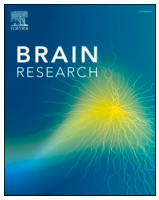
Brain Research 1858 (2025) 149643

Contents lists available at ScienceDirect

Brain Research

journal homepage: www.elsevier.com/locate/brainres



Review

The neuroplastic brain: current breakthroughs and emerging frontiers☆

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ARTICLE INFO

Keywords:
Neuroplasticity
Brain health
Neural reorganization
Therapeutic interventions
Maladaptive plasticity
Neuromodulation
Brain-computer interfaces
Lifestyle modifications

ABSTRACT

Neuroplasticity, the brain's capacity to reorganize itself by forming new neural connections, is central to modern neuroscience. Once believed to occur only during early development, research now shows that plasticity continues throughout the lifespan, supporting learning, memory, and recovery from injury or disease. Substantial progress has been made in understanding the mechanisms underlying neuroplasticity and their therapeutic applications. This overview article examines synaptic plasticity, structural remodeling, neurogenesis, and functional reorganization, highlighting both adaptive (beneficial) and maladaptive (harmful) processes across different life stages. Recent strategies to harness neuroplasticity, ranging from pharmacological agents and lifestyle interventions to cutting-edge technologies like brain-computer interfaces (BCIs) and targeted neuromodulation are evaluated in light of current empirical evidence. Contradictory findings in the literature are addressed, and methodological limitations that hamper widespread clinical adoption are discussed. The ethical and societal implications of deploying novel neuroplasticity-based interventions, including issues of equitable access, data privacy, and the blurred line between treatment and enhancement, are then explored in a structured manner. By integrating mechanistic insights, empirical data, and ethical considerations, the aim is to provide a comprehensive and balanced perspective for researchers, clinicians, and policymakers working to optimize brain health across diverse populations.

1. Introduction

Neuroplasticity is the brain's remarkable capacity to reorganize itself by forming, modifying, and strengthening neural connections in response to both internal experiences and external stimuli (Diniz and Crestani, 2023). Historically viewed as largely confined to early development, it is now recognized as a lifelong process supporting a range of essential functions, including learning, memory, and adaptation (Parisi et al., 2019). Beyond its individual impact, enabling recovery from injury and resilience against cognitive decline, neuroplasticity carries significant societal implications by informing strategies to combat neurological disorders and optimize mental health (Kumar et al., 2023; Zotey et al., 2023).

At the same time, neuroplasticity can act as a double-edged sword (Allred and Jones, 2008). While adaptive changes foster skill acquisition, rehabilitation, and healthy aging, maladaptive processes can entrench pathological states such as chronic pain, addiction, and neurological and psychiatric conditions (Marzola et al., 2023). Understanding the mechanisms governing this dual nature is pivotal for designing targeted interventions that harness beneficial plasticity while mitigating harmful rewiring (Hu et al., 2023). This overview provides an in-depth exploration of neuroplasticity's mechanisms, examines emerging therapeutic approaches including pharmacological, lifestyle, and technological strategies, and addresses the broader implications of utilizing neuroplasticity to maintain brain health and prevent disease. By highlighting both the opportunities and challenges inherent in manipulating neuroplastic processes, the aim is to offer a comprehensive framework for advancing research and clinical applications in this rapidly evolving field.

To strengthen the foundation of this review, it is essential to integrate both seminal and recent findings that have shaped our current understanding of neuroplasticity. Landmark studies on long-term potentiation (LTP) and adult neurogenesis laid the groundwork for contemporary models of brain adaptability, while large-scale clinical trials exploring neuromodulation and gene-editing approaches have expanded these concepts toward translational applications, where interested readers are encouraged to explore in depth (McEachern and Shaw, 1999; Will et al., 2008; Bruel-Jungerman et al., 2006; Stuchlik, 2014; von Bernhardi et al., 2017; Mateos-Aparicio and Rodríguez-Moreno, 2019; Johnson and Cohen, 2023).

☆ This article is part of a special issue entitled: '60th Anniversary Special Issue' published in Brain Research.

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https://doi.org/10.1016/j.brainres.2025.149643
Received 12 January 2025; Received in revised form 1 March 2025; Accepted 9 April 2025
Available online 23 April 2025

2. Mechanisms of neuroplasticity

Neuroplasticity (Innocenti, 2022) is underpinned by four interconnected processes (Voss et al., 2017): synaptic plasticity, structural plasticity, neurogenesis, and functional reorganization that enable the brain to adapt to both internal and external changes throughout the lifespan (Sale et al., 2014; Power and Schlaggar, 2017; Pickersgill et al., 2022). These mechanisms are essential for learning, memory, and the restoration of function following injury, yet they can also contribute to the development of pathological states when dysregulated (Mateos-Aparicio and Rodríguez-Moreno, 2019; Appelbaum et al., 2023). Although each mechanism has traditionally been examined in isolation, current research increasingly highlights their interdependence (Wenger et al., 2021).

Many foundational insights into these mechanisms derive from animal studies (Wolpaw, 2012) and small-scale human trials (Mishra and Gazzaley, 2016), highlighting the need for larger, more diverse clinical cohorts. Recognizing such methodological constraints sharpens our critical perspective and shows the necessity of robust translational frameworks or alternatives (Rudroff, 2024) for applying these findings in clinical practice.

2.1. Synaptic plasticity

Synaptic plasticity refers to the modulation of synaptic strength, primarily through LTP and long-term depression (LTD) (Bliss and Cooke, 2011). LTP, widely regarded as a key molecular basis for learning and memory (Hayashi, 2022), enhances synaptic efficacy by increasing receptor density and neurotransmitter release at activated synapses. Frequent practice or repetition of a skill consolidates these strengthened connections, reinforcing the neural circuits involved. For example, an adaptive form of plasticity emerges when synaptic connections are strengthened during skill acquisition, such as practicing a musical instrument, or during the formation of long-term memories, such as learning a new language (Wenger et al., 2021; Wenger et al., 2017; Dayan and Cohen, 2011). In contrast, a maladaptive form arises when excessive LTP in pain pathways leads to central sensitization, contributing to chronic pain conditions like fibromyalgia (Nijs et al., 2023; Ji et al., 2018) or neuropathic pain (Costigan et al., 2009).

LTD, on the other hand, reduces synaptic efficacy, refining synaptic networks and helping maintain an optimal excitatory–inhibitory balance (Castillo et al., 2011). A beneficial instance of LTD occurs when the brain prunes unnecessary synapses to refine motor skills and optimize information processing (Piochon et al., 2016). However, excessive LTD in hippocampal circuits (Tim et al., 2006) may contribute to cognitive decline and memory impairments, as seen in disorders such as Alzheimer's disease (Henstridge et al., 2019).

Nonetheless, contradictory findings persist regarding whether increased synaptic strength always translates directly to improved cognitive or motor function. For instance, while some studies link LTP enhancement to better memory performance, others suggest that overactivation of excitatory pathways can tip the balance toward excitotoxicity (Huang et al., 2005; Gonçalves-Ribeiro et al., 2019). Suboptimal LTD (Monsorno et al., 2023) could also impair necessary synaptic refinement (Cooke and Bliss, 2006), but conclusive evidence in human populations (Howes and Onwordi, 2023) remains limited by small sample sizes and variability in measurement techniques.

Beyond LTP and LTD, homeostatic plasticity (Pozo and Goda, 2010; Chen et al., 2022) sustains an overall balance of excitation and inhibition in neuronal networks. Disruption of these homeostatic mechanisms is implicated in conditions (Lepeta et al., 2016) including epilepsy, schizophrenia, and Alzheimer's disease (Meftah and Gan, 2023), showing the therapeutic potential of interventions that modulate synaptic remodeling, such as pharmacological agents targeting NMDA receptors (Nicosia et al., 2024) or synaptic scaling factors (Wu et al., 2023). A failure in homeostatic plasticity can manifest in conditions like chronic pain (Thapa et al., 2021), where local circuits become persistently over- or underactivated. While animal models have illuminated these pathways (Lamichhane et al., 2024; Sandkühler, 2009), reliable clinical biomarkers and standardized intervention protocols remain underdeveloped.

