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REVIEW ARTICLE

Circulating brain-derived neurotrophic factor as a potential biomarker of cognitive reserve in post-stroke cognitive impairment

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ABSTRACT

Post-stroke cognitive impairment (PSCI) is a prevalent and disabling neurological complication, affecting approximately 40-60% of stroke survivors within the first year and carrying a substantial risk of progression to vascular dementia. The observation that the severity of cognitive dysfunction is frequently disproportionate to the extent of structural brain injury implicates the modulatory role of cognitive reserve (CR). Yet the precise neurobiological mechanism through which CR confers this protection remains incompletely characterised. Brain-derived neurotrophic factor (BDNF), the principal regulator of synaptogenesis, neurogenesis, and long-term potentiation (LTP) via TrkB-mediated PI3K/Akt, MAPK/ERK, and PLC-γ signalling cascades, has emerged as a plausible biological mediator linking CR to post-stroke cognitive outcomes. This structured narrative review examined the biological pathomechanisms through which CR modulates circulating BDNF levels and thereby influences PSCI risk in patients with ischaemic stroke. A systematic search was performed in PubMed/MEDLINE, Scopus, and Google Scholar (January-April 2026), yielding 52 eligible publications (2015-2026) identified through the terms brain-derived neurotrophic factor, cognitive reserve, post-stroke cognitive impairment, neuroplasticity, and ischaemic stroke, with Boolean operators. The review demonstrated that individuals with high CR, quantified using the Cognitive Reserve Index questionnaire (CRIq; score ≥115), exhibit significantly more robust mBDNF responses during the subacute post-stroke phase (days 7-14), the optimal window of neuroplasticity, than those with lower CR. CR determinants, including educational attainment, occupational complexity, and leisure-time cognitive engagement correlate positively with serum BDNF levels through upregulation of activity-dependent BDNF gene expression, enhanced plasmin-mediated proBDNF-to-mBDNF conversion, and promotion of neural efficiency and compensation mechanisms. In addition, high CR was associated with better-preserved frontoparietal control network, salience network, and default mode network integrity, attenuating the neurological impact of diaschisis and global connectivity disruption. Integrating serum BDNF measurement with CRIq assessment at the subacute post-stroke phase offers a clinically applicable strategy for PSCI risk stratification and the personalisation of neuroplasticity-based cognitive rehabilitation programmes.

Keywords: Brain-derived neurotrophic factor, cognitive reserve, ischaemic stroke, neuroplasticity, post-stroke cognitive impairment

ABBREVIATIONS
BDNF: Brain-derived neurotrophic factor
CRIq:Cognitive Reserve Index questionnaire
DALYs: Disability-adjusted life years
DMN: Default mode network
ELISA:Enzyme-linked immunosorbent assay
FPCN: Frontoparietal control network
HPA: hypothalamic-pituitary-adrenal
ICC: Intraclass correlation coefficient
IGF-1: Insulin-like growth factor-1
IL-6: Interleukin-6
KOSCO:Korean stroke cohort for functioning and rehabilitation
LTD: Long-term depression
LTP: Long-term potentiation
MAPK: Mitogen-Activated Protein Kinase
mBDNF: Mature brain-derived neurotrophic factor
p75NTR:Low-affinity pan-neurotrophin receptor
PI3K/Akt:Phosphoinositide 3-kinase/protein kinase B
PLC-γ: Phospholipase C-gamma
proBDNF:Precursor brain-derived neurotrophic factor
PSCI: Post-stroke cognitive impairment
SNP: Single nucleotide polymorphism
REGARDS: Reasons for Geographic and Racial Differences in Stroke
TNF-α: Tumour necrosis factor-alpha
TrkB: Tropomyosin receptor kinase B
Val66Met:Valine-to-methionine substitution at codon 66
VEGF: Vascular endothelial growth factor

INTRODUCTION

Stroke is the second leading cause of death and the primary cause of disability in the adult population worldwide. The World Stroke Organization Global Stroke Fact Sheet 2025 reports more than 12.2 million new stroke cases per year, approximately 6.5 million deaths, and 143 million disability-adjusted life years (DALYs) lost.[1] In Indonesia, stroke prevalence has increased from 7 per 1,000 population in 2013 to 10.9 per 1,000 population according to the 2018 National Basic Health Research (*Riset Kesehatan Dasar, Riskesdas*), with Bali recording a prevalence of 10-12 per 1,000 population, predominantly among individuals aged ≥55 years.[2] Post-stroke cognitive impairment (PSCI) is one of the major post-stroke complications, affecting approximately 40-60% of patients in the first year and carrying a risk of progression to vascular dementia.[3,4] Post-stroke cognitive impairment encompasses a broad clinical spectrum ranging from mild single-domain deficits to dementia involving memory, attention, executive function, language, and visuospatial ability. This condition is closely associated with increased dependency on caregivers, diminished quality of life, and heightened economic and social burden.[5]

