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NEUROPLASTICITY ACROSS THE LIFESPAN: MECHANISMS, MODULATORS, MALADAPTATION AND TRANSLATIONAL FRONTIERS

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ABSTRACT

Neuroplasticity, the capacity of the nervous system to alter its structure, function and connectivity in response to intrinsic and extrinsic stimuli, has moved from a developmental curiosity to a central organising principle of contemporary neuroscience and a plausible therapeutic target across neurology, psychiatry, pharmacology and rehabilitation medicine. This condensed review synthesises current mechanistic and translational evidence within a single integrated framework. Four interdependent pillars of plasticity are delineated: synaptic modification, comprising long-term potentiation, long-term depression, spike-timing dependence, metaplasticity and homeostatic scaling; structural remodelling, comprising spine turnover, dendritic and axonal growth, pruning and activity-dependent myelination; neurogenesis; and system-level functional reorganisation, comprising map plasticity, vicariation and diaschisis. These neuron-centred processes are permitted or constrained by a supporting tissue environment of astrocytes, microglia, oligodendrocytes, extracellular matrix and the neurovascular unit, and converge on a common molecular substrate dominated by calcium-dependent glutamatergic signalling, brain-derived neurotrophic factor-TrkB transduction, transcriptional and epigenetic control, and neurosteroid modulation. Plastic capacity follows a non-monotonic lifespan trajectory, being high and experience-expectant during critical periods, progressively gated in adulthood, and attenuated but not abolished in senescence. Critically, plasticity is directionally neutral: identical mechanisms underwrite skill acquisition and recovery on the one hand, and central sensitisation, addiction, dystonia and epileptogenesis on the other. The current interventional armamentarium is appraised, spanning task-specific rehabilitation, aerobic exercise, cognitive and social enrichment, structured psychological techniques including clinical hypnosis, sleep and dietary optimisation, non-invasive and paired neuromodulation, plasticity-promoting pharmacology, brain-computer interfaces and artificial-intelligence-guided personalisation, with the maturity of supporting evidence graded for each. Persistent obstacles include biomarker non-equivalence, heterogeneity of dose and timing, short follow-up, and unresolved ethical questions concerning equitable access, neural data privacy and the therapy-enhancement boundary. The decisive translational challenge is no longer whether plasticity can be induced, but whether it can be reliably steered.

KEYWORDS: Neuroplasticity, Synaptic plasticity, Neurogenesis, Maladaptive plasticity, Neurorehabilitation.

INTRODUCTION

Neuroplasticity is most usefully defined as the ability of the nervous system to change its activity in response to intrinsic or extrinsic stimuli by reorganising its structure, functions or connections1. The term is capacious, and its breadth has been criticised as diluting explanatory value: it has been applied to phenomena spanning milliseconds of receptor trafficking to decades of cortical map reconfiguration2. Nevertheless, the unifying insight is durable - the adult brain is not a fixed wiring diagram but a continuously renegotiated one, and the rules governing that renegotiation change with age, context and state3.

The conceptual lineage is well documented. Plasticity entered scientific discourse at the close of the nineteenth century, was formalised terminologically in the mid-twentieth, and acquired a mechanistic vocabulary only after the electrophysiological and molecular advances of the 1970s onwards4. Two developments transformed the field from description to intervention. First, the demonstration that plasticity persists in the mature brain reframed learning, rehabilitation and cognitive ageing as manipulable processes rather than fixed endowments5,6. Second, the recognition that environmental and behavioural variables act as genuine biological modulators - an endogenous pharmacotherapy - legitimised exercise, enrichment, training and structured psychological interventions as mechanistically grounded therapeutics rather than adjuncts7,8,9.

Equally consequential was the realisation that plasticity is a double-edged sword10. The same activity-dependent rules that consolidate a motor skill can consolidate a pain state; the same reward-circuit potentiation that supports goal-directed learning can entrench compulsive drug seeking11,12. Plasticity is therefore not synonymous with recovery, and a demonstrable change in cortical excitability, activation pattern or connectivity may equally reflect efficient restitution, inefficient compensation, disinhibition or frank maladaptation1. This directional neutrality is the single most important framing device for clinical translation, and it structures the present review.

This article offers a condensed but integrative synthesis. It delineates the mechanistic taxonomy of plasticity and its supporting tissue and molecular substrates; traces its lifespan trajectory and hormonal modulation13; examines maladaptive plasticity as a unifying pathophysiological concept; appraises the interventional landscape by evidence maturity; and identifies methodological, biomarker and ethical bottlenecks. The aim is to provide researchers, clinicians, pharmaceutical scientists and policymakers with a compact, critically appraised framework rather than an exhaustive catalogue.