2.2. Structural plasticity

Structural plasticity involves physical changes in neural architecture, including synaptogenesis (the formation of new synapses), dendritic branching, and synaptic pruning (Leuner and Gould, 2010; Kolb and Gibb, 2011). Synaptogenesis and dendritic remodeling can lead to adaptive outcomes (Schlaug, 2001), as demonstrated by increases in dendritic complexity in the motor cortex when individuals learn to play a musical instrument (Schlaug, 2001), ultimately resulting in refined and more efficient motor control. However, these same mechanisms can turn maladaptive if abnormal dendritic growth or spine formation occurs in response to certain drugs of abuse, such as cocaine, reinforcing addictive behaviors (Nestler and Lüscher, 2019; Russo and Nestler, 2013) by over-strengthening reward-related circuits (Forbes and Goodman, 2014). Similarly, synaptic pruning serves an essential adaptive function by eliminating underused or weak synapses during adolescence and adulthood, thereby optimizing neural pathways (Sakai, 2020). When pruning is excessive, however, it may contribute to disorders such as schizophrenia, in which key synaptic connections are disrupted (Howes and Onwordi, 2023; Chafee and Averbeck, 2022; Germann et al., 2021).

In the context of injury recovery, structural plasticity is vital for reestablishing function. Following a stroke, for instance, *peri*-infarct areas often undergo dendritic sprouting and synapse formation, facilitating the restoration of motor or language capabilities (Campos et al., 2023). Recent advances in two-photon microscopy (Li et al., 2023) and other high-resolution imaging tools make it possible to observe these structural changes in real-time, both in animal models and clinical settings, providing deeper insights into the mechanisms and potential therapeutic applications of structural plasticity (Murphy, 2015; Xiong et al., 2023). In practice, translating knowledge of structural plasticity into therapy presents hurdles. Techniques like two-photon microscopy have validated structural changes in animal models, but real-time imaging in humans is complex, expensive, and rarely standardized across research centers (Ayaz et al., 2022).

2.3. Neuronal plasticity and network adaptations

Neuronal plasticity refers to the ability of individual neurons to modify their intrinsic properties in response to learning, experience, and environmental stimuli (von Bernhardi et al., 2017). This adaptation occurs through two primary mechanisms: (1) intrinsic plasticity, which involves changes in the electrophysiological properties of individual neurons, and (2) network-level plasticity, which reflects large-scale reorganization of neural circuits and connectivity patterns (von Bernhardi et al., 2017; Oberman and Pascual-Leone, 2013; Stampanoni Bassi et al., 2019). While synaptic plasticity and structural remodeling dictate changes at the level of synapses and dendrites, neuronal plasticity ensures that neurons themselves adjust their excitability, responsiveness, and integration into functional networks (Wenger et al., 2021; Gipson and Olive, 2017; Chen and Nedivi, 2010). These adaptations are fundamental to learning, memory consolidation, and functional recovery after neurological injury. However, when dysregulated, they can contribute to maladaptive conditions such as epilepsy, addiction, and psychiatric disorders (Marzola et al., 2023; Sale et al., 2014; Cramer et al., 2011).

Intrinsic Neuronal Plasticity: Ion Channel Regulation and Excitability

At the single-cell level, neurons undergo intrinsic plasticity by adjusting their excitability and firing properties through modifications

in ion channel expression, neurotransmitter receptor density, and metabolic activity (Debanne et al., 2019). Changes in ion channel dynamics, such as the upregulation of voltage-gated sodium and calcium channels, can increase neuronal excitability, enhancing responsiveness to incoming stimuli (Daoudal and Debanne, 2003). Conversely, the downregulation of excitatory ion channels or increased potassium channel activity can reduce neuronal firing rates, promoting stability in neural networks and preventing excessive activation (Desai, 2003).

This intrinsic plasticity is particularly crucial for homeostatic regulation in response to prolonged synaptic activity. For instance, during skill acquisition, neurons in the motor cortex display a reduced threshold for firing and increased action potential precision, optimizing motor control (Paz et al., 2009). Similarly, in hippocampal neurons, the expression of NMDA and AMPA receptors is dynamically regulated to fine-tune synaptic strength during memory formation (Titley et al., 2017). However, dysregulation of these mechanisms can lead to pathological states: in epilepsy, excessive excitability and impaired inhibition drive hyperactive neuronal circuits, leading to recurrent seizures (Scharfman, 2002; Knowles et al., 2022).

Network-Level Plasticity: Functional Connectivity and Large-Scale Adaptations

Beyond changes in individual neurons, network-level plasticity encompasses shifts in functional connectivity between brain regions, allowing for adaptation to new experiences, learning, and compensatory mechanisms after injury (Pascual-Leone et al., 2011). This process involves synaptic remodeling, axonal sprouting, and dynamic reconfiguration of neuronal ensembles, which refine cognitive and motor functions (Kelly and Castellanos, 2014).

One of the most well-documented examples of network plasticity occurs during memory consolidation, where neuronal circuits in the hippocampus and prefrontal cortex undergo coordinated oscillatory changes to stabilize newly learned information (Squire et al., 2015; Geva-Sagiv et al., 2023). These network shifts facilitate the transition from hippocampal-dependent learning to long-term storage in cortical regions, ensuring more efficient retrieval (Buzsáki, 2015; Preston and Eichenbaum, 2013).

In response to neurological injury, the brain can undergo compensatory network reorganization (Chen et al., 2002; Hylin et al., 2017). After a stroke affecting motor areas, adjacent cortical regions, and contralateral motor networks are recruited to assume lost function, enabling partial motor recovery (Ward et al., 2003; Jones, 2017). This reorganization is facilitated by increased interhemispheric connectivity and strengthening of pre-existing but underutilized pathways (Grefkes and Fink, 2011). However, when network-level plasticity is maladaptive, it can reinforce pathological states (Costigan et al., 2009). In chronic pain conditions, for instance, excessive connectivity between pain-processing regions (e.g., thalamus, somatosensory cortex, anterior cingulate cortex) leads to persistent pain perception, even in the absence of ongoing nociceptive stimuli (Kuner and Flor, 2016).

Therapeutic Interventions Targeting Neuronal Plasticity

Given the profound role of neuronal plasticity in both adaptive and maladaptive processes, various therapeutic strategies (Kumar et al., 2023; Colavitta and Barrantes, 2023) aim to enhance beneficial neuronal adaptation while mitigating pathological remodeling.

1. Pharmacological Modulation
   - o BDNF-enhancing drugs: Brain-derived neurotrophic factor (BDNF) plays a key role in neuronal plasticity. Drugs that increase BDNF expression, such as SSRIs (fluoxetine) or ketamine, have been shown to restore synaptic and neuronal plasticity in depression (Casarotto et al., 2022; Casarotto et al., 2021).
   - o Ion channel modulators: Anti-epileptic drugs such as gabapentin and lamotrigine regulate neuronal excitability by stabilizing ion channel function, reducing hyperexcitability in conditions like epilepsy (Czapińska-Ciepiela et al., 2024) and neuropathic pain (Eijkelkamp et al., 2012).
2. Non-Invasive Neuromodulation
   - o Transcranial Magnetic Stimulation (TMS): Repetitive TMS can enhance neuronal excitability in underactive brain regions (e.g., dorsolateral prefrontal cortex in depression) or inhibit hyperactive circuits (e.g., motor cortex in dystonia) (Kricheldorff et al., 2022; Jannati et al., 2023; Suppa et al., 2022; Lefaucheur et al., 2020).
   - o Transcranial Direct Current Stimulation (tDCS): tDCS can induce long-term changes in neuronal excitability (Lang et al., 2004), facilitating motor and cognitive recovery in stroke and neuropsychiatric disorders (Nitsche and Paulus, 2011).
3. Cognitive and Behavioral Interventions
   - o Intensive skill training and cognitive therapy can promote functional network reorganization in neurorehabilitation. For example, constraint-induced movement therapy in stroke patients enhances motor network connectivity (Taub and Morris, 2001; Wang et al., 2022).
   - o Mindfulness and cognitive-behavioral therapy (CBT) have been shown to reshape maladaptive prefrontal-limbic circuits in anxiety and PTSD, reducing hyperactivation of fear-related pathways (Yuan et al., 2022; Hölzel et al., 2011).

Neuronal plasticity, therefore, represents a fundamental mechanism by which the brain adapts at both the cellular and network levels. While intrinsic neuronal plasticity fine-tunes individual excitability and firing properties, network-level plasticity dictates how functional circuits reorganize for learning and recovery. However, when these mechanisms become dysregulated, they contribute to disorders ranging from chronic pain and epilepsy to neuropsychiatric diseases. Understanding these processes provides crucial insights into therapeutic strategies, including pharmacological agents, neuromodulation, and behavioral interventions, to harness beneficial plasticity and mitigate maladaptive changes.