A clinically compelling observation is that the degree of cognitive impairment is frequently disproportionate to the extent of structural brain damage. This discordance implicates the role of a protective factor termed cognitive reserve (CR), the brain's adaptive capacity that enables individuals to maintain cognitive function despite significant structural pathology.[6,7] The determinants of CR, encompassing educational attainment, occupational complexity, intellectual engagement, and social participation, cumulatively build neural adaptive capacity across the lifespan.[8]

Brain-derived neurotrophic factor (BDNF) is the principal neurotrophin governing neuroplasticity, neurogenesis, synaptogenesis, and maintenance of synapses in the central

nervous system.[9-11] Multiple studies have established that higher BDNF levels in stroke patients correlate with better neurological outcomes and a lower risk of PSCI.[12,13] Furthermore, CR components including educational attainment and intellectual activity have been shown to correlate positively with serum BDNF levels in healthy older adult populations.[14]

Although the relationships between CR, BDNF, and PSCI have been studied individually across several countries, an integrative understanding of the biological mechanisms linking these three entities remains limited. This review aims to provide a comprehensive synthesis of BDNF's role as a biological mediator linking CR to neuroplasticity and cognitive outcomes following ischaemic stroke, thereby providing a scientific basis for developing neuroplasticity-based rehabilitation intervention strategies.

METHODS

This narrative review was conducted using a structured narrative method. A systematic literature search was performed in PubMed/MEDLINE, Scopus, and Google Scholar from January to April 2026. Search terms included: *brain-derived neurotrophic factor, BDNF, cognitive reserve, post-stroke cognitive impairment, PSCI, neuroplasticity, ischaemic stroke, CRIq,* and their combinations using Boolean AND/OR operators.

Inclusion criteria comprised: (i) original research articles, systematic reviews, meta-analyses, and clinical guidelines published in English or Indonesian; (ii) publications from 2015 to 2026; and (iii) articles addressing CR, BDNF, neuroplasticity, or post-stroke cognitive impairment in adult populations. Exclusion criteria comprised articles without full-text access, single case reports, and articles irrelevant to the review topic. Initially, a total of 90 records were identified through electronic database searching. After removing 14 duplicate records, 76 records underwent title and abstract screening, of which 18 were excluded. The remaining 58 full-text articles were assessed for eligibility. Six articles were excluded because of unavailable full text (n = 3), irrelevance to the review objectives (n = 2), or an inappropriate study population (n = 1). Ultimately, 52 studies met all eligibility criteria and were included in the qualitative synthesis. The study selection process, including identification, screening, eligibility assessment, and final inclusion of the selected articles, is illustrated in Figure 1.

Epidemiology and burden of post-stroke cognitive impairment

Stroke is defined as an acute neurological deficit syndrome caused by vascular injury to the brain, spinal cord, or retina attributable to a vascular aetiology.[15] Cognitive impairment is among the most frequent post-stroke morbidities and exerts the greatest impact on patients' functional independence. Global epidemiological data indicate that approximately 40-60% of stroke patients develop PSCI within the first year post-stroke, with the estimated incidence of post-stroke dementia reaching 10% in the first year and exceeding 30% within five years.[16]

The Reasons for Geographic and Racial Differences in Stroke (REGARDS) cohort demonstrated that stroke triggers an immediate, accelerated cognitive decline, particularly pronounced in older survivors.[4,17] Cohort data indicate an incidence of new-onset post-stroke dementia beyond six months of 1.7% per year, varying with stroke severity.[4,16] The Framingham Heart Study further indicates that stroke doubles the risk of dementia within ten years, even after demographic adjustment.[4,18] Early cognitive impairment detectable within the first days following ischaemic stroke onset has been independently associated with worse short- and long-term functional outcomes.[19,20]

Post-stroke cognitive impairment independently increases long-term mortality risk even after adjustment for vascular risk factors.[21] A multicentre study involving more than 2,000 stroke patients demonstrated sex-based differences, with women showing a higher propensity for post-stroke cognitive impairment than men after adjustment for age and educational level.[22] The risk profile of PSCI encompasses advanced age, low educational attainment, recurrent stroke, strategic lesion location, vascular comorbidities such as hypertension and diabetes mellitus, and systemic inflammatory processes.[5]