MATERIALS AND METHODS:

Search strategy and study selection

This work is a narrative review with a structured search component. PubMed/MEDLINE, Scopus, Web of Science and Google Scholar were interrogated for records published between January 2006 and June 2026 using combinations of the term's neuroplasticity, brain plasticity, synaptic plasticity, long-term potentiation, long-term depression, adult neurogenesis, functional reorganisation, maladaptive plasticity, cognitive reserve, neurorehabilitation, neuromodulation, brain-computer interface and lifestyle intervention. Reference lists of retrieved reviews were hand-searched to identify additional sources.

Inclusion and exclusion criteria

Peer-reviewed original research, systematic reviews, meta-analyses, randomised controlled trials, authoritative narrative reviews and clinical practice guidelines published in English were eligible. Records were excluded if published before 2006, if available only as conference abstracts or preprints, or if the reported outcome could not be related to a defined plasticity mechanism. Priority was given to meta-analyses, guideline documents and pivotal randomised trials where these existed, and to mechanistic primary studies where they did not.

Data synthesis

One hundred and fifty-four sources met the criteria and were retained. Evidence was synthesised qualitatively and organised around four mechanistic pillars of plasticity, their supporting tissue and molecular substrates, their lifespan trajectory, their maladaptive expression and their therapeutic modulation. Interventions were graded descriptively by maturity of supporting evidence (guideline-supported, multiple randomised controlled trials, single pivotal trial, early-phase or preclinical). No quantitative pooling was undertaken, and no formal risk-of-bias instrument was applied; the review is therefore narrative rather than systematic, and the descriptive evidence grading reflects the authors' appraisal of the cited literature.

RESULTS AND DISCUSSION:

A mechanistic taxonomy of neuroplasticity

Neuroplasticity is best 2onceptualized not as a single process but as four interdependent mechanistic pillars operating on nested spatial and temporal scales, embedded within a permissive tissue environment and converging on a shared molecular substrate (Figure 1; Table 1).

Table 1. Core mechanisms of neuroplasticity: adaptive and maladaptive expression, and representative interventions

Mechanism	Principal processes	Adaptive expression	Maladaptive expression	Representative interventions
Synaptic plasticity	LTP, LTD, spike-timing dependence, metaplasticity, homeostatic scaling, intrinsic excitability	Skill and language learning; memory consolidation; refinement of motor programmes	Central sensitisation in chronic pain; excessive LTD and synapse loss in Alzheimer's disease	NMDA receptor modulators; cognitive training; paired stimulation
Structural plasticity	Spine formation and stabilisation, dendritic branching, axonal sprouting, pruning, activity-dependent myelination	Peri-lesional sprouting after stroke; training-induced remodelling; myelin plasticity with motor learning	Drug-induced spine remodelling in reward circuits; excessive adolescent pruning in schizophrenia; maladaptive myelination in epilepsy	Task-specific rehabilitation; exercise; remyelination-promoting agents

Mechanism	Principal processes	Adaptive expression	Maladaptive expression	Representative interventions
Neurogenesis	Precursor proliferation, differentiation, survival, circuit integration	Pattern separation; cognitive flexibility; stress-response regulation	Stress- and glucocorticoid-related suppression in depression and ageing	Aerobic exercise; enrichment; antidepressants; ketamine
Functional reorganisation	Map plasticity, vicariation, equipotentiality, diaschisis resolution	Contralesional and peri-lesional recruitment supporting motor and language recovery	Aberrant somatosensory reorganisation in phantom limb pain; compensation that impedes restitution	Constraint-induced therapy; rTMS and tDCS; brain-computer interfaces
Supporting tissue plasticity	Astrocytic, microglial, oligodendrocytic, extracellular matrix and neurovascular adaptation	Metabolic and trophic support; complement-mediated synaptic refinement; angiogenesis	Reactive gliosis; chronic neuroinflammation; perineuronal-net plasticity brakes; blood-brain barrier breakdown	Anti-inflammatory strategies; vascular risk-factor control; exercise

