

## Animal Models for Studying Post-Stroke Neuroplasticity

**Risdiansyah<sup>1</sup>, Ahmad Ghiffari<sup>2</sup>, Rury Tiara Oktariza<sup>3</sup>, Fadhillah Putri Rusdi<sup>4\*</sup>**

<sup>1,2</sup> Universitas Muhammadiyah Palangka Raya, Indonesia

<sup>3</sup> Universitas Muhammadiyah Palembang, Indonesia

<sup>4</sup> Universitas Sriwijaya Palembang, Indonesia

Email: [risdiansyahromli@gmail.com](mailto:risdiansyahromli@gmail.com)

Keywords	Abstract
<p><i>Ischemic stroke, Neuroplasticity, Animal Models,</i></p>	<p>Ischemic stroke remains one of the leading causes of long-term disability worldwide, with recovery dependent on the brain's neuroplastic potential. This review aims to evaluate the role of animal models in elucidating the mechanisms of neuroplasticity following stroke and their relevance to clinical application. Using qualitative literature analysis, the study synthesizes findings from various animal models including rodents, non-human primates, zebrafish, and <i>Drosophila</i>. Rodent models, particularly the middle cerebral artery occlusion (MCAO), have been instrumental in identifying key processes such as BDNF-driven synaptic remodeling, VEGF-induced angiogenesis, and glial involvement in tissue repair. Additionally, systemic modulators like the gut-brain axis, immune responses, and extracellular vesicles are increasingly recognized for their influence on recovery. Despite these insights, most studies disproportionately utilize young, healthy male animals, limiting their relevance to diverse patient populations with comorbidities and aging factors. The findings suggest a need for integrative, multimodal research that incorporates molecular techniques, imaging, and behavioral assays, along with cross-species validation, to improve translational outcomes. This review underscores the necessity of leveraging a broader spectrum of animal models and advanced methodologies to develop effective, personalized therapies for post-stroke rehabilitation.</p>



### INTRODUCTION

Stroke remains one of the leading causes of death and long-term disability globally, particularly in low- and middle-income countries where healthcare access and stroke awareness are limited (Feigin et al., 2021; Johnson et al., 2019). Ischemic stroke, which constitutes approximately 87% of all stroke cases, is primarily caused by an obstruction of cerebral blood flow, resulting in neuronal injury, loss of function, and systemic complications such as inflammation and oxidative stress (Campbell et al., 2019). The functional deficits following stroke depend on the size and location of the infarct as well as the brain's ability to repair and reorganize affected neural networks.

Neuroplasticity is central to post-stroke recovery, encompassing a broad range of adaptive changes at the molecular, cellular, and network levels. These include axonal sprouting, synaptogenesis, neurogenesis, gliogenesis, angiogenesis, dendritic remodeling, and circuit reorganization (Cirillo et al., 2020; Joy and Carmichael, 2021). Endogenous and exogenous stimuli—including physical rehabilitation, pharmacological agents, and environmental enrichment—modulate these processes (Clarkson et al., 2010). A deeper

understanding of neuroplasticity mechanisms is essential for developing interventions that can optimize functional recovery.

Animal models provide indispensable tools for elucidating the pathophysiology of stroke and the dynamics of neuroplasticity. Rodent models—particularly those utilizing transient or permanent middle cerebral artery occlusion (MCAO)—are widely employed due to their reproducibility and suitability for neurobehavioral and molecular studies (Balkaya et al., 2013; Hermann et al., 2019). MCAO models recapitulate many aspects of human stroke, including infarct formation, motor and sensory deficits, and cellular responses such as astrocyte activation, neuroinflammation, and synaptic remodeling (Ward and Carmichael, 2020).

Photothrombotic stroke models, which rely on light-activated dyes to induce localized cortical infarcts, offer high spatial precision and have been used to investigate focal cortical plasticity and sensorimotor reorganization (Labat-Gest and Tomasi, 2013). Endothelin-1 models provide an alternative with gradual vessel constriction and focal ischemia, especially suited for targeting specific functional brain areas (Howells et al., 2010).