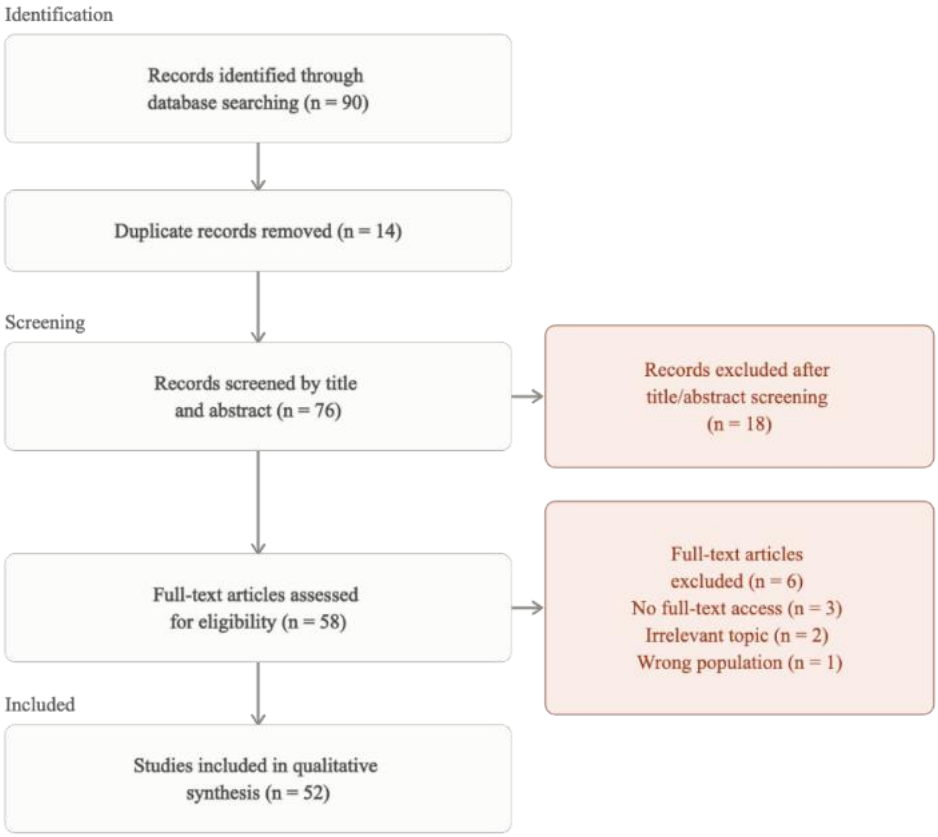

Figure 1. Flow diagram of the literature selection process

Concept and mechanisms of cognitive reserve

Cognitive reserve (CR) refers to the adaptive capacity of the brain to sustain cognitive function despite the presence of structural or functional pathology.[6] This construct explains the clinical phenomenon in which individuals with comparable degrees of brain damage attributable to ageing, stroke, or neurodegenerative processes exhibit markedly different clinical manifestations. CR is not a static anatomical reserve but rather a dynamic capacity of the brain to optimise or modify information-processing strategies, thereby minimising the clinical impact of tissue damage.[8]

According to Stern [6], two principal mechanisms underlie CR: (i) neural efficiency, which denotes an individual's capacity to engage brain networks more efficiently and economically when completing cognitive tasks; and (ii) neural compensation, an adaptive mechanism involving the recruitment of alternative neural networks when primary networks are compromised. Pappalettera et al.[23] further delineate these mechanisms as neural reserve, the intrinsic capacity of healthy brain networks to optimise performance and neural compensation, entailing reorganisation of functional connectivity in response to injury.

From a connectomics perspective, CR is associated with the maintenance of network topological efficiency at both global and local levels. Three large-scale brain networks are central to CR mechanisms: (i) the frontoparietal control network (FPCN), responsible for executive control, attentional regulation, and cognitive flexibility; (ii) the salience network (SN), functioning as a stimulus detection and prioritisation system; and (iii) the Default Mode Network (DMN), governing episodic memory, self-referential processing, and long-term memory consolidation.[6,23] Individuals with high CR exhibit better-preserved functional connectivity integrity across these networks in the presence of pathological burden.

The Korean stroke cohort for functioning and rehabilitation (KOSCO) study reported that stroke patients with high CR had a significantly lower risk of developing PSCI and demonstrated superior cognitive recovery compared with those with low CR.[24] Additional studies have demonstrated that high CR attenuates the decline in executive function for up to six years post-stroke and supports learning capacity and adaptive engagement throughout the rehabilitation process.[25,26]

Measurement properties of questionnaires assessing cognitive reserve

Numerous instruments have been developed to quantify CR, including life-experience-based questionnaires.[27] The Cognitive Reserve Index questionnaire (CRIq), developed by Nucci et al.[28] is a comprehensive instrument measuring CR in a lifespan-oriented framework across three core domains: (i) the education domain, assessing duration and level of formal schooling; (ii) the working activity domain, evaluating the duration and cognitive complexity of occupational activity; and (iii) the leisure time domain, capturing cognitively stimulating activities such as reading, social engagement, cultural participation, and physical activity.