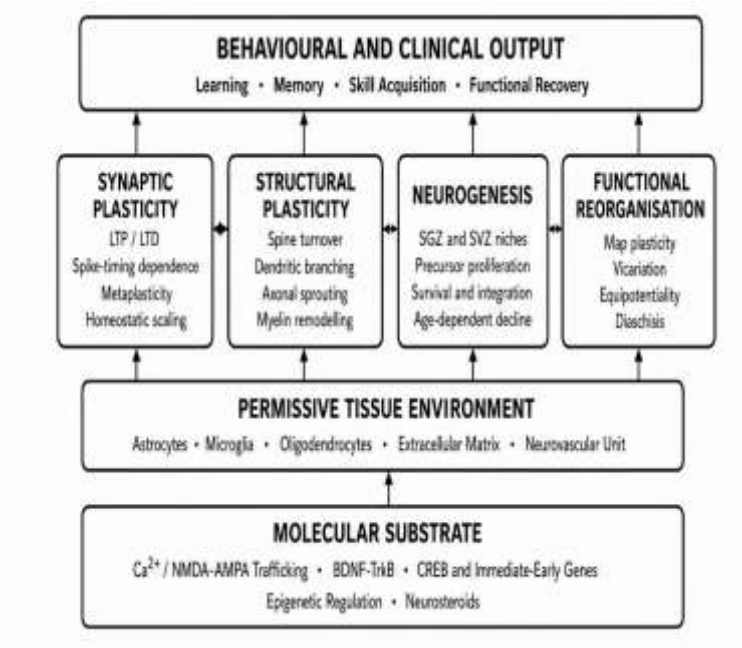

Figure 1. Integrated architecture of neuroplasticity. Four interdependent neuronal pillars generate behavioural and clinical output; these operate within a permissive tissue environment and converge on a shared molecular substrate, with modulators (dashed) acting across all levels.

Synaptic plasticity

Synaptic plasticity - experience-dependent, persistent modification of the efficacy of neuronal connections - remains the canonical cellular correlate of learning and memory14. Long-term potentiation (LTP) and long-term depression (LTD) constitute its bidirectional core15. LTP is initiated by coincident pre- and postsynaptic activity, gated by the voltage- and ligand-dependent N-methyl-D-aspartate (NMDA) receptor, and expressed through calcium-dependent kinase cascades that drive alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptor insertion, enlargement of the postsynaptic density and, in its late protein-synthesis-dependent phase, transcription-dependent structural consolidation16,17. LTD reduces synaptic weight through receptor internalisation and phosphatase-dominated signalling, and is not merely the erasure of LTP but a computationally necessary process that sharpens signal-to-noise, prevents saturation and supports refinement of motor and cognitive representations18,19,20.

Three refinements have enriched this framework. Spike-timing-dependent plasticity replaces coarse correlational rules with millisecond-resolution causality, and is itself strongly gated by neuromodulators including dopamine, acetylcholine and noradrenaline - providing a mechanistic account of why attention, salience and reward determine what is learned21. Homeostatic plasticity, including synaptic scaling and adjustment of intrinsic excitability, maintains network firing within a functional range over hours to days and prevents the runaway dynamics that purely Hebbian rules would otherwise produce22,23. Intrinsic plasticity, mediated by regulated expression of voltage-gated sodium, calcium and potassium

conductance, allows individual neurons to shift their input-output function independently of synaptic weight, thereby tuning excitability during skill acquisition and, when dysregulated, contributing to hyperexcitable states24.
Failure of these controls defines a growing family of synaptopathies in which the primary lesion is synaptic rather than somatic. Alzheimer's disease is increasingly conceptualised in these terms, with synapse loss correlating with cognitive decline more closely than plaque burden, and with oligomeric species impairing LTP and facilitating pathological LTD25,26,27. This reframing is of direct pharmaceutical relevance, since it identifies synaptic maintenance rather than plaque clearance as a tractable therapeutic endpoint.

Structural plasticity

Structural plasticity provides the anatomical instantiation of functional change28,29. Chronic in vivo two-photon imaging has established that dendritic spines undergo continuous turnover, that learning produces rapid spine formation in task-relevant cortex, and - critically - that the subset of newly formed spines which is stabilised, rather than the total number formed, predicts long-term retention of a skill30. Complementary work demonstrates bidirectional specificity: fear conditioning and extinction elicit opposing spine dynamics within the same dendritic branches, indicating that structural remodelling encodes the valence and content of experience rather than merely its occurrence31,32.
Human structural neuroimaging supports an expansion-renormalisation dynamic, in which grey-matter volume in trained regions increases transiently during early skill acquisition and partially normalises as performance plateaus and representations become more efficient33. This has important interpretive consequences: greater volume is not uniformly better, and cross-sectional structural differences may index the stage of learning rather than its magnitude.
Pruning is the developmental counterpart of growth. Complement-tagged, microglia-mediated elimination of weak or underused synapses refines circuits during postnatal life and adolescence, converting an exuberant early network into an efficient mature one34,35. Finally, activity-dependent myelination has emerged as a genuine fourth axis of structural plasticity: oligodendrocyte precursor proliferation and myelin sheath remodelling are experience-regulated, alter conduction velocity and therefore network synchrony, and have been demonstrated in humans following motor skill training36,37.

