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NEUROPLASTICITY IN THE RECOVERY OF COGNITIVE FUNCTIONS AFTER ISCHEMIC STROKE: INTEGRATION OF BIOMARKERS AND THERAPEUTIC STRATEGIES IN REHABILITATION (LITERATURE REVIEW)

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Background. Ischemic stroke is one of the leading causes of disability worldwide and is characterised by a sudden loss of blood supply to the brain and subsequent neuronal death. After the acute phase, patients often experience long-term impairment of cognitive functions, including attention, processing speed, memory, and executive functions. The restoration of these cognitive abilities has not only medical but also social and economic significance, as it determines patients' quality of life and their ability to return to daily activities and work.

Aim. To analyse and systematise modern literature data on the mechanisms of neuroplasticity, biomarkers, and the effectiveness of various therapeutic strategies in restoring cognitive functions following ischemic stroke.

Materials and Methods. The study was conducted as a narrative literature review using methods of theoretical generalisation, analysis, and synthesis of results. The literature search was conducted from 2020 through 2025 in the scientometric databases PubMed, Scopus, Web of Science, Google Scholar. The study was conducted as a private initiative; it did not receive any grant funding and was not officially registered.

Research Ethics. Only studies whose authors adhered to ethical research standards were included.

Results. The analysis demonstrated that cognitive impairment affects 30–70% of stroke survivors within the first year, while the prevalence of post-stroke dementia at 1 year was estimated at 18.4% when prestroke dementia was excluded. Given the limited effectiveness of traditional correction methods, modern studies justify the need for a multidisciplinary, personalised approach to the restoration of brain functions. This review summarises data regarding the mechanisms of neuroplasticity, the role of biomarkers and the effectiveness of various rehabilitation strategies for improving cognitive functions after a stroke and presents a synthesis of scientific data.

Conclusions. Neuroplasticity is a key mechanism for cognitive recovery after ischemic stroke. Understanding its dynamics can inform more accurate prognostication and optimisation of rehabilitation interventions. Available evidence supports several rehabilitation strategies, while biomarkers remain promising tools for prognosis and monitoring that require further clinical validation.

Keywords: *therapy, neurology, brain-derived neurotrophic factor, transcranial magnetic stimulation, virtual reality.*

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Цитуйте українською: Павлович ОС, Патєй ПМ, Ушко ЯА. Нейропластичність у відновленні когнітивних функцій після ішемічного інсульту: інтеграція біомаркерів та терапевтичних стратегій у реабілітації (огляд літератури). Медицина сьогодні і завтра. 2026;95(1):9c. In press. DOI: https://doi.org/10.35339/msz.2026.95.1.ppu [англійською].

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Abbreviations

ADL – Activities of Daily Living.
BDNF – Brain-Derived Neurotrophic Factor.
CBT – Cognitive Behavioural Therapy.
CCT – Computerised Cognitive Training.
DSTB – Digit Span Test Backward.
FMA – Fugl-Meyer Assessment.
GDF-10 – Growth Differentiation Factor 10.
MD – Mean Difference.
MMSE – Mini-Mental State Examination.
MoCA – Montreal Cognitive Assessment.
PSCI – Post-Stroke Cognitive Impairment.
RCT – Randomised Controlled Trial.
rTMS – repetitive Transcranial Magnetic Stimulation.
SMD – Standardised Mean Difference.
SOD – Superoxide Dismutase.
tDCS – transcranial Direct Current Stimulation.
TMT-A – Trail Making Test, Part A.
TMT-B – Trail Making Test, Part B.
uPAR – urokinase-type Plasminogen Activator Receptor.
VR – Virtual Reality.

Introduction

At present, ischemic stroke remains one of the most urgent medical and social challenges. Globally, approximately 15 million stroke cases occur each year, and stroke is the second-leading cause of death and the third-leading cause of disability [1; 2]. Survival after stroke is frequently accompanied by impairments of motor function, sensation, speech, and cognition. Cognitive impairments can include deficits in memory, attention, executive functions, language, and orientation. Cognitive impairment persists in 30–70% of stroke survivors [1]. A systematic review and meta-analysis estimated the prevalence of post-stroke dementia at 18.4% (95% CI 7.4–38.7) at 1 year when prestroke dementia was excluded [3].