The CRIq produces standardised scores with a population mean of 100 and a standard deviation of 15, enabling classification of individual CR levels within a normative distribution. According to the systematic review by Kartschmit et al.[8] the CRIq exhibits the most consistent reliability among available CR measurement tools, as evidenced by an intraclass correlation coefficient (ICC) of ≥0.87 indicating excellent test-retest reproducibility. A three-tier classification, low (≤84), moderate (85-114), and high (≥115), has demonstrated good clinical validity in evaluating the relationship between CR and post-stroke cognitive function, as shown in the longitudinal study by Ou et al.[29] involving patients with acute ischaemic stroke followed for up to six months.

Dynamic CR components, such as ongoing cognitive and social activities, exert a stronger contributory effect on post-stroke cognitive function than do static proxies, such as formal education alone.[30] The systematic review and meta-analysis by Contador et al.[25] confirms that higher CR is consistently associated with a reduced risk of PSCI, less severe cognitive deficits, and superior rehabilitation response.

Conventional assessment of cognitive reserve has relied predominantly on static sociodemographic proxies, namely years of formal education, occupational complexity, and engagement in intellectually stimulating activities, yet such approaches have been criticised for their inability to directly capture the underlying neurobiological dynamics that govern the brain's adaptive capacity.[31] With advancing insight into neuroplasticity mechanisms, a paradigm shift has emerged toward the application of systemic neurobiological biomarkers as objective indicators of cognitive function and cerebral reserve capacity.[32] Among the biomarkers investigated, brain-derived neurotrophic factor (BDNF) has emerged as the most consistently implicated in synaptic plasticity, memory consolidation, and post-stroke neurological recovery, with higher circulating BDNF levels correlating significantly with improved functional outcomes.[33-36]

Molecular biology of brain-derived neurotrophic factor

Brain-derived neurotrophic factor is the principal member of the neurotrophin family, governing the development, maintenance, and function of the central nervous system.[9] Structurally, BDNF is encoded by a gene with a complex exon organisation (exons I-IX) regulated by multiple alternative promoters, permitting neuronal-activity-specific transcriptional regulation. The BDNF gene is transcribed from several promoters, particularly promoters I, IV, and VI, generating transcript variants that allow spatially and temporally distinct BDNF expression across brain regions.[9]

In molecular physiology, BDNF undergoes sequential proteolytic processing: pre-proBDNF, generated from mRNA translation, undergoes protein folding and cleavage to produce proBDNF and subsequently mature BDNF (mBDNF). These two principal forms of BDNF exert distinct, and often opposing, biological effects.[9] ProBDNF binds preferentially to the p75 neurotrophin receptor (p75NTR) and elicits detrimental effects, including neuronal apoptosis, long-term depression (LTD) of synaptic strength, and synaptic pruning. In contrast, mBDNF exhibits high affinity for the tropomyosin receptor kinase B (TrkB) receptor and activates neuroprotective intracellular signalling cascades.[9]

The three principal intracellular signalling pathways activated by mBDNF via TrkB are: (i) the PI3K/Akt (phosphoinositide 3-kinase/protein kinase B) pathway, producing pro-survival effects through inhibition of pro-apoptotic proteins; (ii) the MAPK/ERK (mitogen-activated protein kinase/extracellular signal-regulated kinase) pathway, regulating gene expression involved in long-term synaptic plasticity and long-term potentiation (LTP); and (iii) the PLC-γ (phospholipase C-gamma) pathway, modulating neuronal excitability and synaptic transmission.[9,29] The equilibrium between proBDNF and mBDNF levels constitutes a critical determinant of the direction of neuroplastic

responses, particularly following brain injury such as stroke.

The Val66Met single-nucleotide polymorphism (SNP) in the proBDNF domain, a valine-to-methionine substitution at codon 66 of the BDNF gene is the most extensively studied BDNF genetic variant.[9] This substitution impairs activity-dependent BDNF packaging and secretion, such that Met allele carriers exhibit lower BDNF levels under conditions of neural stimulation, with functional consequences including reduced synaptic plasticity, hippocampal volume reduction, and impaired episodic memory consolidation.[9,33,34]

Distribution and measurement of BDNF in the peripheral circulation

In the peripheral circulation, BDNF exists in two principal compartments, serum and plasma, with clinically meaningful differences in characteristics.[9] Platelets constitute the primary source of BDNF in peripheral blood; they sequester mBDNF from plasma during megakaryocyte development in the bone marrow and store it within alpha granules. Consequently, serum BDNF concentrations released upon platelet activation during coagulation are substantially higher than plasma concentrations.

