Salazar LF et al. 2024							
Maira Jaqueline da Cunha et al. 2023							
Chih--Chin Hsu et al. 2021							
Yijun Wang et al. 2024							
Umi Budi Rahayu et al. 2020							
Sara Gorna et al. 2025							
Clare Maguire et al. 2023							

Domains:
D1: Randomization process
D1b: Deviations from intended interventions
D2: Missing outcome data
D3: Measurement of the outcome
D4: Follow-up
D5: Selection of the reported result

Judgement
 High
 Some concerns
 Low

Figure 3: Summary of the risk of bias and applicability concerns for each study based on the PEDro scale.

	Risk of bias domains						
	D1	D1b	D2	D3	D4	D5	Overall
Study Tianxiao Chen et al. 2025							
Stefano Brunelli et al. 2025							
Lidia Wlodarczyk et al. 2023							
Madhurika kate et al. 2024							

Domains:
D1: Selection of participants
D1b: Ascertainment of exposure
D2: Baseline outcome absence
D3: Comparability
D4: Outcome assessment
D5: Follow-up

Judgement
 Low

Figure 4: Summary of the risk of bias and applicability concerns for each study based on the NOS scale.

DISCUSSION:

Post stroke rehabilitation is challenging as the recovery relies on structural and functional reorganization of the neuronal networks called 'neuroplasticity' [27]. Neurotrophic biomarkers such as BDNF, NGF, NT-3, NSE, VEGF & IGF-1 presents an insight of neuroplastic alterations occurring in response to the rehabilitation interventions. This systematic review examined the possible neurotrophic biomarkers that exhibit neuroplasticity which are as follows: BDNF, NGF, GDNF, VEGF, IGF-1, Irisin, NT-3, NSE, NfL, A β 42/A β 40 & Total Tau. But the expressions of these markers were variable depending upon the neuronal adaptation following stroke rehabilitation. The neuronal responses are solely dependent on rehabilitation, yet akin, there are various factors that influence rehabilitation outcomes thereby suppressing the potential of neuroplasticity [4]. They are dependent on the interactions between stroke factors [phase of stroke] and rehabilitation factors [type & duration of rehabilitation]. It is also important to understand that all neuronal markers cannot be evaluated irrespective of the phase of stroke or rehabilitation intervention. The relevance of these biomarkers are activated by appropriate rehabilitation mechanisms targeting the neuroplastic changes, angiogenesis or neuronal injury [28,29].

The phase of stroke is mandatory to be considered before commencing the rehabilitation intervention. There are 3 phases of stroke: Acute [>1 month]; Subacute [>6 months] and Chronic [>6 months]. Immediately after the stroke, predominant changes expected are the neuronal damage targeting membranes and axons which initiates the neuroimmune response. Hence evaluating the neuronal injury markers such as NSE, NfL, Total Tau or A β 42/A β 40 would be ideal in the acute phase. Along with it any other inflammatory markers can be evaluated for assuring the neuroimmune response in par with the neuroplasticity [30,31]. Within days or weeks upon rehabilitation there will be endogenous repair mechanisms/neurorepair activation such as synaptic reorganization, synaptic strengthening, axonal sprouting,

angiogenesis and neurogenesis. The ideal markers to be evaluated in the subacute phase would be BDNF, NGF, VEGF, NT-3 and IGF-1 [32–34]. After months, the recovery would be extremely slow and the spontaneous response to rehabilitation declines due to persistent damage. Compensatory plasticity is predominant in this stage, so requirements of structured rehabilitation and neuromodulation can initiate neuroplasticity but still the recovery is not assured. BDNF, GDNF & NT-3 supports neuronal survival and circuit reorganization in the chronic stage [6,35]. BDNF immediately upregulates in response to neuroplastic stimulation and promotes synaptic plasticity unlike other neurotrophic biomarkers. BDNF is an activity dependent neurotrophic factor and it has multiple promoters for faster transcription. One transcription factor that immediately activates BDNF after rehabilitation intervention is Cyclic AMP Response Element- Binding Protein [CREB] via calcium influx. Hence BDNF can be utilized to assess neuroplasticity irrespective of the phase of stroke [36]. Also, it is necessary to analyze a panel of neurotrophic biomarkers rather than relying on a single biomarker relevance for confirmatory assessment.