2.4. Neurogenesis

Neurogenesis refers to the generation of new neurons, predominantly in the hippocampus (dentate gyrus) and, to a lesser extent, in the subventricular zone (Ming and Song, 2011; Vaz et al., 2022). Although the rate of neurogenesis declines with age, it remains integral to learning, memory, emotional regulation, and cognitive flexibility (Toda et al., 2019; Amelchenko et al., 2023). When neurogenesis is robust, such as in individuals exposed to enriched environments that include complex spatial tasks, exercise, and social interaction, it can enhance cognitive performance and help regulate stress responses (Schloesser et al., 2010). However, chronic stress and elevated cortisol levels can diminish hippocampal neurogenesis, potentially exacerbating conditions like depression and anxiety (Schoenfeld and Gould, 2012). Current research exploring pharmacological approaches, including agents that upregulate brain-derived neurotrophic factor (BDNF) (Ibrahim et al., 2022), and genetic strategies aimed at stimulating hippocampal growth shows promise for mitigating age-related cognitive decline and improving outcomes in neurodegenerative diseases (Numakawa and Kajihara, 2024) such as Parkinson's and Huntington's (Vassal et al., 2025).

Elevated neurogenesis, supported by exercise (van Praag, 2008) and enriched environments (Brown et al., 2003), correlates with improved mood and memory. However, some studies fail to show robust gains in humans, and the degree to which newly generated neurons integrate into existing circuits remains debated (Gonçalves et al., 2016; Kempermann et al., 2018; Gage and Temple, 2013). Inter-individual variability (e.g., genetic predispositions, sex hormones) may also complicate the reproducibility of findings.

2.5. Functional reorganization

Functional reorganization allows the brain to compensate for neural

damage by reallocating tasks to alternative or underutilized regions (Castellanos et al., 2011). For example, following a stroke that affects the left motor cortex, the contralateral (right) motor cortex may assume partial control of motor functions in the affected limb, thereby facilitating recovery (Ward, 2004). This adaptive shift can be further enhanced through targeted therapies such as constraint-induced movement therapy (Sawaki et al., 2008). However, in cases of chronic pain or phantom limb pain, reorganization in somatosensory or motor cortices may perpetuate pain signals or aberrant sensations in the absence of actual peripheral input (Karl et al., 2001; Culp and Abdi, 2022). Modern neuroimaging techniques including functional MRI (fMRI) and positron emission tomography (PET) have illustrated how function can be redistributed to adjacent or contralateral regions (Seifert and Maihöfner, 2011; Gunduz et al., 2020). In addition, non-invasive neuromodulation methods (e.g., transcranial magnetic stimulation) and BCIs seek to optimize this reorganization, thereby improving rehabilitation outcomes in stroke, spinal cord injury, and other conditions, though clinical outcomes are often heterogeneous, reflecting diverse patient profiles and inconsistent stimulation protocols (Li et al., 2023; Calderone et al., 2024; Eliason et al., 2024).

In summary, these four mechanisms highlight the dynamic capacity of the brain to reshape itself in response to changing conditions (Table 1). While adaptive (good) plasticity facilitates learning, recovery, and healthy aging, maladaptive (bad) plasticity can entrench chronic pain, addiction, and other neurological or psychiatric conditions. Ongoing research seeks to harness beneficial plasticity while mitigating maladaptive processes, reflecting a promising avenue for improving clinical outcomes across a range of disorders.

While these four mechanisms of neuroplasticity—synaptic plasticity, structural plasticity, neurogenesis, and functional reorganization—enable the brain to adapt and recover, their effects are not universally beneficial. Depending on the context, plasticity can manifest as either adaptive (beneficial) or maladaptive (harmful) changes, influencing both normal brain function and disease progression. The following section explores this dual nature of neuroplasticity, highlighting its role in learning, recovery, and pathological conditions.

3. Adaptive and maladaptive plasticity

As summarized in Table 1, each of the four neuroplastic mechanisms can manifest as either adaptive or maladaptive changes, depending on factors such as the nature of the stimulus, individual genetic predispositions, and environmental conditions. While neuroplasticity is essential for brain health, its effects are not universally beneficial. The distinction between adaptive and maladaptive plasticity highlights the importance of targeted interventions to promote positive outcomes.

Adaptive plasticity supports learning, memory, and recovery from injury by allowing the brain to compensate for age-related changes, maintain cognitive function, and rebound from neurological insults. For instance, physical rehabilitation programs for stroke patients utilize adaptive plasticity by encouraging the use of impaired limbs, thus reinforcing neural circuits that promote functional recovery, effectively "re-teaching" the brain how to execute movements (Aderinto et al., 2023). Lifelong intellectual engagement and social interaction may build cognitive reserve (Scarmeas and Stern, 2003), buffering age-related declines (Piolatto et al., 2022). Results from prospective cohort studies have been encouraging, though causality is often difficult to disentangle from confounding factors (Lindenberger, 2014).

The point to consider is that neuroplasticity processes can be beneficial or harmful depending on context (Price and Duman, 2020), genetic background, and environmental exposures. For instance, while chronic stress can upregulate synaptic connections in fear-related circuits, reinforcing anxiety, appropriate exposure-based therapies can reshape these pathways adaptively (Kenwood et al., 2022; Daviu et al., 2019; Zhang et al., 2021).

By contrast, maladaptive plasticity reinforces negative patterns that exacerbate neurological or psychiatric conditions. Chronic pain (Kiritoshi et al., 2024) is a prime example, in which heightened connectivity within pain-processing circuits continues to generate discomfort long after the initial injury has healed. Neuroimaging (Martucci and Mackey, 2018; Martucci et al., 2014) has shown hyperconnectivity in pain-processing networks among chronic pain sufferers. Targeted interventions (e.g., neuromodulation, cognitive-behavioral therapy) can sometimes break this cycle (Bazzari and Bazzari, 2022), though optimal timing and individual variability remain hotly debated.

Likewise, maladaptive changes in reward pathways can underlie addiction, and anxiety disorders are often characterized by excessive connectivity in fear-processing networks (Shin and Liberzon, 2010; Lüthi and Lüscher, 2014). Addressing these pathological patterns necessitates interventions that disrupt harmful circuitry and restore equilibrium. Cognitive-behavioral therapy, neuromodulation, and pharmacological agents targeting these maladaptive pathways are all critical components in this effort. For instance, in terms of addiction (Cooper et al., 2017), repeated drug exposure can strengthen reward-related circuits, entrenching compulsive behaviors. While this is well-documented in preclinical models, clinical translation is hampered by

Table 1
Snapshot of Mechanisms, Examples, and Interventions.

CNS Component	Adaptive (Good) Plasticity	Maladaptive (Bad) Plasticity	Current State-of-the-Art Interventions
Synaptic Plasticity (LTP, LTD, synaptic scaling)	– LTP driving skill acquisition (e.g., musical training, language learning). – LTD refining synaptic networks for efficiency.	– Excessive LTP in pain pathways contributing to chronic pain. – Excessive LTD in the hippocampus (e.g., Alzheimer's disease).	– Pharmacological modulators (NMDA receptor agonists/antagonists). – Synaptic scaling therapies. – Cognitive training programs.
Neuronal Plasticity (Neurogenesis, dendritic remodeling)	– Enhanced hippocampal neuron production via exercise and enriched environments. – Improved memory and emotional regulation.	– Reduced neurogenesis due to chronic stress (e.g., elevated cortisol). – Links to depressive and anxiety disorders.	– Pharmacological agents boosting BDNF or growth factors. – Gene therapy approaches. – Lifestyle interventions (diet/exercise).
Supporting Tissue Plasticity (Glial, vascular, extracellular matrix changes)	– Astrocyte-mediated synaptic support for learning. – Microglial pruning optimizing synaptic efficiency. – Vascular adaptations promoting oxygenation and metabolic support.	– Reactive gliosis disrupting neural function. – Excessive synaptic pruning linked to schizophrenia. – Blood-brain barrier breakdown in neurodegenerative conditions.	– Anti-inflammatory therapies targeting glial dysregulation. – Vascular-targeted interventions (e.g., exercise, neurovascular drugs). – Real-time plasticity monitoring.
Functional Reorganization (Result of the above plasticity mechanisms)	– Contralateral cortical takeover in stroke rehab. – Brain-computer interfaces (BCIs) supporting recovery.	– Aberrant reorganization in chronic or phantom limb pain. – Unhelpful rewiring sustaining compulsive/addictive behaviors.	– Non-invasive neuromodulation (TMS, tDCS). – Constraint-induced movement therapy. – BCI training for motor/cognitive improvement.

Abbreviations: LTP, long-term potentiation; LTD, long-term depression; BDNF, brain-derived neurotrophic factor; BCI, brain-computer interface; TMS, transcranial magnetic stimulation; tDCS, transcranial direct current stimulation.

variability in addiction subtypes and comorbid mental health conditions (Russo and Nestler, 2013; Corley et al., 2024).