Stroke disrupts both the structural and functional integrity of the brain. Such disorders significantly impair quality of life, reduce the ability to self-care and increase the risk of recurrent vascular events. Neuroplasticity refers to the brain's ability to reorganise neural connections following injury or learning. Biomarker research has sought indicators associated with post-stroke cognitive impairment [4], while mechanistic reviews describe synaptic reorganisation, axonal sprouting, and network remodelling as adaptive processes that may contribute to recovery [5].

Studies of rTMS, rehabilitation-related biomarkers, and acupuncture-associated neuroimaging indicate that different rehabilitation interventions can modify functional networks or neuroplasticity-related signals [6–8]. Individual brain resources – commonly described as cognitive reserve – also influence recovery; higher cognitive reserve is associated with more favourable rehabilitation outcomes [9; 10].

Numerous studies are devoted to studying the issue of treating cognitive disorders that have arisen after ischemic stroke. Standard cognitive rehabilitation methods have shown limited efficacy, and no universal approach has been found to date. One of the current challenges is to identify optimal rehabilitation strategies that combine different methods to maximise the effective stimulation of neuroplasticity.

Current literature emphasises the need for a multimodal, individualised approach to stroke recovery that may combine neurostimulation, pharmacotherapy, and training according to patient characteristics and rehabilitation goals [1].

Despite significant advancements, significant gaps remain in understanding the interaction of biomarkers, neuroplastic mechanisms, and specific therapeutic strategies for patients recovering from ischemic stroke.

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The **aim** of the work is to analyse and systematise current literature data concerning the mechanisms of neuroplasticity, biomarkers and the effectiveness of various therapeutic strategies in restoring cognitive functions following ischemic stroke.

Materials and Methods

This study was conducted as a narrative literature review. Scientific publications from 2020 through 2025 on neuroplasticity after ischemic stroke and rehabilitation approaches were searched in PubMed, Scopus, Web of Science, and Google Scholar. Methods of theoretical generalisation, comparative analysis, and synthesis of results were used. Search terms were applied individually and in Boolean combinations and included "ischemic stroke", "post-stroke cognitive impairment", "neuroplasticity", "cognitive rehabilitation", "cognitive reserve", "brain-derived neurotrophic factor" OR "BDNF", "biomarkers", "physical exercise", "computerised cognitive training", "virtual reality", "repetitive transcranial magnetic stimulation" OR "rTMS", "transcranial direct current stimulation" OR "tDCS", "acupuncture", and "pharmacotherapy". Sources were selected purposively for relevance to the mechanisms or markers of neuroplasticity, cognitive outcomes after ischemic stroke, and rehabilitation interventions; duplicate records, publications outside 2020–2025, and sources unrelated to the aim were not retained. No preregistered protocol, PRISMA flow diagram, duplicate independent screening, or formal risk-of-bias assessment is reported; accordingly, the present synthesis is treated as a narrative review rather than a systematic review. Four sources were used only for context: an editorial [2] and an epidemiological meta-analysis [3] for background epidemiology, a conceptual framework article [10] for cognitive reserve, and a study protocol [11] as a methodological source. These four publications were not included in the analytical narrative synthesis.

Of the 22 sources listed in the reference list, 18 publications were used in the analytical narrative synthesis, while four sources [2; 3; 10; 11] provided epidemiological, conceptual, or methodological context. The selected evidence was synthesised through theoretical generalisation, comparative analysis, and narrative synthesis.

Research Ethics

Only studies whose authors adhered to established ethical standards for conducting research were included in this review.

Results

Current scientific studies have provided data on the role of neuroplasticity as a key mechanism for the recovery of cognitive functions following ischemic stroke. It has been established that neuroplastic processes occur dynamically and understanding these dynamics can help predict the course of cognitive recovery and optimise rehabilitation interventions according to individual patient characteristics.