Stroke recovery is influenced by the type & duration of rehabilitation interventions. The most commonly adopted rehabilitation intervention types are multimodal/conventional rehabilitation, task-specific/ motor skill, exercise based rehabilitation or neuromodulation assisted rehabilitation. Each of the exercise programs have different targeted mechanisms to activate neuroplasticity. The duration required for each of these aforementioned interventions are variable. Multimodal/conventional rehabilitation involves motor, cognitive and functional activities therefore a sustained long term stimulation of 8-12 weeks are required for recovery or even more depending upon the individual characteristics as well. This initiates neurogenesis, angiogenesis and synaptic remodelling. This type of conventional exercise is ideal for acute or early subacute phase of stroke when the brain is vulnerable for neuroplasticity [37]. Task-specific/ motor skill accentuates the hebbian plasticity and motor

cortex reorganization via specific neural pathways [38]. This rehabilitation concentrates on repetitive simple tasks that usually mimic functional movements of daily activities and train motor learning. 3-6 weeks of consistent training is required to accelerate the spontaneous neuroplasticity which is apt for the subacute phase of stroke. Exercise based rehabilitation utilizes moderate to high intensity exercises that require a constant stimulation of 4-8 weeks to bring about positive neuroplastic changes. It accelerates cerebral blood flow via metabolic activities and stimulates hippocampal and cortical plasticity [39]. This type of rehabilitation can be useful specifically in the late subacute phase [3-6 months]. Neuromodulation assisted rehabilitation directly promotes cortical excitability via electrical & magnetic stimulation rather than other techniques which rely on motor learning. This

technique requires minimal duration of 2-4 weeks of repeated therapy ideal for chronic stroke phase [6,40]. Therefore, type & duration of the rehabilitation intervention has a supreme role in the recovery of stroke. The ideal neuronal stimulation through rehabilitation type and duration of intervention for post stroke recovery according to phases of stroke are summarized in table 2. Hence assessment of neurotrophic biomarkers should be appropriate according to stroke factors and rehabilitation factors for confirmatory assessment of neuroplastic changes in stroke patients. Optimal biomarker assessments will pave the way for devising a personalized rehabilitation intervention according to the rate of recovery of stroke patients. This further enhances the quality of life restoring the functional independence and hope of the patients.

Table 2: A comprehensive summary of effective rehabilitation type, duration, relevant neurotrophic biomarkers & its function with post stroke recovery across phases of stroke.

Stroke phase	Intervention type depending on the intensity of exercise	Minimal Duration time	Neurotrophic Biomarkers	Neuroplastic Mechanism
Acute [< 1 month]	Multimodal/ conventional rehabilitation	8-12 weeks	NSE, NfL, Total Tau, A β 42/A β 40 ratio, BDNF	Initial neuronal damage
Subacute [<6 months]: [i] Early [1-3 months] [ii] Late [3-6 months]	Task-specific/ motor skill & Exercise based rehabilitation	3-8 weeks	BDNF, NGF, VEGF, NT-3, IGF-1	Neuronal repair activation
Chronic [>6 months]	Neuromodulation assisted rehabilitation	2-4 weeks	BDNF, GDNF, NT-3	Compensatory plasticity.

The variability in the expression of neurotrophic biomarkers can also be because of hormone profile, metabolism & biological response to rehabilitation pertaining to different age groups & gender. The absence of such stratified analysis will limit the comprehensive elucidation of expression of neurotrophic biomarkers and recovery of stroke to some extent. Hence, considering the demographic variables is needful to better apprehend the rehabilitation outcomes and recovery rate in individuals post stroke.

CONCLUSION:

The neurotrophic biomarkers are crucial to apprehend the biological mechanisms of neuroplasticity associating the recovery post stroke. The highly reliable neuronal markers are BDNF, NGF, VEGF, NT-3, IGF-1 & GDNF across phases of stroke. Monitoring the expression of these markers allows one to visualize the effectiveness of rehabilitation intervention. Further, a comprehensive approach of analyzing the demographic factors, stroke factors and rehabilitation intervention factors cumulatively will yield a tailor-made intervention program targeting early motor recovery post stroke.