Interactions Between Neuroplasticity Mechanisms Under Pathological Conditions

Neuroplasticity mechanisms do not operate in isolation – rather, they interact dynamically across different levels, particularly in pathological states where dysregulated plasticity at one level often triggers maladaptive changes at others. The complex interplay between synaptic, structural, neuronal, and network-level plasticity is crucial for understanding how neurological and psychiatric disorders emerge and persist (Oberman and Pascual-Leone, 2013; Gulyaeva, 2017).

One striking example of cross-mechanism interactions is found in chronic pain. Persistent pain is not merely a result of enhanced synaptic plasticity in pain pathways (excessive LTP in nociceptive circuits) but also involves structural remodeling, including dendritic spine reorganization in the somatosensory cortex and anterior cingulate cortex. Over time, these maladaptive changes lead to network-level alterations, increasing connectivity between pain-processing regions such as the thalamus, insula, and prefrontal cortex (Kuner and Flor, 2016). This progressive shift in functional connectivity reinforces pain perception even in the absence of continued nociceptive input, making chronic pain a disorder of network reorganization rather than a simple response to peripheral injury (Kim et al., 2017; Song and Zhang, 2024). Interestingly, glial plasticity (Sancho et al., 2021; Bellamy et al., 2015) is recognized as playing a role in neuronal plasticity (Sancho et al., 2021; Dzyubenko and Hermann, 2023; Ben Achour and Pascual, 2010). For instance, microglia play a crucial role in modulating post-injury neuroplasticity, influencing different types of chronic pain—nociceptive, neuropathic, and nociplastic. Understanding ectopic plasticity in somatosensory circuits may help uncover distinct pain mechanisms. Future molecular and genetic studies on microglia-mediated neuroplasticity could pave the way for novel chronic pain therapies (Hiraga et al., 2022).

Similarly, schizophrenia illustrates the devastating effects of excessive structural and functional plasticity (Stephan et al., 2006). Recent evidence suggests that exaggerated synaptic pruning during adolescence (structural plasticity) may contribute to the disruption of prefrontal-limbic connectivity (network-level plasticity), weakening top-down regulation of emotional and cognitive processes (Howes and Onwordi, 2023; Chafee and Averbeck, 2022). This excessive pruning reduces synaptic density, impairing information processing in the prefrontal cortex and contributing to core cognitive and emotional deficits characteristic of schizophrenia (Howes and Onwordi, 2023).

In addiction, maladaptive synaptic plasticity interacts with long-term network reorganization in dopaminergic reward circuits. Repeated drug exposure induces LTP at excitatory synapses in the ventral tegmental area and nucleus accumbens, strengthening compulsive drug-seeking behaviors (Nestler and Lüscher, 2019). These synaptic changes eventually remodel structural plasticity, altering dendritic architecture in reward-related brain regions, making addiction a disorder of deeply engrained maladaptive neuroplasticity (Volkow et al., 2019). Interestingly, addictive substances and drugs commonly target the mesocorticolimbic dopamine (DA) system, which originates in the ventral tegmental area (VTA) and extends its projections primarily to the nucleus accumbens (NAc) and prefrontal cortex (PFC). These drugs influence glutamatergic and GABAergic synaptic transmission within these brain regions. The resulting modifications, referred to as drug-evoked synaptic plasticity (Lüscher and Malenka, 2011), persist beyond the drug's presence in the brain and contribute to the restructuring of neural circuits. While these initial alterations alone may not be sufficient to drive addiction, repeated exposure can reinforce them, ultimately playing a role in the development of addictive behaviors (Lüscher and Malenka, 2011).

Moreover, neurogenesis dysfunction in depression exemplifies the intricate relationship between plasticity mechanisms. Chronic stress and elevated cortisol levels suppress hippocampal neurogenesis, leading to reduced structural plasticity and impaired synaptic integration of new neurons (Schoenfeld and Gould, 2012). This loss of neurogenesis correlates with weakened hippocampal-prefrontal connectivity (network-level dysfunction), a hallmark of depression-related cognitive deficits. Given the role of neurogenesis in emotional regulation, impaired neurogenesis may underlie the persistent affective and cognitive symptoms of major depressive disorder (Liu et al., 2017; Leschik et al., 2021).

Given these cross-mechanism interactions, effective therapeutic interventions must target multiple levels of neuroplasticity simultaneously (Kumar et al., 2023). Attempts, including cognitive training, physical activity, non-invasive brain stimulation, and pharmaceuticals that enhance neuroplasticity and improve function, have been reported. Emerging approaches like virtual reality (VR), music therapy, neural rehabilitation techniques, and brain-computer interfaces (BCIs) show promise (Evancho et al., 2023; Chatterjee et al., 2021), though challenges remain, such as the need for personalized treatments and standardized protocols (Kumar et al., 2023).

4. Neuroplasticity across the lifespan

Understanding how neuroplastic mechanisms interact under pathological conditions is also crucial for developing precise, multimodal therapies that address both local synaptic dysfunction and large-scale network imbalances. Differentiating between adaptive and maladaptive plasticity is key to designing interventions that enhance beneficial outcomes while minimizing harmful effects. However, neuroplasticity is not static throughout life – it evolves from early development to aging, shaped by genetic, environmental, and lifestyle factors (Oberman and Pascual-Leone, 2013; Pascual-Leone et al., 2011). The next section explores these lifespan-related changes and their implications for cognitive resilience, neurodegenerative diseases, and rehabilitation strategies.

Neuroplasticity is not a fixed process; rather, it evolves throughout the lifespan (Marzola et al., 2023) and is significantly influenced by age (Navakkode and Kennedy, 2024), gender, hormonal fluctuations, and environmental factors (Power and Schlaggar, 2017). While the fundamental mechanisms of plasticity remain similar at different stages (Stiles, 2000), their capacity and efficiency can vary considerably, shaping cognitive function, emotional resilience, and susceptibility to neurological disorders (Valenzuela, 2019). Epigenetic modifications, which dynamically regulate gene expression in response to environmental influences, also contribute to these lifespan changes in neuroplastic potential (Nayak et al., 2022). Collectively, it is important to recall that plasticity's efficiency also evolves with age, shaped by hormonal dynamics, environmental contexts, and epigenetic factors.

4.1. Early development

During early development, neuroplasticity is at its peak (Hensch, 2005), enabling rapid learning and adaptation (Oberman and Pascual-Leone, 2013). Synaptogenesis and pruning occur extensively in this period (Hensch, 2005), sculpting neural circuits based on environmental inputs. Critical periods (Cisneros-Franco et al., 2020), windows of heightened sensitivity to specific stimuli, underlie language acquisition, visual processing, and other core skills. Positive experiences, such as stimulation, nurturing caregiving, and rich social interaction, bolster healthy circuit formation and long-term cognitive outcomes (Hensch and Bilimoria, 2012). By contrast, adverse childhood experiences—including neglect, trauma, or chronic stress can result in maladaptive plasticity and enduring susceptibility to mood disorders (Murphy et al., 2022; Bick and Nelson, 2016), emphasizing the importance of supportive environments in establishing a resilient neurobiological foundation.

4.2. Adulthood

In adulthood, neuroplasticity persists but is modulated by lifestyle

factors (Phillips, 2017) like education, physical activity (Erickson et al., 2011), social engagement, and diet (Fakhoury et al., 2022). Cognitive reserve, built through sustained learning and intellectual pursuits, confers resilience against age-related decline and certain neurological diseases (Cordeiro et al., 2024). Although less pronounced than in early development, adults can still form new synaptic connections, reorganize existing circuits, and adapt to evolving cognitive demands, particularly when regularly engaged in mentally stimulating or physically active pursuits (Hauptman et al., 2024). Studies also highlight the role of psychosocial factors, such as meaningful social relationships and stress management, in preserving and even enhancing adult neuroplasticity (Davidson and McEwen, 2012).

Nonetheless, contradictory data suggest that not all adults respond equally; genetic factors (e.g., BDNF polymorphisms (Antal et al., 2010)) may underlie differential responsiveness.

4.3. Aging and gender differences

Aging often brings about a gradual reduction in neuroplastic capacity, characterized by declines in neurogenesis, synaptic density, and metabolic activity (Navakkode and Kennedy, 2024). These changes increase susceptibility to cognitive impairments and age-related neurodegenerative conditions, such as Alzheimer's disease or Parkinson's disease. Although the foundational mechanisms of plasticity persist, they may function with less efficiency and require greater stimulation (for instance, through enriched environments or structured training) to achieve significant reorganization (Kesidou et al., 2023).