Neurogenesis

Adult neurogenesis remains the most conceptually attractive and empirically contested pillar. In rodents, the sub granular zone of the hippocampal dentate gyrus and the subventricular zone generate new neurons that mature through a defined transcriptional programme, pass through a transient window of heightened excitability and enhanced plasticity, and integrate into existing circuits38,39,40. Functionally, adult-born granule cells have been implicated in pattern separation, cognitive flexibility, contextual memory and regulation of the stress response41. Newborn neurons have additionally been described in non-canonical niches including hypothalamus, striatum, amygdala and neocortex, though the relative contribution of local precursors versus migration from the subventricular zone remains unresolved42,43.
The human evidence is genuinely contested and should be presented as such. Carbon-dating and immunohistochemical studies have reported persistent hippocampal neurogenesis into the ninth decade44, whereas other groups, using different markers and post-mortem processing, report a sharp decline to undetectable levels after childhood45. Much of the discrepancy is methodological: markers such as doublecortin label immature neurons that may be developmentally generated and long-lived rather than newly born, and no unambiguous niche architecture comparable to that of rodents has been demonstrated in adult humans46,47. A defensible position is that a reservoir of immature, plasticity-competent neurons exists in the adult human hippocampus, but that its rate of replenishment, and therefore its therapeutic tractability, is unproven.
Regardless of the human quantitative question, the regulatory biology is consistent and clinically informative. Neurogenesis is upregulated by voluntary exercise, environmental enrichment and antidepressant exposure, and suppressed by chronic stress and sustained glucocorticoid elevation48,49,50. Notably, adult-born neurons themselves display a critical period during which experience determines their connectivity, providing an elegant recapitulation of developmental principles within the mature brain48.

Functional reorganisation

At the systems level, plasticity manifests as redistribution of function across networks. Historical models offered two competing accounts: equipotentiality, in which the homotopic contralateral region assumes a lost function, and variation, in which regions not originally serving a function are recruited to it51. Modern imaging indicates that neither operates in isolation; post-injury adaptation typically involves early bilateral or peri-lesional over-recruitment followed by progressive re-lateralisation and focusing toward efficient, often ipsilesional, representations, with the degree of consolidation predicting outcome52.
Diaschisis - depressed function in a structurally intact region remote from but connected to the lesion - has been substantially rehabilitated as a concept52. Contemporary taxonomies distinguish diaschisis at rest, for example ipsilateral thalamic hypoperfusion after middle cerebral artery occlusion, observed in a minority of acute cases but a large majority of subacute and chronic ones53; functional and dynamic diaschisis emerging only during task performance; connectional diaschisis reflecting altered interhemispheric coupling54; and connectome diaschisis, in which damage to highly connected hub regions produces disproportionate network-wide dysfunction relative to peripheral nodes52.
Stroke remains the paradigmatic clinical model. Motor recovery involves peri-infarct remapping, altered interhemispheric inhibition and recruitment of premotor and supplementary motor territory54,55,56. However, compensation must be distinguished from restitution: behaviourally successful compensation can be accompanied by persistent, sometimes

maladaptive, network reorganisation, and improvements in performance do not entail restoration of the original circuit55,57. Analogous distinctions apply in post-stroke aphasia, where right-hemisphere recruitment may be supportive, epiphenomenal or actively unhelpful depending on lesion extent and time since onset58,59. In amputation and phantom limb pain, sensorimotor map reorganisation illustrates the same interpretive ambiguity60.

The permissive tissue environment

A neuron-centred account is now clearly incomplete. Astrocytes regulate extracellular glutamate and potassium, supply metabolic substrate, release gliotransmitters including D-serine that are required for NMDA-receptor-dependent LTP, and thus function as active partners rather than passive scaffolding61,62. Microglia surveil the healthy parenchyma, sculpt synapses through complement-dependent phagocytosis, and support post-injury repair; chronic activation converts this role into a pro-inflammatory one that impairs remodelling, and microglial mechanisms are increasingly implicated in the transition to chronic pain63,64,65. Reactive astrocyte phenotypes induced by activated microglia are neurotoxic and are reported across neurodegenerative conditions66. A compelling argument has been advanced that cognitive ageing is defined less by inflammation per se than by glial decline and loss of homeostatic support67.