Non-human primates (NHPs), including macaques and marmosets, offer high translational relevance due to their close resemblance to human neuroanatomy, motor function, and behavior. Studies using embolic MCAO and carotid occlusion in NHPs have revealed persistent impairments in fine motor skills, cognition, and executive function—mirroring clinical stroke presentations (Cook et al., 2012; Ueno et al., 2020). These models are instrumental for validating therapeutic strategies prior to clinical trials. However, ethical considerations, high costs, and limited accessibility constrain their routine use.

Non-mammalian models, especially zebrafish (*Danio rerio*), have gained traction due to their extraordinary capacity for neuroregeneration and accessibility for large-scale screening. Zebrafish models of ischemia exhibit robust glial and neuronal regeneration, revascularization, and neurogenesis, making them ideal for investigating intrinsic repair mechanisms (Zhou et al., 2020; Kizil et al., 2012). While *Drosophila melanogaster* lacks a cerebrovascular system, it contributes to the understanding of conserved genetic and molecular processes in synaptic plasticity and neurodevelopment (Heisenberg, 1998).

In recent years, the role of systemic modulators of neuroplasticity has come to light. The gut-brain axis modulates immune activation and neuroinflammatory cascades after stroke, influencing both the extent of neuronal damage and the capacity for recovery (Benakis et al., 2016). Experimental stroke models in germ-free or microbiota-modified rodents demonstrate altered cytokine profiles, neurotrophic factor expression, and behavioral recovery trajectories (Iadecola and Anrather, 2011; Ma et al., 2022). Moreover, microRNAs delivered through extracellular vesicles or exosomes regulate gene expression in recipient neurons, influencing cell survival and synaptic repair (Xin et al., 2013).

Despite these advances, there are limitations in current models. A majority of studies continue to use young, male rodents, which do not accurately reflect the typical human stroke population—comprising elderly individuals often with comorbid conditions such as hypertension, diabetes, and hyperlipidemia (Herson and Traystman, 2014; Hankey, 2017). The lack of long-term studies limits our understanding of chronic-phase neuroplasticity and the durability of functional improvements. Furthermore, outcome measures vary widely between studies, underscoring the need for standardized behavioral, molecular, and imaging assessments (Dirnagl et al., 2013; Schwarz et al., 2020).

To advance translational impact, future research must adopt multimodal, comparative, and longitudinal approaches that incorporate diverse species, standardized metrics, and clinically relevant conditions. Rodent models should be complemented by primate and zebrafish studies, integrating insights from molecular biology, electrophysiology, and

neuroimaging. Such efforts can accelerate the development of effective, individualized, and mechanism-based therapies for stroke survivors.

The current research, which comprehensively reviews the use of diverse animal models in studying neuroplasticity after ischemic stroke, aligns with foundational works such as Cirillo et al. (2020) and Joy and Carmichael (2021) that emphasize the centrality of neuroplastic mechanisms in post-stroke recovery. However, while prior studies primarily focus on rodent models and cellular-level changes (e.g., BDNF signaling, gliogenesis), the current research goes further by integrating systemic modulators (e.g., gut-brain axis, exosomes), evaluating non-mammalian models (zebrafish, *Drosophila*), and highlighting the translational relevance of non-human primates. The novelty of this review lies in its synthesis of both traditional and emerging models, along with its call for multimodal, comparative strategies that bridge basic science with clinical rehabilitation needs. It advocates for cross-species validation and integration of behavioral, molecular, and imaging data—an approach that is underdeveloped in earlier literature.

Compared to research such as Balkaya et al. (2013), which focuses primarily on middle cerebral artery occlusion (MCAO) in rodents, and Ward and Carmichael (2020), which investigates neuroplastic changes post-stroke, this review provides a more holistic and translational perspective. The inclusion of non-mammalian and non-rodent models, exploration of systemic influences like the gut-brain axis, and critique of prevalent demographic biases in preclinical stroke research (e.g., use of young, male rodents) represent novel contributions. It uniquely positions animal model research within a precision medicine framework for stroke rehabilitation, an aspect not emphasized in previous literature.