Hormonal influences play a significant role in shaping neuroplasticity during aging for both men and women. In women, fluctuations in estrogen levels, especially during menopause, can substantially affect synapse formation, neuroprotection, and the modulation of neurotransmitter systems critical for cognition (Morrison et al., 2006; Sheppard et al., 2019). As estrogen levels decline, some women experience a heightened risk of cognitive decline (Conde et al., 2021) and mood disturbances (Barth et al., 2015; Gava et al., 2019). Although hormone replacement therapy (Cho et al., 2023) can help mitigate certain aspects of this decline (Saleh et al., 2023), its risks and benefits must be evaluated on an individual basis (Cho et al., 2023). In men, testosterone levels decrease gradually with age in a process sometimes referred to as andropause (Singh, 2013). While this decline is less abrupt than menopause, it can influence mood, energy levels, and, in some instances, cognitive performance (Panizzon et al., 2018). Testosterone may play a neuroprotective role, and lower levels have been associated with changes in hippocampal volume and potential vulnerabilities (Zhang et al., 2024) to neurodegenerative disease.

Lifestyle and environmental factors can also mitigate the neuroplastic challenges of aging (Phillips, 2017). Structured exercise programs, including both aerobic and resistance training, have been linked to increased hippocampal volume, improved synaptic function, and elevated levels of BDNF (Erickson et al., 2011; Sleiman et al., 2016). Cognitive training (Gates et al., 2019), whether in the form of computer-based tasks or traditional educational pursuits, helps maintain or even enhance neural plasticity by consistently engaging and challenging brain circuits. Nutritional strategies that emphasize antioxidants and omega-3 fatty acids may support neuroplastic health, potentially slowing cognitive decline and reducing susceptibility to neuroinflammation (Fekete et al., 2023). Gender-specific risks further influence these processes. Women may face a higher incidence of late-onset Alzheimer's disease, partly due to hormonal changes and longer average lifespans, although genetic and epigenetic factors also play a role (Zhu et al., 2021). Men, conversely, might be more prone to vascular and metabolic risks (Nowell et al., 2024) such as hypertension and Type 2 diabetes that can negatively affect neuroplastic outcomes.

These risk profiles present the importance of individualized interventions that account for physiological differences between men and women. Strategies such as targeted hormone therapy, tailored exercise regimens, and personalized nutrition plans (Fekete et al., 2022) make it possible to optimize neuroplastic capacity well into older adulthood. Despite the challenges posed by aging, many older adults retain a notable degree of neural flexibility through continued engagement in enriching activities, evidence-based therapies, and social interaction. Research demonstrates that a multimodal approach (Pickersgill et al., 2022) combining physical exercise, cognitive training, nutrition, and, when appropriate, hormonal support can maintain or even enhance neural plasticity, thereby underscoring the lifelong adaptability of the human brain.

In summary, neuroplastic processes gradually slow with age but do not cease. Structured exercise regimens can elevate BDNF and preserve hippocampal volume. Hormonal shifts, such as declining estrogen in women or testosterone in men, further modulate neuroplastic capacity. Estrogen replacement therapy shows potential in supporting synaptic function in postmenopausal women, but results vary widely depending on dosage, timing, and individual risk profiles. Multimodal interventions combining physical, cognitive, and nutritional strategies often yield the greatest benefits, yet large, long-term randomized trials remain sparse.

As research continues to uncover the complexities of neuroplasticity across the lifespan, new therapeutic opportunities are emerging. Advances in neuroscience, including technological innovations such as brain-computer interfaces, neuromodulation, and gene-editing techniques, offer unprecedented potential to manipulate neuroplasticity for cognitive enhancement and rehabilitation. The following section explores these cutting-edge developments and their implications for clinical applications.

5. Emerging frontiers in neuroplasticity research

Recent advances in neuroscience highlight that neuroplasticity depends on far more than just neurons (Kaczmarek, 2020). Glial cells, the neurovascular unit, and modifiable lifestyle factors all play pivotal roles in shaping neural adaptability (De Luca et al., 2020). Additionally, pharmacological breakthroughs and cutting-edge technologies are providing novel pathways to harness and enhance plasticity in both healthy and clinical populations. Understanding these emerging fields, and the ethical considerations they entail, is essential for translating scientific discoveries into tangible improvements in brain health (Ricci, 2020; Young et al., 2021).

5.1. The role of glial cells and neurovascular health

Although neurons are central to neuroplasticity, glial cells, and the neurovascular unit are equally critical for maintaining healthy brain function. Astrocytes, microglia, and oligodendrocytes provide structural, metabolic, and immunological support that facilitates and regulates synaptic remodeling, while a well-functioning neurovascular unit delivers essential nutrients and removes waste products (Dzyubenko and Hermann, 2023; Kugler et al., 2021).

Astrocytes contribute to synaptic homeostasis through neurotransmitter recycling and the release of gliotransmitters such as glutamate and D-serine. They also help maintain blood–brain barrier integrity, ensuring an optimal ionic and metabolic environment for neuronal firing and plasticity. Dysfunctional astrocytic activity, as observed in certain neurodegenerative diseases, can lead to excitotoxicity and impaired synaptic plasticity (Chalmers et al., 2024; Huffels et al., 2023; Ding et al., 2021).

Microglia, the resident immune cells of the central nervous system, play a nuanced role. Under normal conditions (Tremblay et al., 2011), they prune redundant synapses during development and facilitate repair after injury. When chronically activated, however, microglia release pro-inflammatory cytokines that disrupt synaptic remodeling and may exacerbate neurodegenerative processes, as seen in conditions such as Alzheimer's disease and chronic stress-related disorders (Colonna and

Butovsky, 2017; Schramm and Waisman, 2022).

Oligodendrocytes are responsible for myelinating axons, a process that enhances signal conduction and supports long-term plasticity (Simons et al., 2024). Dynamic changes in myelin (Behrendt et al., 2013; Williamson and Lyons, 2018) have been linked to learning and adaptation; for example, increased myelin deposition in motor circuits often accompanies skill acquisition (Almeida and Lyons, 2017; Lakhani et al., 2016). Therapeutic strategies that promote oligodendrocyte differentiation and remyelination show promise in enhancing plasticity after stroke or in demyelinating diseases like multiple sclerosis (Rodgers et al., 2013; Zhu et al., 2024).

The neurovascular unit (McConnell and Mishra, 2022), composed of endothelial cells, pericytes, and astrocytes, ensures adequate cerebral blood flow, which is indispensable for adaptive plastic changes. Exercise-induced angiogenesis can improve neurovascular coupling, facilitating oxygen and nutrient delivery to active neural circuits in aging brains and aiding recovery following injury (Zedde and Pascarella, 2024), yet translating these findings into specific guidelines (e.g., frequency and intensity of exercise) requires further large-scale studies. Restoring or maintaining neurovascular integrity through antihypertensive agents, antioxidants, or lifestyle interventions can thereby indirectly enhance neuroplasticity (Pekdemir et al., 2024; Terracina et al., 2022).

Systemic conditions such as hypertension, diabetes, and metabolic syndrome also impact glial function and neurovascular health, further complicating neuroplastic responses (Rojas et al., 2021). Acknowledging these comorbid factors is essential for integrative care protocols that simultaneously address both systemic health and brain adaptability.

5.2. *Lifestyle factors and neuroplasticity*

Lifestyle factors profoundly influence the brain's capacity to reorganize, highlighting the importance of modifiable behaviors such as sleep hygiene, nutritional choices, physical activity, and stress management (Phillips, 2017). These approaches are non-invasive, accessible, and can be integrated into broader therapeutic regimens.

Sleep is crucial for memory consolidation, synaptic pruning, and clearing metabolic waste from the brain (Bah et al., 2019). Chronic sleep deprivation disrupts these processes, impairing cognitive functions and increasing the risk of neurodegenerative diseases (Khan and Al-Jahdali, 2023). Inadequate or fragmented sleep impairs synaptic consolidation and glymphatic clearance (Xie et al., 2013). Optimizing sleep through consistent schedules, reduced evening exposure to blue light (Silvani et al., 2022), and treatment of disorders like sleep apnea enhances neuroplastic capacity. Ensuring high-quality sleep is thus a non-invasive and inclusive approach (Hale et al., 2020) to maintaining neuronal health, though adherence remains an issue in clinical practice.

Diet also shapes synaptic health and neurogenesis (Fadó et al., 2022; Poulose et al., 2017; Rodriguez et al., 2017). Nutrient-rich regimens that incorporate omega-3 fatty acids, antioxidants, and vitamins support synaptic remodeling and reduce inflammation (Zivkovic et al., 2011; Cutuli, 2017; Gomez-Pinilla and Gomez, 2011). Diets high in sugar (Jacques et al., 2019) or trans fats (Tan and Norhaizan, 2019), conversely, promote oxidative stress and impair plasticity. Emerging evidence suggests that dietary approaches such as intermittent fasting (Brocchi et al., 2022; Mattson and Wan, 2005) may bolster synaptic resilience by increasing levels of BDNF (Calabrese et al., 2014) and promoting autophagy (Gudden et al., 2021; Marosi and Mattson, 2014). However, nutritional interventions often produce variable outcomes, partly due to individual metabolic differences and inconsistent adherence.