References:

1. Stroke: A Comprehensive Review of Pathophysiology, Treatment, Long-Term Impact, and Future Directions. MedTechNews.uk. 2025. Available from: <https://medtechnews.uk/research-reports/stroke-a-comprehensive-review-of-pathophysiology-treatment-long-term-impact-and-future-directions/>
2. Barker-Collo S, Feigin VL, Parag V, Lawes CMM, Senior H. Auckland Stroke Outcomes Study. Part 2: Cognition and functional outcomes 5 years poststroke. *Neurology*. 2010 Nov 2;75(18):1608–1616. Available from: <http://dx.doi.org/10.1212/WNL.0b013e3181fb44c8>
3. Ayerbe L, Ayis S, Wolfe CDA, Rudd AG. Natural history, predictors and outcomes of depression after stroke: systematic review and meta-analysis. *Br J Psychiatry*. 2013 Jan;202(1):14–21. Available from: <http://dx.doi.org/10.1192/bjp.bp.111.107664>
4. Mustafa MA. Neuroplasticity in Recovery after Stroke: Mechanisms and Therapeutic Targets. *JPBS*. 2025 Sep 30;1(1):1–11. Available from: <https://physiobiojournal.com/index.php/JPBS/article/view/3>
5. Marín-Medina DS, Arenas-Vargas PA, Arias-Botero JC, Gómez-Vásquez M, Jaramillo-López MF, Gaspar-Toro JM. New approaches to recovery after stroke. *Neurol Sci*. 2024 Jan;45(1). Available from: <https://pubmed.ncbi.nlm.nih.gov/37697027/>
6. Cramer SC, Sur M, Dobkin BH, O'Brien C, Sanger TD, Trojanowski JQ, et al. Harnessing neuroplasticity for clinical applications. *Brain*. 2011 Jun;134(6):1591–1609. Available from: <https://pmc.ncbi.nlm.nih.gov/articles/PMC3102236/>
7. Ding Q, Chen J, Zhang S, Chen S, Li X, Peng Y, et al. Neurophysiological characterization of stroke recovery: A longitudinal TMS and EEG study. *CNS Neurosci Ther*. 2024;30(3). Available from: <https://pmc.ncbi.nlm.nih.gov/articles/PMC10916444/>
8. Rossini PM, Burke D, Chen R, Cohen LG, Daskalakis Z, Di Iorio R, et al. Non-invasive electrical and magnetic stimulation of the brain, spinal cord, roots and peripheral nerves: Basic principles and procedures for routine clinical and research application. An updated report from an I.F.C.N. Committee. *Clin Neurophysiol*. 2015 Jun;126(6):1071–1107. Available from: <http://dx.doi.org/10.1016/j.clinph.2015.02.001>
9. Huang EJ, Reichardt LF. Neurotrophins: Roles in neuronal development and function. *Annu Rev Neurosci*. 2001;24:677–736. Available from: <https://pmc.ncbi.nlm.nih.gov/articles/PMC2758233/>
10. Lu B, Nagappan G, Guan X, Nathan PJ, Wren P. BDNF-based synaptic repair as a disease-modifying strategy for neurodegenerative diseases. *Nat Rev Neurosci*. 2013 Jun;14(6):401–416. Available from: <http://dx.doi.org/10.1038/nrn3505>
11. Dyer AH, Vahdatpour C, Sanfeliu A, Tropea D. The role of Insulin-Like Growth Factor 1 (IGF-1) in brain development, maturation and neuroplasticity. *Neuroscience*. 2016 Jun 14;325:89–99. Available from: <http://dx.doi.org/10.1016/j.neuroscience.2016.03.056>
12. Jin K, Zhu Y, Sun Y, Mao XO, Xie L, Greenberg DA. Vascular endothelial growth factor (VEGF) stimulates neurogenesis in vitro and in vivo. *Proc Natl Acad Sci U S A*. 2002 Sep 3;99(18):11946–11950. Available from: <https://www.pnas.org/doi/abs/10.1073/pnas.182296499>
13. Chen T, Yang J, Yan J, Ding X. Effect of biofeedback electrical stimulation combined with early intensive rehabilitation training on stroke rehabilitation. *Am J Transl Res*. 2025 Jan 15;17(1):652–663. Available from: <http://dx.doi.org/10.62347/FWBS2561>
14. Górna S, Podgórski T, Kleka P, Domaszewska K. Effects of Different Intensities of Endurance Training on Neurotrophin Levels and Functional and Cognitive Outcomes in Post-Ischaemic Stroke Adults: A Randomised Clinical Trial. *Int J Mol Sci*. 2025 Mar 20;26(6):2810. Available from: <https://pmc.ncbi.nlm.nih.gov/articles/PMC11943154/>
15. Wang Y, Liu C, Wang Z, Li Y, Jiang H, Zhang Y, et al. Internet + wearable device training effects on limb function recovery and serum neurocytokine content in stroke patients. *NeuroRehabilitation*. 2024;55(1). Available from: <https://pubmed.ncbi.nlm.nih.gov/39150836/>