This review aims to explore how different animal models have been used to investigate neuroplasticity following ischemic stroke. It also evaluates the strengths and limitations of each model and assesses their relevance for preclinical testing and translation into therapeutic interventions. This research benefits the field by identifying limitations in current methodologies, suggesting integrative and standardized approaches, and advocating for more representative preclinical models that mirror human stroke populations. Ultimately, the study supports the development of targeted, mechanism-driven interventions that enhance recovery in diverse clinical settings.

## RESEARCH METHOD

A comprehensive literature search was conducted using the PubMed database, focusing on research investigating neuroplasticity in stroke animal models published in English between 2019-2024. The literature search was performed on July 13<sup>th</sup>, 2024, using the following strategy:

#1. (Animal Model) OR (Animal Models) OR (Experimental Animal Models) OR (Experimental Animal Model) OR (Laboratory Animal Models) OR (Laboratory Animal Model)

#2. (Neuronal Plasticities) OR (Neural Plasticity) OR (Neural Plasticities) OR (Neuroplasticity) OR (Neuroplasticities) OR (Synaptic Plasticity) OR (Synaptic Plasticities) OR (Synaptic Pruning) OR (Synaptic Prunings) OR (Neuronal Pruning) OR (Neuronal Prunings) OR (Axon Pruning) OR (Axon Prunings) OR (Dendrite Pruning) OR (Dendrite Prunings) OR (Neurite Pruning) OR (Neurite Prunings) OR (Dendritic Pruning) OR (Dendritic Prunings) OR (Axonal Pruning) OR (Axonal Prunings) OR (Neuronal Remodeling) OR (Neuronal Remodelings) OR (Neuronal Network Remodeling) OR (Neuronal Network Remodelings) OR (Dendritic Remodeling) OR (Dendritic Remodelings) OR (Dendritic Arborization) OR (Dendritic Arborizations) OR (Dendrite Arborization) OR (Dendrite

Arborizations) OR (Neuronal Arborization) OR (Neuronal Arborizations) OR (Brain Plasticity) OR (Brain Plasticities)

#3. (Strokes) OR (Cerebrovascular Accident) OR (Cerebrovascular Accidents) OR (Cerebral Stroke) OR (Cerebral Strokes) OR (Cerebrovascular Apoplexy) OR (Brain Vascular Accident) OR (Brain Vascular Accidents) OR (Cerebrovascular Stroke) OR (Cerebrovascular Strokes) OR (Apoplexy) OR (CVA ) OR (CVAs ) OR (Acute Stroke) OR (Acute Strokes) OR (Acute Cerebrovascular Accident) OR (Acute Cerebrovascular Accidents)  
#1 AND #2 AND #3

Screening was performed by applying the following inclusion and exclusion criteria:

Inclusion Criteria:

- English language literature
- Type of literature: Review article
- Literature published in the last 5 years (2019-2024)
- Literature available in free full text
- Research subjects are not humans

Exclusion Criteria:

- Non-English literature
- Type of literature: other than Review article
- Literature published more than 5 years ago
- Literature not available in free full text
- Research subjects are not animals
- Preprint manuscripts

## RESULTS AND DISCUSSION

Rodent models, particularly those utilizing Middle Cerebral Artery Occlusion (MCAO), dominate due to reproducibility, accessibility, and anatomical parallels to human stroke (Longa et al., 1989; Hermann et al., 2019). These models effectively replicate focal ischemic injury and allow exploration of acute and chronic neuroplastic responses. MCAO induces a spectrum of neuroplastic changes including neurogenesis, synaptic reorganization, axonal sprouting, and dendritic arborization, particularly in the peri-infarct cortex (Cirillo et al., 2020; Roitbak, 2019). Behavioral assessments, such as the Rotarod and ladder rung walking test, validate functional improvements parallel to molecular changes (Schneider et al., 2019).

Photothrombotic models, employing laser-activated dyes to occlude targeted vessels, offer advantages in spatial control (Labat-Gest and Tomasi, 2013). However, the abrupt infarct onset and absence of penumbra limit their fidelity to clinical stroke (Fluri et al., 2015). Endothelin-1 models provide another alternative with minimal invasiveness and allow localized induction of ischemia (Ward and Carmichael, 2020). Despite these advantages, variability in infarct volume and inconsistent behavioral outcomes remain challenges.