The extracellular matrix, particularly perineuronal nets ensheathing parvalbumin-positive interneurons, actively constrains plasticity, and its maturation is a principal mechanism closing developmental critical periods61. The neurovascular unit supplies the metabolic and clearance capacity that plastic change demands; exercise-induced angiogenesis improves neurovascular coupling, whereas hypertension, diabetes and blood-brain barrier compromise degrade the substrate for adaptation68,69. Neuroinflammation occupies a dual position: acute inflammatory signalling clears debris and initiates repair, but prolonged neuroinflammation becomes toxic to synapses and network integration70.

Temporal dynamics after injury

Plasticity after focal injury is a staged sequence, and the therapeutic implications differ at each stage (Figure 2). Within the first hours to days, excitotoxicity, oedema and cell death dominate, with loss of specific cortical pathways and recruitment of secondary networks; remote but connected regions enter a state of depressed function52,53. Over the subsequent one to four weeks, a growth-permissive transcriptional programme is transiently expressed, local inhibition is reduced, and cortical territory adjacent to the lesion shifts toward an excitable, plastic state resembling that of the developing brain56. From roughly one to six months, axonal sprouting, synaptogenesis and spine turnover support progressive remapping and vicariation56,57. Beyond six months, whatever configuration has been established tends to consolidate, which is why late-phase interventions must actively destabilise entrenched patterns rather than simply add practice71.

This staged model generates two clinically actionable predictions. First, there is a bounded sensitive window in which a given quantum of rehabilitation yields disproportionate benefit, so that delays attributable to service organisation are not neutral. Second, the window can be functionally narrowed by modifiable systemic factors - uncontrolled pain, sedation, delirium, sleep fragmentation, depression, immobility and unresolved inflammation - meaning that the biological substrate for adaptive change must be actively protected, not merely assumed70,72. Where the substrate is degraded, intensifying therapy alone is unlikely to compensate.

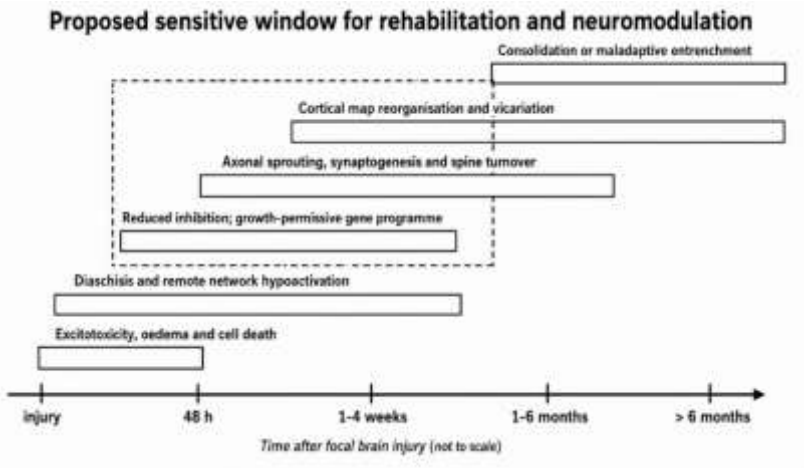

Figure 2. Temporal phases of plasticity after focal brain injury, with the proposed sensitive window for rehabilitation and neuromodulation. The timescale is categorical and not linear.

Molecular substrate

Despite the diversity of these mechanisms, a relatively small set of molecular pathways recurs (Table 2). Calcium entry through NMDA receptors and voltage-gated channels acts as the principal coincidence detector, with the amplitude and kinetics of the calcium transient determining whether kinase-dominated potentiation or phosphatase-dominated depression ensues.

Brain-derived neurotrophic factor (BDNF) signalling through the tropomyosin receptor kinase B (TrkB) receptor is the most consistently implicated permissive signal, linking activity, trophic support, spine stabilisation and neurogenesis73. Evidence that conventional antidepressants and rapid-acting agents bind TrkB directly, thereby facilitating BDNF

signalling rather than acting solely through monoamine transporters, has reframed antidepressant action as fundamentally plasticity-promoting and is of considerable interest for rational drug design74,75,76. Downstream, cyclic adenosine monophosphate response element-binding protein (CREB)-dependent transcription and immediate-early gene induction convert transient activity into persistent change, and CREB signalling capacity declines with age in parallel with reduced learning-related excitability77.