At the same time, the results of individual rehabilitation interventions remain inconsistent, which limits the possibility of applying a single algorithm for combining them. The available data support a personalised approach to selecting a rehabilitation strategy, taking into account the stage of recovery and the patient's individual rehabilitation potential [1; 12]. Cognitive reserve is of particular importance: a higher level of cognitive reserve is associated with a more favourable prognosis for cognitive and functional recovery after a stroke [9].

A review of the literature indicates that different approaches to cognitive rehabilitation after stroke yield variable outcomes (*Table*).

Rehabilitation interventions aimed at stimulating neuroplasticity have been shown to have varying degrees of efficacy in improving cognitive function in patients with ischemic stroke. The main therapeutic strategies include physical activity, cognitive training, neurostimulation, virtual reality, acupuncture, and pharmacotherapy.

According to the network meta-analysis by Wang H. et al. (2025) [13], multimodal exercise programmes combining strength, balance, and aerobic training significantly improved overall cognitive function compared with routine medical care (SMD –5.58, 95% CI –8.00 to –3.16) and ranked highest among the physical-activity modalities assessed. Aerobic exercise also showed a significant benefit (SMD –4.22, 95% CI –7.04 to –1.41). These estimates concern comparisons among physical-activity modalities and do not establish superiority of a broader programme combining exercise with cognitive training, virtual reality, or neurostimulation.

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Table. Effectiveness of basic interventions in restoring cognitive functions following ischemic stroke

Therapeutic strategy	Proven effect	References
Physical exercise (aerobic, mixed programmes)	SMD –5.58 (95% CI –8.00 to –3.16) in global cognition versus routine medical care; multimodal exercise ranked highest among physical-activity modalities	Wang H. et al. (2025)
Computerised cognitive training (CCT)	Improvement in general cognition (SMD +0.46), attention (SMD –0.45), and executive function (SMD +0.39); pooled memory effect was not statistically significant	Gao M. et al. (2025); Feng X. et al. (2025); Kazinczi C. et al. (2024)
Virtual reality (VR)	Significant improvement in TMT-A and TMT-B; MoCA MD +1.45 (95% CI –0.20 to 3.09), not statistically significant	Gunawan H. et al. (2024)
Repetitive transcranial magnetic stimulation (rTMS)	Improvement in general cognition and in attention, language, memory, and visuospatial function; long-term effect reported for general cognition, with substantial heterogeneity	Zhao J. et al. (2024)
Transcranial direct current stimulation (tDCS)	Improvement in general cognitive function (SMD +2.22), executive function (SMD +2.15), and visuospatial function (SMD +2.64); no statistically significant improvement was demonstrated for attention or memory	Zhao J. et al. (2024)
Acupuncture	Cognitive and neuroimaging changes involving the prefrontal cortex and hippocampus; evidence remains heterogeneous	Yang S. et al. (2025)
Pharmacotherapy (nootropics, antidepressants, ginkgo biloba)	Two medication studies in a systematic review yielded pooled MD +4.00 (95% CI 3.48–4.52); evidence for individual agents remains mixed and requires further confirmation	Kreiger K. et al. (2025); Patel J. et al. (2025)

Notes: DSTB – Digit Span Test Backward; MD – Mean Difference; MoCA – Montreal Cognitive Assessment; SMD – Standardised Mean Difference; TMT-A – Trail Making Test, Part A; TMT-B – Trail Making Test, Part B.

Computerised cognitive training (CCT) has evidence of benefit for several cognitive outcomes. A systematic review and meta-analysis by Gao M. et al. (2025) [14] found significant improvements in general cognition (SMD 0.46, 95% CI 0.21–0.71), attention (SMD –0.45, 95% CI –0.64 to –0.25), and executive function (SMD 0.39, 95% CI 0.12–0.67), whereas the pooled effect on memory was not statistically significant. Additional studies support benefits of computer-assisted training and working-memory training, although effects vary by outcome and protocol [15; 16].