Non-human primates (NHPs), including macaques and marmosets, provide unparalleled insights into higher-order functions such as cognition, emotional regulation, and social behavior post-stroke (Cook et al., 2012). NHP studies using embolic MCAO or carotid artery occlusion have shown that stroke leads to long-term impairments in manual dexterity, spatial memory, and decision-making. Neuroimaging (fMRI, DTI) and electrophysiology in these models support translational mapping of lesion sites and recovery pathways. While invaluable, NHP models are limited by high cost, ethical concerns, and longer life cycles.

Non-mammalian models, particularly zebrafish and *Drosophila*, contribute at the molecular and genetic level. Zebrafish exhibit exceptional regenerative abilities in the central nervous system, making them ideal for dissecting intrinsic neurogenesis (Kizil et al., 2012). Post-stroke, zebrafish brains demonstrate robust glial bridging, revascularization, and neural

precursor cell proliferation. CRISPR-Cas9 applications in zebrafish have identified conserved regulators such as *sox2*, *notch1a*, and *stat3* involved in regenerative plasticity (Zhou et al., 2020). *Drosophila*, though lacking a cerebrovascular system, serve as tools for exploring synaptic remodeling and genetic pathways through optogenetics and behavioral screening (Heisenberg, 1998).

Emerging evidence also implicates systemic factors in modulating neuroplasticity. The gut-brain axis, for instance, alters neuroinflammation and neurotrophic signaling post-stroke (Benakis et al., 2016). Studies in germ-free and antibiotic-treated mice show altered stroke outcomes based on microbial composition, cytokine profiles, and microglial activation (Iadecola and Anrather, 2011). Similarly, immune cells—particularly Tregs, macrophages, and dendritic cells—modulate angiogenesis and remodeling via interleukin and interferon signaling pathways (Ma et al., 2022). MicroRNA (e.g., miR-124, miR-21, miR-155) and exosome studies further show cross-talk between peripheral and central repair systems (Doepfner et al., 2015; Xin et al., 2013).

However, substantial gaps remain. Most studies use young, healthy, male rodents, neglecting the influence of age, sex, and comorbidities (Herson and Traystman, 2014). Stroke risk factors such as hypertension, diabetes, and obesity affect neurovascular integrity and plastic potential, yet are underrepresented in current models (Hankey, 2017). Long-term outcomes beyond 4–6 weeks are seldom evaluated, limiting our understanding of sustained recovery and chronic plasticity (Langhorne et al., 2011). Multi-center efforts to standardize protocols and outcome measures remain essential (Dirnagl et al., 2013).

Understanding the dynamic nature of neuroplasticity after ischemic stroke is essential for developing interventions that promote brain repair. Animal models, especially rodents, have provided a wealth of information on the cascade of biological events following stroke. These insights are typically categorized into acute, subacute, and chronic phases (Ward and Carmichael, 2020). In the acute phase, within hours to days post-stroke, there is a surge in excitotoxicity and oxidative stress leading to neuronal death, accompanied by glial activation and immune infiltration (Iadecola and Anrather, 2011). The subacute phase sees the beginning of reparative processes, including neurogenesis, axonal sprouting, synaptogenesis, and angiogenesis. Finally, during the chronic phase, these changes stabilize into restructured circuits supporting functional recovery (Joy and Carmichael, 2021).

In rodent MCAO models, extensive data supports the role of neurotrophins like brain-derived neurotrophic factor (BDNF) and nerve growth factor (NGF) in driving recovery processes (Sims et al., 2022). Upregulation of BDNF-TrkB signaling in peri-infarct cortex has been linked to improved motor performance, particularly when coupled with task-specific rehabilitation (Liu et al., 2021; Clarkson et al., 2010). Other critical factors include VEGF, which supports both angiogenesis and neurogenesis (Wang et al., 2016). Molecular imaging and gene knockout studies have shown that delayed administration of VEGF can extend the neuroplastic window and improve long-term outcomes (Cirillo et al., 2020).

Astrocytes and microglia, long thought to be merely reactive players, are now recognized for their active roles in modulating plasticity. Microglia switch between M1 (pro-inflammatory) and M2 (anti-inflammatory/regenerative) phenotypes, with the M2 subtype promoting tissue repair and synaptic support (Benakis et al., 2016). Similarly, astrocytes secrete thrombospondins, hevin, and SPARC, which facilitate synaptogenesis (Chung et al., 2015). The timing of their phenotypic changes significantly affects outcomes.