Above this sits an epigenetic layer - DNA methylation, histone modification and non-coding RNA regulation - that renders plastic capacity itself experience- and environment-dependent, offering a molecular account of how early-life adversity, nutrition and stress produce durable shifts in plastic set-point78. Finally, locally synthesised neurosteroids are not merely peripheral endocrine signals: hippocampal neurons express the full enzymatic machinery for de novo oestradiol and androgen synthesis, and this local production regulates spine density, synaptic transmission and LTP in a sex-dependent manner79,80.

The practical significance of this convergence is that mechanistically distinct interventions frequently act on the same limited set of nodes. Exercise, enriched environment, antidepressant exposure, ketamine, psychedelics and several neuromodulation protocols all ultimately increase BDNF-TrkB signalling and downstream transcriptional activity, which explains both their overlapping efficacy and the difficulty of demonstrating additivity when they are combined. It also predicts a ceiling: once the shared substrate is maximally engaged, further intensification of any single modality yields diminishing returns and may cross into the descending limb of the dose-response relationship (Figure 5A). Conversely, interventions acting at genuinely different levels - a permissive pharmacological or stimulation-based intervention paired with a behaviourally specific training signal - are more plausible candidates for synergy, since one supplies capacity and the other supplies direction8,71.

Table 2. Key molecular mediators of plasticity and their translational relevance

Mediator	Principal role	Translational relevance
NMDA and AMPA receptors; Ca2+ signalling	Coincidence detection; direction of synaptic change	Ketamine; memantine; antiepileptic ion-channel modulators
BDNF-TrkB	Trophic permissiveness; spine stabilisation; neurogenesis	Antidepressants; psychedelics; exercise; TrkB agonists
CREB and immediate-early genes	Transcription-dependent consolidation	Target for age-related cognitive decline
Epigenetic regulators	Setting of plastic capacity by environment	Histone deacetylase inhibitors; epigenetic editing (preclinical)
Neurosteroids (oestradiol, androgens)	Sex-dependent spine and synaptic regulation	Hormone therapy timing; sex-stratified trial design
Glial and immune mediators	Permissive versus inhibitory tissue state	Anti-inflammatory adjuncts; microglial modulation

Neuroplasticity across the lifespan

Plastic capacity is neither constant nor monotonically declining; distinct forms follow distinct trajectories (Figure 3; Table 3)81.

During early development, exuberant synaptogenesis is followed by activity-dependent pruning, and critical periods - bounded windows of experience-expectant plasticity during which specific inputs are required for normal circuit formation - dominate82,83. Speech perception, binocular vision and language acquisition are the best-characterised examples84. Critical-period closure is now understood as an active, brake-imposing process involving maturation of parvalbumin interneuron networks, perineuronal net deposition and myelin-associated inhibitory signalling, which is in principle reversible - an insight driving attempts to pharmacologically or behaviourally reopen windows in adulthood85.

The same windows that confer opportunity confer vulnerability. Neglect, maltreatment, poverty and chronic early stress engage hypothalamic-pituitary-adrenal axis dysregulation, alter hippocampal and prefrontal-amygdala development, reduce dendritic complexity and neurogenesis in animal models, and are associated in humans with reduced cortical thickness and elevated lifetime psychiatric risk86,87,88. Adolescence is defined by protracted prefrontal maturation, continued synaptic pruning, and reorganisation of prefrontal-limbic connectivity underlying gains in executive control, social cognition and emotion regulation89; this transitional configuration confers both learning advantage and heightened stress sensitivity, and is the developmental window in which many psychiatric disorders first manifest90.

Adult plasticity is not abolished but conditionally gated: it requires greater drive, salience and repetition, and is strongly modulated by education, physical activity, social engagement and diet91. Individual variability is substantial and partly genetic; BDNF polymorphisms, among others, predict differential responsiveness to plasticity-inducing protocols, which has direct implications for the reproducibility of neuromodulation trials13. Ageing brings reduced neurogenic output, decreased spine and synapse density, impaired LTP induction and maintenance, altered calcium homeostasis with enhanced afterhyperpolarisation and LTD bias, and diminished neuromodulator availability92,93,94,95,96. These changes are graded rather than categorical, and the transition to pathological ageing is better indexed by cognitive trajectory than by any single structural measure.