Serum is the matrix most widely employed in clinical research, yielding higher, more stable, and more sensitive measurements than plasma.[37] Serum BDNF levels have been shown to correlate with cognitive function and post-stroke neurological outcomes.[12,13] BDNF is typically quantified using an enzyme-linked immunosorbent assay (ELISA), which measures total BDNF without distinguishing proBDNF from mBDNF.

Serum and plasma BDNF concentrations exhibit significant diurnal variation, peaking in the morning and declining progressively throughout the day, in a pattern that correlates positively with the circadian rhythm of cortisol.[38] Ehrhardt et al.[38] found that serum BDNF demonstrates greater diurnal amplitude than plasma BDNF owing to the contribution of platelet-derived BDNF release during coagulation. These findings underscore the importance of standardising blood collection protocols, particularly sampling time, given the potential influence of circadian rhythms and sleep-related physiological changes on circulating biomarker concentrations, thereby improving the comparability and interpretability of biomarker measurements.

Post-stroke BDNF dynamics: three temporal phases

The role of mBDNF in synaptogenesis and post-stroke neuroplasticity evolves dynamically across three temporally distinct phases.[9,34] Understanding this temporal framework is pivotal for identifying the optimal window for BDNF measurement as a neuroplasticity biomarker.

Acute phase (0-72 hours): BDNF levels undergo sharp fluctuations due to cellular stress responses, glutamatergic excitotoxicity, calcium influx, and neuroinflammation. mBDNF begins activating TrkB receptors to provide early neuroprotection and modulate existing synapses; however, structural synaptogenesis has not yet predominated, and BDNF levels at this stage do not reliably reflect stable neuroplastic capacity.[9]

Subacute phase (days 7 to 28): mBDNF reaches its peak functional role through active synaptogenesis, dendritic growth, with LTP reinforcement underpinning cognitive and motor recovery. This period represents the optimal window of plasticity, during which BDNF levels stabilise and correlate with neural network reorganisation.[34] Accordingly, to assess the relationship between BDNF and CR, the optimal time period for BDNF measurement is between days 7 and 14 post-stroke, given that the acute-phase variability has subsided and BDNF activity reflects active neuroplastic adaptation.[12,34]

Chronic phase (≥1 month): BDNF expression tends to decline but continues to contribute to synaptic connectivity maintenance and long-term remodelling, influenced by extrinsic factors including physical activity, cognitive stimulation, and sustained rehabilitation.[34] These temporal distinctions apply to both ischaemic and haemorrhagic stroke, although nuanced biological differences exist between the two subtypes.

Brain-derived neurotrophic factor as a neuroplasticity mediator: relationship with cognitive reserve

Brain-derived neurotrophic factor plays a central role in neuroplasticity, the brain's capacity to adapt to structural and functional alterations in response to experience or injury.[33] In relation to CR, BDNF functions as a biological mediator linking environmental and experiential factors, including educational engagement, intellectual activity, and physical exercise, to the brain's capacity to maintain cognitive function despite structural damage.

Collins et al.[14] demonstrated a significant positive association of serum BDNF levels and

CR components with cognitive performance in healthy older adult populations. Physical activity, a primary CR determinant, consistently elevates BDNF levels through upregulation of gene expression and enhanced neurotrophin secretion.[39] The comprehensive review by Dadkhah et al.[34] confirmed that aerobic exercise consistently increases serum BDNF and is associated with improved cognitive function following stroke.

In the context of brain reserve, BDNF contributes to structural brain integrity, including brain volume, synaptic density, and neuronal network complexity. Individuals with higher BDNF expression tend to demonstrate better-preserved brain architecture, enabling them to tolerate neuropathological insults without significant clinical manifestation.[33,35,40,41] Genetic and epigenetic factors, including the Val66Met polymorphism and epigenomic modifications, further modulate brain reserve capacity by regulating BDNF expression and secretion.[40,41]

Within the concept of brain resilience, BDNF mediates the brain's functional adaptability to stressors or injury, including stroke, through the maintenance or restoration of neurological function.[12] Brain resilience reflects the dynamic capacity for neural network compensation and reorganisation, critically dependent on BDNF-mediated neuroplasticity mechanisms. Individuals with high CR exhibit more optimal BDNF responses during post-stroke recovery, contributing to superior neural network efficiency and flexibility.[13,14]