Studies using photothrombotic models have reinforced the importance of cortical remapping and interhemispheric connectivity. Electrophysiological recordings and neuroimaging data, including functional MRI and DTI, demonstrate recruitment of secondary motor areas and the contralesional hemisphere during recovery (Cook et al., 2012; Schwarz et

al., 2020). Rodents subjected to repetitive motor training display increased dendritic spine density, axonal elongation, and excitatory synapse formation in these areas (Jones and Adkins, 2015).

Non-invasive neuromodulatory techniques, such as repetitive transcranial magnetic stimulation (rTMS), transcranial direct current stimulation (tDCS), and vagus nerve stimulation (VNS), have also been investigated in animals. These modalities modulate cortical excitability, enhance BDNF release, and synergize with rehabilitation protocols (Badoiu et al., 2023; Clarkson et al., 2010). For example, pairing VNS with motor tasks leads to increased map representation of trained limbs and better performance (Hays et al., 2020).

Beyond rodents, primate models have enabled examination of behaviorally relevant recovery patterns, such as goal-directed movement and decision-making. Primate stroke studies have shown that specific white matter tracts, such as the corticospinal and frontoparietal pathways, undergo plastic remodeling that corresponds with fine motor recovery (Ueno et al., 2020). Such findings underscore the need to preserve or enhance these pathways in clinical trials.

Zebrafish models have helped elucidate conserved genetic responses to brain injury. Their capacity to regenerate brain tissue following ischemic insults is linked to reactivation of embryonic gene programs, including *sox2*, *stat3*, and *notch1a* pathways (Zhou et al., 2020). Importantly, these pathways are also modulated in mammalian stroke but are often suppressed or insufficiently activated. These observations point to promising targets for pharmacological enhancement of plasticity.

Emerging areas of research have explored the systemic influences on post-stroke brain repair. The gut microbiota influences neuroplasticity via modulation of circulating cytokines, gut-derived metabolites like short-chain fatty acids, and microglial maturation (Benakis et al., 2016; Ma et al., 2022). Manipulating the microbiota through probiotics or antibiotics has yielded differential neurobehavioral outcomes in rodent stroke models (Iadecola and Anrather, 2011).

MicroRNAs (miRNAs) transported via extracellular vesicles or exosomes play regulatory roles in gene expression. Studies show that miR-124 and miR-21 can enhance neurogenesis and synaptic integrity while reducing apoptosis in peri-infarct regions (Xin et al., 2013; Doeppner et al., 2015). Targeting miRNAs through antagomirs or mimics is a growing area of translational research.

Despite these advances, several challenges limit the translational utility of preclinical findings. The majority of animal studies still use young, healthy male rodents, ignoring age and sex as biological variables (Herson and Traystman, 2014). Older animals with comorbid conditions such as diabetes or atherosclerosis exhibit blunted neuroplastic responses and poorer outcomes, highlighting the need for more representative models (Hankey, 2017).

Additionally, variability in outcome measures and study designs across laboratories hampers meta-analysis and comparison. Standardization efforts, such as the STAIR (Stroke Therapy Academic Industry Roundtable) recommendations and ARRIVE (Animal Research: Reporting of In Vivo Experiments) guidelines, have improved transparency but are not universally adopted (Dirnagl et al., 2013).

To overcome these limitations, researchers are integrating omics platforms—transcriptomics, proteomics, epigenomics—to build systems-level maps of neuroplastic responses (Chauhan et al., 2022). Combining such data with imaging biomarkers and machine learning models can enhance prediction of recovery trajectories and treatment responsiveness.