Oestradiol, progesterone and androgens exert genomic and non-genomic effects on spine density, synaptic transmission and neurogenesis, with substantial sex-dependence in which pathway predominates79,80. The menopausal transition, and more gradual androgen decline in men, alter the hormonal milieu supporting plasticity97; evidence on hormone therapy remains contingent on timing, formulation and individual risk, and does not support blanket recommendation. Finally, cognitive reserve - the efficiency with which an individual deploys available neural resources - together with brain reserve and maintenance provides the dominant framework for explaining why comparable pathology produces divergent clinical expression98, and consensus definitions now distinguish these constructs explicitly, which is essential for coherent measurement across studies99.

Table 3. Neuroplasticity across the lifespan

Stage	Dominant processes	Functional consequence	Principal vulnerability
Prenatal to infancy	Neurogenesis, migration, exuberant synaptogenesis, early myelination	Rapid experience-expectant circuit construction	Teratogens; malnutrition; maternal infection and stress
Early childhood	Critical periods; pruning onset; rapid language and sensory tuning	Efficient acquisition of language, vision and social cognition	Neglect; deprivation; poverty; maltreatment
Adolescence	Prefrontal maturation; continued pruning; prefrontal-limbic reorganisation	Emerging executive control and social cognition	Onset window for psychiatric disorder; substance exposure
Adulthood	Gated experience-dependent plasticity; adult neurogenesis; reserve accrual	Skill acquisition and rehabilitation potential retained	Chronic stress; sedentary behaviour; sleep debt; metabolic disease
Ageing	Reduced neurogenesis and spine density; impaired LTP; Ca2+ dysregulation; glial decline	Slower, higher-threshold plasticity; reliance on reserve	Neurodegeneration; vascular comorbidity; hormonal decline

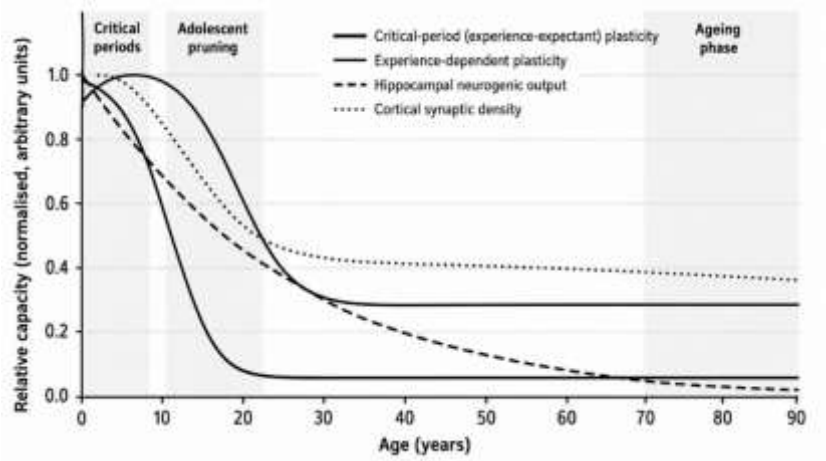

Figure 3. Schematic lifespan trajectories of distinct forms of plastic capacity, normalised to arbitrary units. Curves are conceptual syntheses of the cited literature and are not fitted to primary data.

Maladaptive plasticity as a unifying pathophysiology

If plasticity is directionally neutral, then a substantial class of chronic neurological and psychiatric disease can be reframed as disorders of misdirected learning (Figure 4; Table 4).

Chronic pain is the clearest exemplar. Persistent nociceptive input, potentiated by inflammatory and glial signalling, drives excessive LTP-like amplification in dorsal horn and supraspinal pain pathways - central sensitisation - accompanied by structural remodelling in somatosensory, insular and cingulate cortices and by altered connectivity among pain-processing regions100,101. Once established, pain becomes progressively decoupled from peripheral pathology and increasingly dependent on self-sustaining network dynamics, which explains both the failure of peripherally directed pharmacotherapy and the rationale for centrally directed intervention102,103. Phantom limb pain represents the same principle in the absence of any peripheral substrate104.