Pathomechanisms linking cognitive reserve, BDNF, and PSCI

A comprehensive understanding of the pathomechanisms connecting CR, BDNF, and PSCI requires integrating brain reserve, cognitive reserve, and brain resilience within the context of ischaemic injury.[40] Genetic and lifetime sociodemographic environmental factors, encompassing educational attainment, occupational complexity, and cognitive stimulation, collectively shape brain reserve and CR, thereby determining brain resilience as the mediator between brain injury and cognitive outcome.[41]

Following ischaemic brain injury, in addition to direct infarct tissue damage, diaschisis may result in reduced function in anatomically intact areas connected to the lesion zone via long-range white matter tracts. This mechanism produces widespread functional connectivity disruption beyond the infarct territory, including global cognitive networks such as the DMN and the frontoparietal executive network.[42] Individuals with high CR are better equipped to sustain brain resilience through compensatory and cortical reorganisation mechanisms, thereby attenuating the cognitive impact of brain damage.

At the neurobiological level, high CR is associated with more optimal BDNF expression and response following stroke.[12,14] Post-ischaemia BDNF, acting via TrkB, facilitates synaptogenesis, neurogenesis, and neural network reorganisation, all critical components of brain resilience. Patients with high CR who do not develop PSCI are hypothesised to exhibit higher mBDNF levels, reflecting more optimal neuroplastic capacity, compared with high-CR patients who nonetheless develop PSCI despite equivalent protective factors.[12,13]

Chang et al.[12] reported in a large stroke cohort that high serum BDNF levels were significantly associated with a decreased risk of PSCI after adjustment for potential confounders. This finding was corroborated by Shin et al.[13] who demonstrated the strong prognostic value of BDNF for post-stroke functional recovery. Conceptually, this relationship can be framed within the mechanism-outcome gap model, a scenario in which two individuals with comparable neural injury demonstrate markedly different cognitive and functional outcomes, partly mediated by differences in CR capacity and BDNF expression.[43-45]

Factors influencing serum BDNF levels: implications for CR

Serum BDNF concentrations are modulated by a range of biological, clinical, and environmental factors reflecting neuroplastic dynamics.[9] Appreciation of these factors is critical for the valid interpretation of BDNF levels in the context of post-stroke CR research.

Age is a principal biological determinant: advancing age is associated with a progressive decline in BDNF levels, contributing to age-related cognitive decline.[46] Physical activity, particularly aerobic exercise, consistently elevates BDNF through stimulation of BDNF gene expression and enhanced neurotrophin release from neurons and peripheral tissues.[34,39] This effect is germane to CR research, as physical activity constitutes a key component of the CRIq

Leisure Time domain that contributes to CR enhancement.

The Val66Met genetic polymorphism influences BDNF secretion and transport, whereas epigenetic modifications, including DNA methylation and histone acetylation, can modulate BDNF expression at the transcriptional level.[35,36] Psychological conditions, including post-stroke depression, reported in 25-33% of patients, as well as systemic inflammation and comorbidities such as diabetes mellitus and cardiovascular disease, contribute to BDNF level variability.[37,46-..49]

In the post-stroke subacute phase, serum BDNF is influenced by stroke severity: more extensive lesions tend to be associated with lower BDNF levels and poorer cognitive outcomes.[12] However, individuals with high CR demonstrate more robust BDNF recovery responses, such that subacute BDNF levels in these individuals reflect not merely the extent of neuronal injury but also the adaptive potential and brain recovery capacity.[14,50]

Diurnal BDNF variation and the influence of the sleep-wake cycle constitute important methodological considerations.[38] Acute short-term sleep deprivation transiently increases serum BDNF as a neuroadaptive compensatory response; however, chronic sleep deprivation and insomnia are associated with persistent BDNF reduction through hypothalamic-pituitary-adrenal (HPA) axis dysregulation, cortisol hypersecretion, and tumour necrosis factor-alpha (TNF-α) elevation.[50] In post-stroke patients, who frequently suffer sleep disturbances as comorbidities, BDNF fluctuations induced by sleep-wake cycle disruption can confound biomarker interpretation, underscoring the imperative of standardising specimen collection.[38]

Recent advances: integration of biomarkers and neuroimaging in the quantification of CR

Advances through 2025-2026 reflect a paradigm shift from sociodemographic proxy-based approaches to neurobiological biomarker- and neuroimaging-based approaches in the quantification of CR.[32] Traditional CR measurement has relied on static proxies such as educational attainment and occupational complexity; however, this approach fails to capture the underlying neurobiological dynamics of adaptive brain capacity.