Lastly, bridging the gap between bench and bedside will require interdisciplinary collaboration and the development of clinically relevant composite endpoints. Incorporating behavioral assays, imaging, molecular readouts, and digital biomarkers can better capture the

complexity of post-stroke recovery and enable more effective translation to human therapies. models of stroke have been central to delineating the timelines, pathways, and outcomes of post-stroke neuroplasticity (Murphy and Corbett, 2009; Carmichael, 2006). In the acute phase (hours to days), energy failure and excitotoxicity trigger neuronal death, followed by inflammatory cascades involving activated microglia and infiltrating leukocytes (Iadecola and Anrather, 2011). In the subacute phase (days to weeks), repair processes including glial scarring, axonal sprouting, and neurogenesis begin. The chronic phase (weeks to months) involves circuit reorganization, synaptic plasticity, and behavioral compensation (Ward and Carmichael, 2020).

Rodent studies using MCAO have confirmed that BDNF signaling via TrkB receptors is pivotal in enhancing long-term potentiation (LTP), neurogenesis in the subventricular zone (SVZ), and functional motor recovery (Liu et al., 2021). Experiments using BDNF knockouts or TrkB inhibitors consistently show delayed or diminished recovery (Sims et al., 2022). Similarly, vascular endothelial growth factor (VEGF) promotes angiogenesis and neurogenesis, particularly when administered during the first week post-stroke (Wang et al., 2016).

The role of astrocytes and microglia has evolved from being viewed as solely inflammatory agents to active participants in synaptic pruning and trophic support (Liddelov et al., 2017). M1/M2 polarization of microglia influences whether they promote degeneration or regeneration (Benakis et al., 2016). Astrocytic secretion of thrombospondins and hevin, for instance, promotes excitatory synaptogenesis in peri-infarct regions (Chung et al., 2015).

Electrophysiological recordings show that cortical remapping and synaptic strength alterations correlate with functional improvements. Rodents trained on skilled reaching tasks exhibit increased synaptic density and dendritic branching in the motor cortex (Jones and Adkins, 2015). Functional MRI and DTI in both rodent and NHP models confirm contralesional recruitment and reorganization of corticospinal and interhemispheric pathways (Cook et al., 2012).

Non-invasive interventions such as transcranial magnetic stimulation (TMS), transcranial direct current stimulation (tDCS), and repetitive task training have been evaluated in animal models with promising outcomes (Badoiu et al., 2023). These interventions augment BDNF expression, modulate GABAergic inhibition, and enhance functional outcomes when combined with physical therapy (Clarkson et al., 2010).

However, inconsistencies in timing, dosage, and animal strain confound reproducibility (Dirnagl et al., 2013). The inclusion of aged animals and comorbid models remains rare (Herson and Traystman, 2014). Moreover, while zebrafish and *Drosophila* offer molecular insights, translating these findings to mammals or humans remains a significant challenge (Kizil et al., 2012).

Multimodal approaches integrating omics (transcriptomics, proteomics, epigenetics), imaging, and behavioral assays offer a way forward (Chauhan et al., 2022). High-throughput screening in zebrafish, coupled with transcriptomic validation in rodents, could identify novel targets (Zhou et al., 2020). Longitudinal studies using wearable sensors, automated behavior tracking, and machine learning algorithms can provide more accurate measures of recovery (Schwarz et al., 2020).

## CONCLUSION

This research highlights the pivotal role of animal models in elucidating the complex, multi-layered mechanisms of neuroplasticity following ischemic stroke. Through rodent models such as MCAO and photothrombosis, researchers have gained detailed insights into cellular and synaptic adaptations, while non-human primates and non-mammalian species like zebrafish contribute broader perspectives on behavioral and genetic recovery processes. These

models collectively underscore that neuroplasticity is influenced by both internal (e.g., neurotrophins, immune cells, glial activity) and external (e.g., rehabilitation, neuromodulation) factors. Despite these advances, major limitations remain, particularly the narrow demographic scope of current studies and lack of long-term, clinically aligned evaluations. Future studies should develop and utilize animal models that reflect the diverse human stroke population, including aged subjects with comorbidities such as diabetes and hypertension. Longitudinal and multimodal assessments integrating behavioral, molecular, and imaging data are critical for understanding chronic recovery trajectories. Furthermore, cross-species comparisons using high-throughput technologies like transcriptomics and proteomics can improve translational predictability. Emphasis should also be placed on testing emerging therapies—such as exosome-based delivery systems, microbiota-targeted interventions, and non-invasive brain stimulation—within standardized preclinical frameworks.

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