Virtual reality (VR) has also shown benefits in selected cognitive domains. In the meta-analysis by Gunawan H. et al. (2024) [17], VR significantly reduced completion time on TMT-A (MD –26.43, 95% CI –43.18 to –9.68) and TMT-B (MD –59.23, 95% CI –103.21 to –15.25). The pooled MoCA difference favoured VR but was not statistically significant (MD +1.45, 95% CI –0.20 to 3.09).

Non-invasive brain stimulation has shown significant cognitive effects. A meta-analysis by Zhao J. et al. (2024) [18] found that rTMS improved general cognition immediately after treatment (SMD 2.58, 95% CI 1.44–3.71) and at longer follow-up (SMD 2.33, 95% CI 0.87–3.78), with significant effects in attention, language, memory, and visuospatial function. For tDCS, significant effects were reported for general cognition (SMD 2.22), executive function (SMD 2.15), and visuospatial function (SMD 2.64), whereas pooled effects on attention and memory were not statistically significant. Considerable heterogeneity and uncertainty about optimal stimulation parameters remain.

Pharmacological evidence is mixed across individual agents. Patel J. et al. (2025) [12] describe uncertain or inconsistent findings for levodopa and selective serotonin reuptake inhibitors, while ginkgo diterpene lactone meglumine has shown promising cognitive effects in selected studies. In the systematic review by Kreiger K. et al. (2025) [1], two medication studies yielded a pooled MD of 4.00 (95% CI 3.48–4.52), although the evidence base comprised only two pharmacotherapy studies. Acupuncture also shows potential benefit, but heterogeneity and the need for larger confirmatory trials limit certainty [1; 8]. Neuroimaging reviews describe modulation of the hippocampus and prefrontal cortex in association with acupuncture interventions [8].

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Available evidence supports an individualised multimodal rehabilitation strategy rather than a fixed combination proven to be superior. Physical and cognitive components may be combined, but direct comparative evidence for synergistic or sustained superiority of a specific cross-modal package remains insufficient [1; 13]. Considerable variability in outcomes further supports tailoring rehabilitation and monitoring response with objective clinical and, where appropriate, biological measures.

Biochemical, neuroimaging, and neurophysiological biomarkers are being investigated as potential tools for personalising rehabilitation. They may help predict recovery, monitor response, and inform protocol adjustment, but their validity, reproducibility, and clinically useful thresholds vary across studies. Standardised methods for data collection, analysis, and interpretation are therefore still needed.

Several studies have evaluated biomarkers related to neuroplasticity and recovery after ischemic stroke. Serum BDNF has been studied in relation to cognitive or functional recovery [7; 19], while endostatin, GDF-10, and uPAR have been investigated as candidate recovery-related biomarkers [20; 21]. A meta-analysis by Chen G. et al. (2023) [7] found that rehabilitation interventions were associated with increased serum BDNF, and higher BDNF was associated with functional improvement.

In a cohort study by Setyopranoto I. et al. (2024) [19], the mean BDNF concentration on day 5 among patients with acute ischemic stroke was [24.54±6.42] ng/mL and on day 30 was [24.86±8.51] ng/mL. Patients with PSCI (MoCA<26) had lower BDNF levels on day 5 ([22.86±5.97] ng/mL) than those without cognitive impairment ([28.01±5.99] ng/mL, $p<0.001$). In a randomised trial by Li F. et al. (2025) [22], serum BDNF increased significantly in the intervention group compared with controls ($p<0.001$), and the change in BDNF correlated with improvement in MMSE scores ($r=0.58$, $p<0.001$).