Physical exercise is one of the most potent enhancers of neuroplasticity (Hötting and Röder, 2013), stimulating BDNF release and angiogenesis (Zalouli et al., 2023). Aerobic activities have been linked to increased hippocampal neurogenesis and improved synaptic function, whereas resistance training can augment executive function and working memory (Erickson et al., 2011; Tharmaratnam et al., 2017; Kandola et al., 2016). Combining aerobic and strength-based exercises (Ho et al., 2024) appears to have synergistic effects on both cognition and emotional well-being. Synergistic effects have also been reported following a combination of cognitive therapy and exercise (Ji et al., 2023; Bherer et al., 2021).

Stress management is equally critical. Although acute stress can sometimes sharpen cognitive performance, chronic stress elevates cortisol levels and drives neuroinflammation, leading to maladaptive changes in fear- or anxiety-related circuits (James et al., 2023). Chronic stress also elevates cortisol, leading to hippocampal atrophy and weakened synaptic connections (James et al., 2023). Techniques such as mindfulness-based stress reduction, cognitive-behavioral therapy, and relaxation practices have shown promise to help break the cycle of chronic stress (Hofmann and Gómez, 2017), and for restoring plasticity (Yue et al., 2023), but require systematic, longer-term trials to validate (Calderone et al., 2024).

Finally, social engagement and cognitive enrichment further bolster adaptive changes in brain structure and function. Meaningful social interactions and mentally stimulating pursuits, such as learning new languages (Li et al., 2024) or acquiring new skills, help maintain the cognitive reserve and mitigate age-related decline in neural flexibility (Li et al., 2024; Du et al., 2023).

As lifestyle interventions gain traction, emerging biomarkers (e.g., serum BDNF, synaptic density markers like SV2A, and functional connectivity patterns) offer promising ways to measure the impact of these approaches (Pisani et al., 2023; Krishnamurthy and Pradhan, 2023; Wang et al., 2024). Although their clinical adoption remains limited by cost and standardization issues, these biomarkers (Moqri et al., 2023) could, in the future, guide individualized treatment plans.

5.3. *Pharmacological innovations in neuroplasticity*

Pharmacological interventions designed to modulate neuroplastic mechanisms are gaining momentum for their potential to treat an array of neurological and psychiatric conditions (Kumar et al., 2023). New-generation drugs focus on synaptic remodeling, neurogenesis, and neuroinflammation (Mottahedin et al., 2017), often in tandem with behavioral or technological therapies.

Psychedelics such as psilocybin, ketamine, and LSD have demonstrated rapid and sustained effects on synaptic remodeling. Acting on serotonin or NMDA receptors (Johnston et al., 2023; Krystal et al., 2019; Moliner et al., 2023), these agents promote dendritic spine formation and enhance functional connectivity in mood-regulating circuits. Ketamine, an NMDA receptor antagonist, increases BDNF levels in the prefrontal cortex, while psilocybin may "reset" dysregulated networks in depression and anxiety disorders (Krystal et al., 2023). Although these compounds hold promise, concerns regarding misuse, regulatory constraints, and long-term safety emphasize the need for carefully controlled large-scale clinical studies (Pilecki et al., 2021).

BDNF modulators represent another promising avenue. While traditional antidepressants indirectly elevate BDNF over extended periods (Björkholm and Monteggia, 2016; Yang et al., 2020), newer agents aim to more directly target BDNF signaling pathways. Molecules like 7,8-dihydroxyflavone (Szarowicz et al., 2022) and other TrkB receptor agonists (Chen et al., 2021) have shown efficacy in enhancing synaptic function and resilience in preclinical models of neurodegeneration and stroke recovery (Cichon et al., 2020).

Therefore, targeting BDNF pathways offers a more direct route to augment synaptic plasticity and neurogenesis, however, the challenge lies in achieving region-specific effects without triggering excitotoxicity.

Anti-inflammatory therapies focus on mitigating neuroinflammation, which impairs synaptic remodeling (Mottahedin et al., 2017; Cangalaya et al., 2023). Agents such as IL-1 receptor antagonists or minocycline can reduce the release of inflammatory mediators and protect synapses from damage (Piccioni et al., 2021). Meanwhile,

neurogenesis enhancers such as P7C3 and certain neurosteroids (e.g., pregnenolone) aim to bolster hippocampal neuron survival (Pieper et al., 2010), with the potential to alleviate mood disorders (Pinna, 2020) and cognitive impairments when combined with rehabilitative measures. Therefore, by mitigating neuroinflammation, these treatments may protect synaptic integrity (Zhang et al., 2023). However, outcomes in human trials have been inconsistent, highlighting complex immune–neural interactions.

5.4. Technological advancements

Technological innovations are rapidly transforming neuroplasticity research and intervention, enabling more precise modulation of brain activity (Jangwan et al., 2022; Ziegler et al., 2022). However, these tools also raise important ethical issues related to equity, safety, and informed consent.

Brain-Computer Interfaces (BCIs) translate neural signals into commands for external devices, providing novel rehabilitation strategies for stroke or spinal cord injury and offering real-time neurofeedback to optimize plastic changes (Young et al., 2021). Translating neural signals into actionable commands can enhance stroke rehabilitation (Marín-Medina et al., 2024; Cantillo-Negrete et al., 2023) and communication in patients with ALS (Milekovic et al., 2018). Yet BCIs remain expensive, technically challenging, and subject to high dropout rates in long-term trials. Although BCIs can be life-changing, issues of data privacy and user autonomy must be carefully addressed (Livanis et al., 2024).

Non-invasive neuromodulation techniques, including transcranial magnetic stimulation (TMS) and transcranial direct current stimulation (tDCS), offer targeted ways to influence synaptic efficiency without surgery (Davidson et al., 2024; Mattioli et al., 2024). High-definition tDCS and closed-loop TMS systems that adapt stimulation in real-time hold promise for personalized therapies, but robust data on long-term safety and efficacy remain essential before widespread adoption (Aderinto et al., 2024). It has been reported that efficacy varies with patient-specific factors like cortical thickness (Baeken et al., 2021) and functional connectivity patterns (Morya et al., 2019).

TMS has been widely used for treatment-resistant depression and has also gained traction in post-stroke rehabilitation. A clinical study involving patients with major depressive disorder (MDD) who failed multiple antidepressant therapies found that high-frequency TMS applied to the dorsolateral prefrontal cortex led to a 60 % remission rate, demonstrating its potential in modulating neuroplasticity for mood regulation (George, 2010). In stroke recovery, TMS has been applied to induce neuroplastic reorganization in perilesional areas, improving motor function. In a controlled trial, stroke patients receiving TMS before physical therapy exhibited enhanced motor recovery compared to standard physiotherapy alone (Kim et al., 2020). Their findings illustrate how TMS-induced plasticity can facilitate functional rehabilitation in stroke survivors. Neurogenomics, Epigenetics, and Advanced Neuroimaging further extend the frontier. Gene-editing approaches using CRISPR technology could modulate the expression of key synaptic proteins or neurotrophic factors, while epigenetic therapies involving histone deacetylase inhibitors may reactivate dormant pathways in aging or diseased brains (Day, 2019; Liu et al., 2023). CRISPR-based gene editing to modulate neurotrophic factors remains largely preclinical (Parambi et al., 2022). Meanwhile, advanced neuroimaging combined with artificial intelligence supports real-time analysis of neural dynamics, guiding precision interventions (Monsour et al., 2022; Brahma and Vimal, 2024). Ethical considerations are also substantial, given the potential for "enhancement" beyond therapeutic needs (Chatterjee, 2013; Müller and Rotter, 2017).

Gene-editing technologies, particularly CRISPR-based interventions, are beginning to show promise in neurodegenerative and neuromuscular disorders. One of the most well-documented clinical cases is the approval of gene therapy for Spinal Muscular Atrophy (SMA) using onasemnogene abeparvovec (Zolgensma®) (Mendell et al., 2017). This therapy delivers a functional copy of the SMN1 gene, effectively halting disease progression in infants diagnosed with SMA. While primarily used for neurodevelopmental disorders, these breakthroughs suggest a future where targeted genetic therapies could be applied to enhance neuroplastic recovery in conditions such as stroke, traumatic brain injury, and neurodegenerative diseases.

Artificial Intelligence (AI) is revolutionizing early diagnosis and personalized treatment planning in neuroplasticity research (Calderone et al., 2024), for example in classifying Alzheimer's disease and mild cognitive impairment (Tascedda et al., 2024). AI-assisted neuroimaging and predictive models can allow for early diagnosis (Mirkin and Albensi, 2023) and intervention strategies, such as cognitive training and pharmacological treatments before major cognitive decline occurs.