16. PEDro. PEDro scale. 2016. Available from: <https://pedro.org.au/english/resources/pedro-scale/>
17. Newcastle-Ottawa Scale (NOS). Available from: <https://ohri.ca/en/who-we-are/core-facilities-and-platforms/ottawa-methods-centre/newcastle-ottawa-scale>
18. Moustafa EBS, Darwish MH, El-Tamawy MS, Mostafa M, St AE, Khalifa HA. Plasticity Biomarkers, Interleukin-6 and Motor Performance Responses to Trans-auricular Vagus Nerve Stimulation Post-Stroke: A Randomized Controlled Trial. *Am J Phys Med Rehabil*. 2025 Oct 4. Available from: <https://pubmed.ncbi.nlm.nih.gov/41224215/>
19. García-Salazar LF, Pereira ND, Silva ESM, Ribeiro JAM, Nagai OG, Mendes ZR, et al. Could aerobic exercise applied before constraint-induced movement therapy change circulating molecular biomarkers in chronic post-stroke? *Physiother Theory Pract*. 2025 Jun;41(6). Available from: <https://pubmed.ncbi.nlm.nih.gov/39370701/>
20. da Cunha MJ, Pires DG, Peres A, Maurer S, Horn K, Souza PA. tDCS does not add effect to foot drop stimulator and gait training in improving clinical parameters and neuroplasticity biomarkers in chronic post-stroke: randomized controlled trial. *Int J Neurosci*. 2024 Dec;134(12). Available from: <https://pubmed.ncbi.nlm.nih.gov/37855112/>
21. Brunelli S, Nourbakhsh S, Grimaldi L, Calvani A, Gentileschi N, Mucci R, et al. Lower baseline serum neuronal-specific enolase levels predict better rate of recovery of functional walking ability in post-acute stroke patients. *Neurol Sci*. 2025 Dec 25;47(1). Available from: <https://pubmed.ncbi.nlm.nih.gov/41447407/>
22. Hsu CC, Fu TC, Huang SC, Chen CP, Wang JS. Increased serum brain-derived neurotrophic factor with high-intensity interval training in stroke patients: A randomized controlled trial. *Ann Phys Rehabil Med*. 2021 Jul;64(4). Available from: <https://pubmed.ncbi.nlm.nih.gov/32344098/>
23. Rahayu UB, Wibowo S, Setyopranoto I, Hibatullah RM. Effectiveness of physiotherapy interventions in brain plasticity, balance and functional ability in stroke survivors: A randomized controlled trial. *NeuroRehabilitation*. 2020;47(4). Available from: <https://pubmed.ncbi.nlm.nih.gov/33164953/>
24. Maguire C, Betschart M, Pohl J, Primani F, Taeymans J, Hund-Georgiadis M. Effects of moderate-intensity aerobic exercise on serum BDNF and motor learning in the upper limb in patients after chronic stroke: A randomized controlled feasibility study with embedded health economic evaluation. *NeuroRehabilitation*. 2023;52(3). Available from: <https://pubmed.ncbi.nlm.nih.gov/36806518/>
25. Kate M, Kumar KV, Nayak A, Shirali A. Comparing distributed versus massed practice on functional recovery and Brain-Derived Neurotrophic Factor (BDNF) in acute stroke subjects. *J Neurosci Rural Pract*. 2024 Apr;15(2). Available from: <https://pubmed.ncbi.nlm.nih.gov/38746529/>
26. Włodarczyk L, Cichoń N, Karbownik MS, Saso L, Saluk J, Miller E. Circulating serum VEGF, IGF-1 and MMP-9 and expression of their genes as potential prognostic markers of recovery in post-stroke rehabilitation—A prospective observational study. *Brain Sci*. 2023 May 23;13(6):846. Available from: <https://pmc.ncbi.nlm.nih.gov/articles/PMC10296181/>
27. Frizzell TO, Phull E, Khan M, Song X, Grajauskas LA, Gawryluk J, et al. Imaging functional neuroplasticity in human white matter tracts. *Brain Struct Funct*. 2022;227(1):381–392. Available from: <https://link.springer.com/article/10.1007/s00429-021-02407-4>
28. Nudo RJ. Recovery after brain injury: mechanisms and principles. *Front Hum Neurosci*. 2013 Dec 24;7:887. Available from: <https://public-pages-files-2025.frontiersin.org/journals/human-neuroscience/articles/10.3389/fnhum.2013.00887/pdf>
29. Berretta A, Tzeng YC, Clarkson AN. Post-stroke recovery: the role of activity-dependent release of brain-derived neurotrophic factor. *Expert Rev Neurother*. 2014 Nov;14(11):1335–1344. Available from: <http://dx.doi.org/10.1586/14737175.2014.969242>
30. Pryzmont M, Kosciuczuk U, Maciejczyk M. Biomarkers of traumatic brain injury: narrative review and future prospects in neurointensive care. *Front Med*. 2025 Jun 3;12:1539159. Available from: <https://public-pages-files-2025.frontiersin.org/journals/medicine/articles/10.3389/fmed.2025.1539159/pdf>