Other candidate biomarkers are also under investigation. Garcia-Rodriguez N. et al. (2025) [20] reported that higher baseline GDF-10 and uPAR were associated with less favourable motor or strength outcomes during follow-up, while a reduction in endostatin and an increase in GDF-10 during the first month of rehabilitation were associated with greater functional or motor improvement. For example, a decrease in endostatin of 25.75 ng/mL was associated with a 4.55-point improvement in FMA ($p=0.04$). These findings support endostatin, GDF-10, and uPAR as candidate biomarkers of recovery during post-stroke rehabilitation rather than established clinical markers. Qian S. et al. (2020) [21] separately reported an association between acute-phase plasma endostatin and post-stroke cognitive impairment.

Discussion

Across intervention categories, evidence supports several potentially useful approaches, but it does not establish that a programme combining physical exercise, cognitive training, and neuromodulation is superior to individual interventions. Wang H. et al. (2025) [13] found multimodal exercise superior to other physical-activity modalities, whereas broader comparisons across rehabilitation categories remain heterogeneous [1]. Many studies use small samples and heterogeneous designs, and cognitive outcomes are measured with different neuropsychological tests and follow-up intervals, limiting direct cross-study comparison.

Neurostimulation demonstrates significant cognitive benefits, but the durability and generalisability of these effects remain uncertain. Meta-analyses report significant effects of rTMS and tDCS together with substantial between-study heterogeneity and a continuing need for larger, methodologically consistent trials [1; 18].

Physical exercise generally shows beneficial effects on post-stroke cognition, with multimodal exercise ranking highest among the physical-activity modalities assessed in a network meta-analysis [13]. The psychological dimension remains less well studied: CBT may complement rehabilitation, particularly through mood and behavioural mechanisms, but durable effects on post-stroke cognitive recovery are not established [12]. Acupuncture has shown cognitive and neuroimaging changes, but the evidence remains heterogeneous and

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largely exploratory [8]. Circulating biomarkers and neuroimaging measures are also being examined for monitoring recovery; BDNF, endostatin, GDF-10, and uPAR show associations with cognitive or functional outcomes, but their clinical utility requires further validation [7; 19–22].

Conclusions

Neuroplasticity constitutes the foundation for the restoration of cognitive functions following ischemic stroke, encompassing alterations in synaptic connections, remodelling of network organisation and mobilisation of reserve neuronal pathways. Understanding these mechanisms can inform targeted and personalised rehabilitation strategies. Available evidence indicates that physical exercise, computerised cognitive training, virtual reality and neuromodulation may each contribute to cognitive recovery after stroke. Multidisciplinary rehabilitation incorporating several of these approaches appears promising; however, current comparative evidence is insufficient to determine whether their combined use provides superior cognitive outcomes compared with individual interventions.

The integration of biomarkers into prognosis and monitoring is an active area of research rather than an established component of routine rehabilitation. Peripheral biochemical markers, neuroimaging measures, and neurophysiological indicators may help characterise neuroplastic changes, estimate recovery trajectories, and assess response to interventions. However, their clinical use requires further validation of reproducibility, thresholds, and incremental prognostic value beyond clinical and neuropsychological assessment.

Prospects for Further Research

The analysis identifies several unresolved questions that should define subsequent research. The first concerns the temporal organisation of rehabilitation: the optimal timing, sequence, and dose-response relationships for physical exercise, CCT, VR, rTMS, and tDCS remain undetermined. The potential benefit of multimodal programmes therefore requires clarification of whether effects are additive, synergistic, or dependent on the stage of recovery. A second problem is the heterogeneity of cognitive outcomes: differences in neuropsychological instruments and follow-up intervals limit cross-study comparison and prevent definition of clinically meaningful cognitive change. A third unresolved area is biomarker validation. Associations of BDNF, GDF-10, uPAR, and endostatin with recovery have not yet established their specificity for cognitive neuroplasticity, clinically useful thresholds, or incremental prognostic value beyond clinical and neuropsychological predictors. Their longitudinal dynamics should be examined together with neuroimaging and neurophysiological measures to determine whether peripheral biomarker changes correspond to reorganisation of functional brain networks. The durability of cognitive gains after rTMS, tDCS, VR, and combined training also remains insufficiently defined. Finally, the modifying effects of age, infarct topography and volume, cognitive reserve, comorbidity, and psychological factors should be incorporated into prospective models of rehabilitation response to identify patient profiles most likely to benefit from specific interventions.