Furthermore, AI-driven personalized neuromodulation is now being explored in traumatic brain injury (TBI) rehabilitation (Uparela-Reyes et al., 2024). Using machine learning algorithms (Saxena et al., 2024), real-time EEG-based AI systems have been developed to optimize TMS stimulation protocols based on individual brain activity patterns. This adaptive approach enhances neuroplastic recovery, increasing the efficacy of neuromodulation for restoring cognitive and motor functions post-TBI.

These cases highlight the transformative impact of emerging neurotechnology in real-world clinical settings. The integration of BCIs, TMS, gene therapy, and AI-based diagnostics is redefining neurorehabilitation, moving the field toward precision medicine approaches tailored to individual neuroplasticity profiles (Carè et al., 2024). Future research should focus on scaling these technologies for widespread clinical adoption, optimizing accessibility, and ensuring ethical implementation (Onciul et al., 2025). These emerging frontiers in the neuroplasticity research field are summarized in Table 2.

While these emerging technologies mark significant advancements in neuroplasticity research, they also present challenges related to clinical validation, accessibility, and ethical considerations. Safely and effectively integrating these innovations into mainstream medical practice requires addressing key limitations and refining future research directions. The next section explores current limitations and gaps in ethical, societal, and methodological dimensions, as well as future priorities for advancing neuroplasticity-based interventions.

6. Gaps, limitations, and future directions

While innovations in neuroplasticity research and related brain technologies hold enormous promise, they raise profound ethical considerations that must be addressed to ensure responsible development

Table 2
Emerging Technologies in Neuroplasticity.

Technology	Mechanism/Approach	Potential Applications
Brain–Computer Interfaces (BCIs)	Translate neural activity into external commands for real-time neurofeedback.	Stroke and ALS rehabilitation; adaptive neural retraining; communication aids for severe motor impairments.
Non-Invasive Neuromodulation (TMS, tDCS)	Modulate cortical excitability and synaptic efficiency without surgery.	Depression therapy; motor recovery following stroke; augmentation of cognitive training.
Neurogenomics and Epigenetics	Use CRISPR-based gene editing or histone deacetylase inhibitors to alter the expression of key genes.	Targeted manipulation of neurotrophic factors; reactivation of dormant plasticity mechanisms in aging and neurodegenerative conditions.
Advanced Neuroimaging + AI	Employ real-time monitoring of functional connectivity combined with machine learning.	Individualized treatment plans; precision neuromodulation; and enhanced diagnostic capabilities.

and equitable access (Garden et al., 2016). The financial cost of advanced neuroimaging tools, sophisticated therapeutic devices, and personalized genetic tests can be prohibitively high, potentially exacerbating existing healthcare disparities. If only certain socioeconomic groups can afford these new interventions, the gap between those who can access high-quality, cutting-edge treatments and those who cannot may widen considerably. To mitigate this risk, policymakers, researchers, and clinicians must actively pursue cost-reducing measures, develop funding mechanisms or subsidies, and explore scalable solutions that make these tools widely available.

Another critical dimension is data security. As neuroplasticity research increasingly relies on large datasets, often including detailed genetic information, brain imaging, and behavioral profiles, privacy becomes a paramount concern (White et al., 2022). Instances of personal health data being misused or sold without consent show the need for robust data governance frameworks. Such frameworks must ensure that data is encrypted, de-identified wherever possible, and accessible only under protocols that protect participant confidentiality. In parallel, informed consent practices should be revisited and refined. Researchers and clinicians must fully disclose the potential risks associated with data collection and storage, including possibilities of breaches or unauthorized secondary use. Participants should also be clearly informed about how their data might be shared among institutions or commercial partners, and they must retain the right to withdraw from studies without fear of compromising their standard of care (Filkins et al., 2016).

Beyond issues of access and privacy, the line between therapeutic intervention and elective brain "enhancements" remains blurry and hotly debated. While interventions to restore function, such as stroke rehabilitation (Cervera et al., 2018) or cognitive training for neurodegenerative conditions (Young et al., 2021), are widely supported, the ethical landscape becomes more complex when interventions aim to confer advantages beyond the restoration of normal function. If brain-computer interfaces or neurostimulation techniques can augment memory, attention, or other cognitive capacities in otherwise healthy individuals, questions arise about fairness and autonomy (Gordon and Seth, 2024). The possibility of "upgrades" that confer competitive edges, especially in educational, professional, or even military contexts could create new forms of social stratification. Regulatory bodies, bioethicists, and professional organizations must collaborate to establish clear guidelines that delineate acceptable therapeutic uses from more controversial enhancement applications.

Underscoring all these considerations is the principle of autonomy (Florijn, 2022): individuals should have the freedom to make informed decisions about their brains and bodies. This includes the right to refuse certain interventions or data collection procedures, as well as the capacity to weigh benefits and risks for themselves. However, informed decision-making is complicated by the novelty and complexity of cutting-edge neurotechnologies. Many patients or research participants might not fully grasp the long-term implications of allowing researchers to collect and store highly intimate neural data. Clear, empathetic communication, along with ethical oversight from independent review boards, can help individuals navigate this frontier responsibly.

Finally, well-being and patient protection should guide every step of clinical and research processes. Researchers and healthcare providers must remain vigilant against the potential psychological impact of receiving data-driven predictions about one's cognitive future, such as risk profiles for dementia or mental health disorders. Proper counseling and psychological support mechanisms should be in place to help individuals interpret and cope with this information. Moreover, stringent regulation and transparent peer review are necessary to ensure that any commercial interests do not overshadow patient welfare. In sum, ethical safeguards around access, data privacy, autonomy, and definitions of therapeutic benefit versus enhancement must evolve in tandem with scientific progress. This requires collaboration among healthcare professionals, researchers, ethicists, legal experts, and patients themselves, ensuring that as we move forward in harnessing neuroplasticity's potential, we do so in a manner that upholds equity, respects personal freedoms, and maintains public trust.

The key ethical concerns to be addressed systematically are provided in Table 3. By systematically addressing these ethical domains, practitioners, researchers, and policymakers can work toward a more equitable and responsible deployment of neuroplasticity-based interventions.

Another important consideration is the quality of evidence. While neuroplasticity-based interventions show significant promise, the strength of supporting evidence varies widely across treatment modalities. Some approaches, such as pharmacological modulation (e.g., BDNF enhancers, SSRIs) and TMS for depression, are supported by large-scale clinical trials, whereas others, like gene-editing techniques and AI-driven neuromodulation, remain in the experimental stage. To provide a clearer assessment of research quality, Table 4 categorizes key neuroplasticity interventions based on the level of scientific evidence available from randomized controlled trials (RCTs), systematic reviews, and preclinical studies.

Future research must therefore address key gaps in neuroplasticity interventions to ensure their efficacy and clinical applicability. Long-term studies are needed to assess the effectiveness of personalized neuromodulation techniques, such as AI-driven TMS protocols. Additionally, larger multicenter trials should be conducted to evaluate the potential of BCIs and gene-editing applications in neurorehabilitation. Strengthening biomarker validation is also essential to identify which patients are most likely to benefit from pharmacological and lifestyle-

Table 3
Ethical domains, key concerns, and potential strategies.

Domain	Ethical Concern	Key Concerns	Potential Strategies
1	Cost and Access	High-tech interventions remain expensive and risk excluding vulnerable populations, exacerbating inequities.	Develop subsidies or scalable solutions; pursue policy reforms; create low-cost versions of key technologies.
2	Data Privacy and Governance	Risks of unauthorized access, misuse, or monetization of sensitive information; participants may be unaware of future data use.	Implement strict encryption and de-identification protocols; ensure transparent consent; establish oversight committees.
3	Therapy vs. Enhancement	Performance boosts in healthy individuals could deepen social inequalities; and blur the line between medical treatment and elective upgrades.	Establish clear guidelines distinguishing therapy from enhancement; convene ethics committees; foster public discourse on equity.
4	Autonomy and Informed Consent	Evolving brain technologies challenge existing consent frameworks; participants may not fully grasp long-term implications.	Use iterative, multi-stage consent; provide user-friendly educational resources; require independent ethics oversight.
5	Psychological Impact and Well-being	Access to predictive data (e.g., dementia risk) can cause anxiety or stigma; and insufficient support for distressing outcomes.	Incorporate counseling services; develop referral systems for mental health support; involve psychologists in research design.
6	Commercial and Regulatory Oversight	Private companies might exploit consumers; unclear standards can compromise patient welfare; risk of profit overshadowing safety.	Enforce evidence-based marketing, transparent labeling, and peer-reviewed data; align international regulations; prioritize patient well-being.