Li et al.[31] proposed quantification of CR through neuroadaptive biomarkers based on structural-functional interactions, demonstrating that CR can be modelled as the network's compensatory capacity against pathological burden. Advances in functional and structural neuroimaging, including resting-state fMRI-based functional connectivity analysis and MRI radiomics, now enable in vivo quantification of CR and brain reserve through assessment of neural network integrity and cortical reorganisation patterns.[50]

Among candidate biomarkers, BDNF most consistently associates with synaptic plasticity, memory consolidation, and post-stroke neurological recovery, establishing it as the primary biomarker for neuroplasticity-based research.[12,13,37] Although other biomarkers, including interleukin-6 (IL-6), tumour necrosis factor-alpha (TNF-α), insulin-like growth factor-1 (IGF-1), vascular endothelial growth factor (VEGF), and endogenous antioxidants (superoxide dismutase, catalase, glutathione peroxidase), also modulate neuroplasticity, BDNF more consistently demonstrates direct associations with synaptic plasticity and neurological recovery.[37]

The integration of systemic neurobiological biomarkers and neuroimaging opens avenues for developing more accurate PSCI prediction strategies and more precisely targeted rehabilitation interventions in post-stroke populations.[31,32] A recent multivariate clinical prediction model developed by Kusec et al.[51] combining clinical factors, neuroimaging data, and patient demographic characteristics, demonstrated superior multidomain PSCI predictive capacity compared with single-modality approaches.

Clinical implications and future research directions

An integrative understanding of the relationships among CR, BDNF, and PSCI carries significant clinical implications. Assessment of the cognitive reserve index using standardised instruments such as the CRIq can be integrated into the initial evaluation of stroke patients, facilitating the identification of individuals at high risk for PSCI and supporting more precisely tailored cognitive rehabilitation programme planning.[28,29]