31. Khalil M, Teunissen CE, Lehmann S, Otto M, Piehl F, Ziemssen T, et al. Neurofilaments as biomarkers in neurological disorders—towards clinical application. *Nat Rev Neurol*. 2024 May;20(5):269–287. Available from: <https://www.nature.com/articles/s41582-024-00955-x>
32. Kostenko EV, Petrova LV, Egorov PD, et al. Neurotrophic factors as markers of stroke recovery: a review. *Bull Rehabil Med*. 2025;24(3):123–139. Available from: <https://journals.eco-vector.com/2078-1962/article/view/676547>
33. Cosky EEP, Ding Y. The role of vascular endothelial growth factor in angiogenesis and brain circulation after stroke. *Brain Circ*. 2018;4(2):73–81. Available from: <https://pmc.ncbi.nlm.nih.gov/articles/PMC6126238/>
34. Åberg ND, Åberg D, Jood K, Nilsson M, Blomstrand C, Kuhn HG, et al. Altered levels of circulating insulin-like growth factor I (IGF-I) following ischemic stroke are associated with outcome: A prospective observational study. *BMC Neurol*. 2018 Aug 6;18(1):106. Available from: <https://link.springer.com/article/10.1186/s12883-018-1107-3>
35. Chao MV. Neurotrophins and their receptors: A convergence point for many signalling pathways. *Nat Rev Neurosci*. 2003 Apr;4(4):299–309. Available from: <https://www.nature.com/articles/nrn1078>
36. West AE. Activity-dependent regulation of brain-derived neurotrophic factor transcription. In: *Transcriptional Regulation by Neuronal Activity*. 2008. p.155–173. Available from: https://link.springer.com/chapter/10.1007/978-0-387-73609-9_8
37. Langhorne P, Wu O, Rodgers H, Ashburn A, Bernhardt J. A Very Early Rehabilitation Trial after Stroke (AVERT): A Phase III, multicentre, randomised controlled trial. *Health Technol Assess*. 2017 Sep;21(54):1–120. Available from: <http://dx.doi.org/10.3310/hta21540>
38. Kleim JA, Jones TA. Principles of Experience-Dependent Neural Plasticity: Implications for Rehabilitation After Brain Damage. *J Speech Lang Hear Res*. 2008 Feb;51(1):S239. Available from: [https://pubs.asha.org/doi/10.1044/1092-4388\(2008/018\)](https://pubs.asha.org/doi/10.1044/1092-4388(2008/018))
39. Erickson KI, Voss MW, Prakash RS, Basak C, Szabo A, Chaddock L, et al. Exercise training increases size of hippocampus and improves memory. *Proc Natl Acad Sci U S A*. 2011 Feb 15;108(7):3017–3022. Available from: <https://www.pnas.org/doi/abs/10.1073/pnas.1015950108>
40. Gomez Palacio Schjetnan A, Faraji J, Metz GA, Tatsuno M, Luczak A. Transcranial direct current stimulation in stroke rehabilitation: a review of recent advancements. *Stroke Res Treat*. 2013;2013:170256. Available from: <https://pubmed.ncbi.nlm.nih.gov/23533955/>