Table 4
Quality of Evidence Supporting Neuroplasticity Interventions.

Intervention Type	Clinical Application	Level of Evidence	Example References
Transcranial Magnetic Stimulation (TMS)	Depression, Stroke, Chronic Pain	Moderate	(George, 2010; Lefaucheur et al., 2020)
Transcranial Direct Current Stimulation (tDCS)	Cognitive Enhancement, Stroke Rehabilitation	Moderate	(Brunoni et al., 2017; Nitsche and Paulus, 2011)
BDNF-Enhancing Pharmacological Agents (SSRIs, Ketamine)	Depression, PTSD, Cognitive Resilience	Moderate	(Casarotto et al., 2022; Krystal et al., 2024)
Brain-Computer Interfaces (BCIs)	Stroke Recovery, ALS Communication	Moderate	(Ang et al., 2015; Milekovic et al., 2018)
Cognitive Training Programs	Dementia Prevention, Post-Stroke Rehabilitation	Moderate	(Gates et al., 2019; Bherer et al., 2021; Bherer, 2015)
Gene Therapy (CRISPR, SMN1 replacement)	Spinal Muscular Atrophy, Potential for Stroke & TBI	Emerging	(Mendell et al., 2017)
AI-Assisted Neuroimaging & Personalized Neuromodulation	Alzheimer's Prediction, TBI Recovery	Emerging	(Kahana et al., 2023; Jung et al., 2024)
Neurogenesis-Stimulating Lifestyle Interventions (Exercise, Diet, Sleep Optimization)	Cognitive Longevity, Stress Resilience	Moderate	(Erickson et al., 2011)

based neuroplasticity interventions. By establishing higher methodological standards, future studies can improve the reliability and clinical translation of neuroplasticity-based therapies.

Neuroplasticity research has illuminated crucial pathways for meaningful clinical interventions, yet significant challenges persist in applying these findings at scale. Methodological variability across studies such as differences in intervention length, intensity, and assessment tools, complicates direct comparisons and *meta*-analyses. Small sample sizes also limit statistical power and confidence in reported effects, while reliance on a narrow set of neuroimaging or behavioral metrics hinders a more comprehensive understanding of plastic changes. Further, many investigations offer only short follow-up times, leaving open the question of whether any observed improvements endure beyond the immediate aftermath of an intervention. Even when short-term benefits are substantial, little is known about the necessity of ongoing training or reinforcement to maintain these gains over months or years.

Population-specific factors add another layer of complexity. Children tend to display heightened plastic potential, while older adults face more structural and cognitive challenges. As a result, strategies that work well for one age group may be less effective for another. Research in clinical populations, such as stroke survivors or individuals with Parkinson's disease, may not translate neatly to non-clinical cohorts due to varying etiologies and comorbidities. Additionally, the integration of multi-omics data, including genomics, proteomics, and metabolomics, remains in its infancy, limiting our ability to use biomarkers and genetic insights for personalized interventions. Epigenetic factors like stress, diet, and environmental exposures also play an important role in modulating plastic changes, but they are not yet fully understood or accounted for in most study designs.

Cross-disciplinary collaboration is indispensable if we are to piece together the biological, behavioral, and technological aspects of neuroplasticity. While many studies emphasize biological endpoints, behavioral dimensions, such as adherence, motivation, and psychosocial context are equally vital. In parallel, advances in engineering and data science are driving the development of brain-computer interfaces, wearable sensors, and machine learning algorithms that can capture neural changes in real time, although the practical integration of these tools into clinical and everyday settings is still a work in progress.

Personalized medicine, with its focus on tailoring interventions to individual biomarkers, genetic predispositions, and neural profiles, is poised to shape the future of neuroplasticity research. Biomarker-driven therapies could help clinicians predict which patients will respond best to certain interventions, while adaptive strategies that use real-time feedback from imaging or EEG data might allow for on-the-fly adjustments to intervention intensity or duration. Emerging insights from genetic profiling, especially regarding genes related to neurotrophic factors and synaptic plasticity, offer further promise for precision-based approaches.

Socioeconomic and ethical considerations, however, are inescapable. The high costs of advanced neuroimaging and extended cognitive training can limit broad accessibility, necessitating the development of cost-effective methods that can be implemented in diverse settings. With the rise of personalized, data-heavy interventions, issues of data ownership, patient privacy, and regulatory governance become critical, demanding clear frameworks to ensure both ethical conduct and public trust. These challenges converge in the real-world implementation of neuroplasticity interventions, as they must fit into established clinical workflows while contending with reimbursement structures, provider training needs, and patient adherence constraints. Remote or digital platforms for therapy hold the potential for scaling up services, but they require careful validation to confirm effectiveness and maintain user engagement.

Looking ahead, large-scale, long-term cohort studies could illuminate how neural adaptations accumulate or decline over time, shedding light on whether early interventions can stave off later cognitive and functional decline. Multi-center and international collaborations can help validate findings across various populations and healthcare systems, while concerted translational pipelines will be essential for moving discoveries from the lab to clinics. By addressing methodological inconsistencies, fostering interdisciplinary partnerships, and embracing both precision medicine and cost-efficient delivery, neuroplasticity research can continue to evolve and fulfill its promise of reshaping patient outcomes and deepening our understanding of the human brain.

A visualization of a concise summary, a clear explanation of each limitation, and actionable directions to address these challenges with practical examples can be seen in Table 5.

7. Conclusion

A deeper understanding of neuroplasticity—encompassing synaptic, structural, and functional adaptations—has dramatically expanded therapeutic possibilities. While neuroplasticity-based interventions offer unprecedented opportunities for recovery, learning, and even cognitive enhancement, harnessing plasticity requires balancing optimism with caution.

On one hand, targeted interventions, including lifestyle modifications, novel pharmaceuticals, BCIs, and personalized neuromodulation, hold immense potential to restore function or enhance performance. On the other hand, contradictory findings, methodological inconsistencies, and unresolved ethical concerns highlight the challenges of integrating these innovations into mainstream practice responsibly.

Moving forward, a multidisciplinary approach will be essential. Researchers must prioritize high-quality evidence, ensuring that new interventions undergo rigorous validation through large-scale, long-term clinical trials. Interdisciplinary collaboration – bridging neuroscience, engineering, medicine, and bioethics – will be key to developing clinically viable and ethically responsible solutions. Policymakers and ethicists must establish clear regulatory frameworks that protect patient privacy, promote accessibility, and address the ethical divide between therapeutic intervention and cognitive enhancement.

Table 5
Summary of limitations, future directions, and practical examples in neuroplasticity research.

No.	Category	Description	Possible Directions	Examples
1	Methodological Variability	Inconsistent protocols and small sample sizes.	Standardize protocols and metrics.	Uniform neuroimaging parameters, validated clinical scales.
2	Short Follow-up Times	Positive findings often lose significance quickly.	Conduct long-term, multi-year studies.	Track cognitive training outcomes over 3–5 years.
3	Population-Specific Factors	Plasticity varies significantly by age group.	Include diverse populations in studies.	Pediatric and geriatric neuromodulation research.
4	Incorporation of Multi-Omics	Genomics and proteomics are underutilized.	Integrate multi-omics into research.	Use proteomics to predict TMS or drug responsiveness.
5	Cross-Disciplinary Collaboration	Difficulty integrating neuroscience with other disciplines.	Foster multi-modal, interdisciplinary approaches.	Combine fMRI with wearable behavior-tracking tools.
6	Socioeconomic Feasibility	High costs limit access and scalability.	Develop affordable, scalable solutions.	Low-cost tDCS kits, insurance reimbursement advocacy.
7	Calls for Action & Future Steps	Improve collaboration and analytics for practical solutions.	Expand multi-center, global collaborations.	Test standardized interventions across global networks.

This review has explored the fundamental mechanisms of neuroplasticity, the balance between adaptive and maladaptive changes, and how plasticity evolves across the lifespan. We have examined the latest therapeutic strategies and technological innovations, assessing their current evidence base and clinical potential. However, significant challenges remain, particularly in bridging the gap between experimental findings and real-world applications.

By addressing methodological inconsistencies, refining personalized treatment approaches, and ensuring ethical considerations are met, neuroplasticity research can transition from scientific promise to transformative clinical application. If these collective efforts succeed, neuroplasticity's full potential can be realized in a way that upholds scientific integrity, ensures equitable access, and fosters public trust—ultimately enhancing brain health and human resilience across all stages of life.

Funding information: Not applicable.

CRediT authorship contribution statement

Parisa Gazerani: Writing – review & editing, Writing – original draft, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

No data was used for the research described in the article.

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