Declarations

Conflict of interest is absent.

The authors of the manuscript state that, during the conduct of the study, as well as during the preparation and editing of this manuscript, they did not use any generative artificial intelligence tools or services to perform any tasks listed in the Generative Artificial Intelligence Delegation Taxonomy (GAIDeT, 2025). All stages of the work (from the development of the research concept to the final editing) were performed without the involvement of generative artificial intelligence and exclusively by the authors.

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Authors' Contributions

Contribution / Authors	A	B	C	D	E	F
Pavlovych O.S.	+		+	+	+	+
Patiei P.M.		+			+	+
Ushko Ya.A.			+	+	+	+

Notes:

A – concept;

B – design; C – data collection;

D – statistical processing and interpretation of data;

E – writing or critical editing of the article;

F – approval of the final version for publication and agreement to be responsible for all aspects of the work.

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НЕЙРОПЛАСТИЧНІСТЬ У ВІДНОВЛЕННІ КОГНІТИВНИХ ФУНКЦІЙ ПІСЛЯ ІШЕМІЧНОГО ІНСУЛЬТУ: ІНТЕГРАЦІЯ БІОМАРКЕРІВ ТА ТЕРАПЕВТИЧНИХ СТРАТЕГІЙ У РЕАБІЛІТАЦІЇ (ОГЛЯД ЛІТЕРАТУРИ)

Актуальність. Ішемічний інсульт є однією з основних причин інвалідності у світі, що характеризується раптовою втратою кровопостачання мозку та подальшою нейрональною загибеллю. Після гострої фази пацієнти часто стикаються із тривалими порушеннями когнітивних функцій, включаючи увагу, швидкість обробки інформації, пам'ять та виконавчі функції. Відновлення цих когнітивних функцій має не лише медичне, а й соціальне та економічне значення, оскільки від цього залежить якість життя пацієнтів та їхня здатність повертатися до повсякденної активності та праці.

Мета. Аналіз та систематизація сучасних літературних даних про механізми нейропластичності, біомаркери та ефективність різних терапевтичних стратегій у відновленні когнітивних функцій після ішемічного інсульту.

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Матеріали та методи. Дослідження проведено як наративний огляд літератури з використанням методів теоретичного узагальнення, аналізу та синтезу результатів. Пошук літератури було проведено за 2020–2025 рр. у наукометричних базах даних PubMed, Scopus, Web of Science, Google Scholar. Дослідження виконане як приватна ініціатива, не отримувало грантового фінансування і не було офіційно зареєстроване.

Етика дослідження. У ході роботи були відібрані дослідження, автори яких дотримувалися етичних норм.

Результати. У ході роботи було показано, що когнітивні порушення протягом першого року після інсульту спостерігаються у 30–70 % пацієнтів, тоді як поширеність післяінсультної деменції через 1 рік оцінюється у 18,4 % за виключення деменції, що існувала до інсульту. З огляду на обмежену ефективність традиційних методів корекції, сучасні дослідження обґрунтовують необхідність мультидисциплінарного, персоналізованого підходу до відновлення функцій мозку. У цьому огляді узагальнено дані, що стосуються механізмів нейропластичності, ролі біомаркерів та ефективності різних реабілітаційних стратегій для покращення когнітивних функцій після інсульту, представлено синтез наукових даних.

Висновки. Нейропластичність є ключовим механізмом відновлення когнітивних функцій після ішемічного інсульту. Розуміння її динаміки може сприяти точнішому прогнозуванню та оптимізації реабілітаційних втручань. Наявні дані підтримують застосування кількох реабілітаційних стратегій, тоді як біомаркери залишаються перспективними засобами прогнозування й моніторингу, що потребують подальшої клінічної валідації.

Ключові слова: *терапія, неврологія, нейротрофічний фактор мозку, транскраніальна магнітна стимуляція, віртуальна реальність.*

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