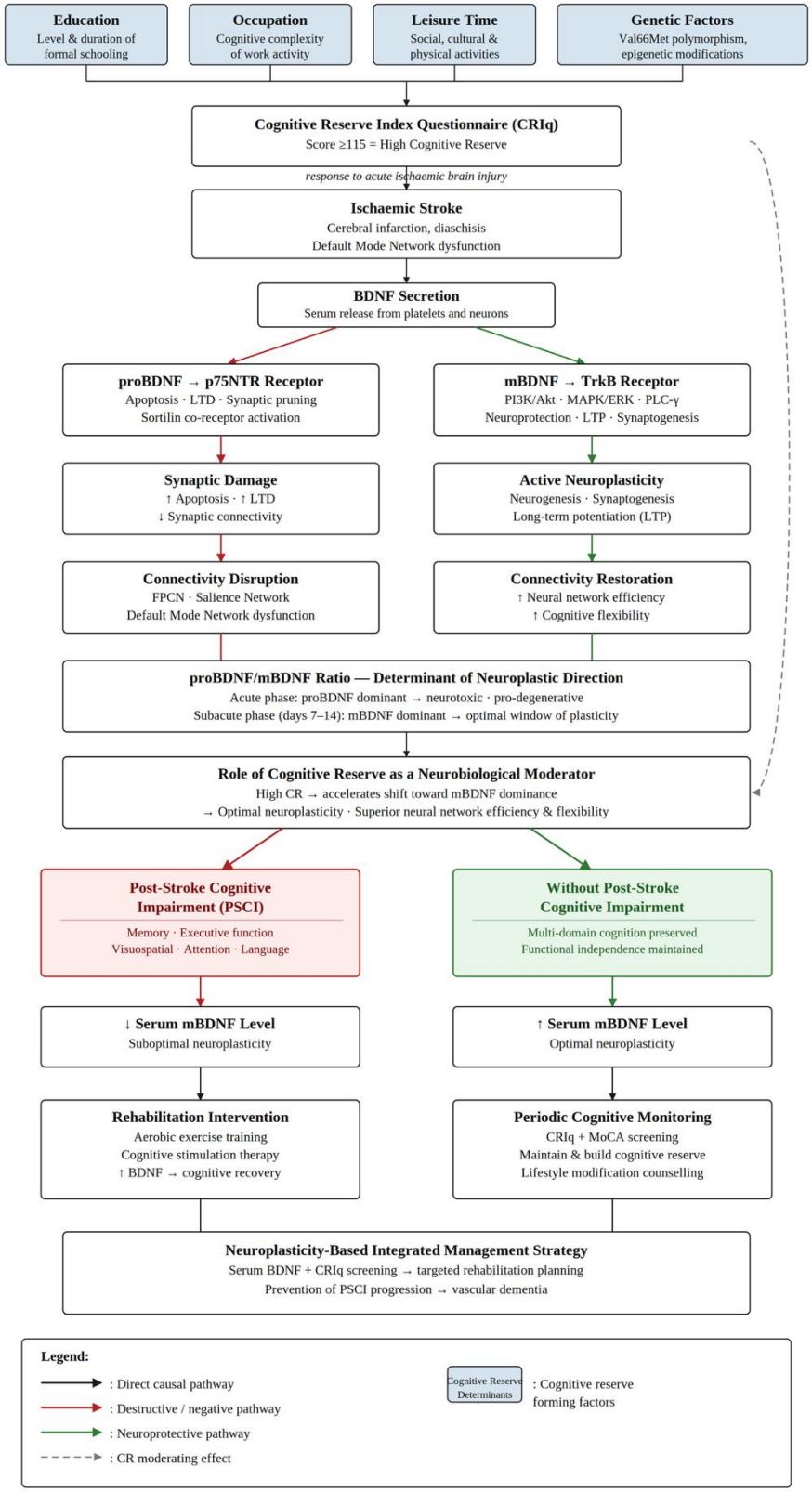

Figure 2. presents a schematic illustration of the pathomechanisms linking CR, BDNF, and PSCI, together with clinical outcome pathways and neuroplasticity-based management strategies

Interventions proven to augment BDNF levels, including aerobic exercise, cognitive stimulation, and structured neurological rehabilitation, have the potential to simultaneously strengthen CR and optimise post-stroke neuroplasticity.[26,39,52] The study by Aisyah et al.[39] in Indonesian stroke patients with cognitive impairment demonstrated that aerobic exercise significantly elevated serum BDNF and correlated with improved cognitive function, supporting the clinical relevance of BDNF-based intervention strategies.

The development of cognitive screening protocols integrating the CR index, followed by targeted cognitive stimulation, may represent an integral component of neurological rehabilitation management in post-stroke patients at tertiary referral centres. For investigators, data on the relationship between the CR index and serum BDNF in the Indonesian post-stroke ischaemic population, currently extremely limited, can serve as a foundation for designing methodologically rigorous clinical trials or neuroplasticity-based intervention studies.

Several limitations warrant consideration in the interpretation of this review. The majority of available evidence derives from studies conducted in Western or East Asian populations, and generalisability to the Indonesian population, characterised by distinct socioeconomic and cultural profiles, requires further validation. Additionally, heterogeneity in BDNF measurement methods, variability in post-stroke measurement timing, and divergent definitions of cognitive impairment across studies limit cross-study comparability.

CONCLUSION

Brain-derived neurotrophic factor functions as a key biological mediator linking CR to neuroplasticity and post-stroke cognitive recovery following ischaemic stroke. Individuals with high CR, forged through accumulated cognitive stimulation from education, occupational complexity, and leisure activities, exhibit more optimal BDNF responses during the post-stroke subacute phase, contributing to superior neural network efficiency and flexibility through neural efficiency and neural compensation mechanisms. Higher serum BDNF levels consistently associate with a reduced risk of PSCI and better functional outcomes, while CR determinants correlate positively with BDNF levels.

CR assessment using the CRIq alongside serum BDNF measurement during the post-stroke subacute phase (days 7-14) is a promising integrated approach for PSCI risk stratification and more precisely targeted rehabilitation planning. Population-based research in Indonesia examining the relationship between the CR index and serum BDNF in patients with post-ischaemic stroke is urgently needed to generate local scientific evidence that can underpin the development of neuroplasticity-based cognitive screening and rehabilitation intervention protocols at tertiary referral healthcare facilities.

Conflict of Interest

The authors declare no conflict of interest related to the preparation of this article.

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Authors' Contributions

EES contributed to conception, design, data acquisition, literature analysis, drafting, and final approval. KW contributed to critical revision, supervision, and final approval. DKIU contributed to critical revision, supervision, and final approval. All authors have read and approved the final manuscript.

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Data Availability Statement

No new data were generated or analysed in the course of this review. All data supporting the findings discussed are derived from previously published studies, which are cited throughout the text and listed in full in the References section.

Declaration of AI Usage in Scientific Writings

During the preparation of this manuscript, the authors used Claude Sonnet 5 (Anthropic) to refine the visual presentation of a flow diagram of the literature selection process and a schematic diagram illustrating the pathomechanistic links between cognitive reserve, brain-derived neurotrophic factor (BDNF), and post-stroke cognitive impairment (PSCI), which had been originally conceptualised by the authors. The

authors reviewed and verified the scientific accuracy and content of both figures and take full responsibility for their final form and interpretation. No generative artificial intelligence tool was used to generate original data, analyses, or scientific conclusions, nor is any AI tool credited as an author, in accordance with ICMJE authorship criteria.

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