Addiction reflects drug-evoked synaptic plasticity in mesocorticolimbic circuitry. Repeated exposure potentiates excitatory synapses in the ventral tegmental area and nucleus accumbens, remodels dendritic architecture in reward-related regions, and progressively shifts behavioural control from goal-directed to habitual systems105,106,107; these changes persist long after drug clearance, providing a mechanistic account of relapse vulnerability. Schizophrenia has been reframed as a disorder of synaptic density, in which excessive adolescent pruning weakens prefrontal recurrent

connectivity and degrades top-down regulation, with in vivo imaging of synaptic vesicle protein providing convergent support108,109. Epilepsy illustrates plasticity-driven disease progression, encompassing aberrant mossy fibre sprouting, altered intrinsic excitability and, more recently, maladaptive myelination that promotes seizure propagation110. Depression involves the opposite polarity - stress- and glucocorticoid-mediated loss of hippocampal and prefrontal synaptic and neurogenic capacity, with weakened hippocampal-prefrontal coupling, and with rapid antidepressant action attributable to restoration of that capacity111,112. In neurodegeneration, impaired neurogenesis and synaptic failure appear early and interact bidirectionally with proteinopathy and neuroinflammation113.

These disorders also illustrate that plasticity mechanisms rarely fail in isolation. Chronic pain begins with synaptic amplification, proceeds to structural remodelling of cortical dendrites, and culminates in stable network-level reconfiguration; by the time the network state is established, reversing the synaptic change alone is insufficient100,103. Depression shows the reciprocal pattern, in which neurogenic suppression, dendritic atrophy and weakened hippocampal-prefrontal coupling reinforce one another111,112. Addiction couples synaptic potentiation to structural remodelling and then to a shift in the balance of network control105,107. This cross-level propagation carries a clear therapeutic corollary: interventions targeting a single level are likely to be insufficient once a disorder has consolidated, and the window in which single-level intervention can succeed is probably early. It also argues for stage-specific rather than diagnosis-specific treatment algorithms. The therapeutic implication is uniform: the target is not the quantity of plasticity but its direction.

Table 4. Maladaptive plasticity in representative disorders

Disorder	Predominant mechanism	Clinical expression
Chronic pain	Excessive LTP in nociceptive pathways; cortical remodelling; network hyperconnectivity	Pain decoupled from peripheral pathology; treatment resistance
Addiction	Drug-evoked potentiation in ventral tegmental area and nucleus accumbens; dendritic remodelling	Compulsive use; persistent relapse liability
Schizophrenia	Excessive adolescent pruning; reduced synaptic density	Impaired prefrontal integration; cognitive and negative symptoms
Epilepsy	Aberrant sprouting; intrinsic hyperexcitability; maladaptive myelination	Progressive seizure burden
Depression	Stress-related synaptic and neurogenic loss	Cognitive and affective symptoms; response to rapid-acting agents
Phantom limb pain and dystonia	Aberrant sensorimotor map reorganisation	Persistent pain; task-specific motor dysfunction

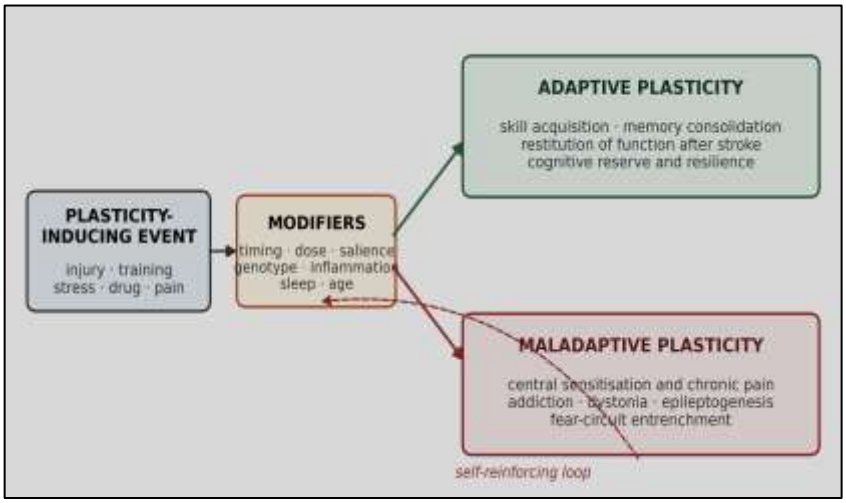

Figure 4. Bifurcation model of plasticity outcome. A common plasticity-inducing event, filtered through modifiers of timing, dose, salience, genotype, inflammatory state, sleep and age, yields either adaptive or maladaptive outcomes, with maladaptive outcomes feeding back to reinforce the inducing conditions (dashed).

Harnessing plasticity: the interventional landscape

Interventions can be ordered by mechanistic precision and evidence maturity (Figure 5B; Table 5). A recurring principle is the inverted-U dose-response (Figure 5A): insufficient drive produces no change, appropriate drive produces adaptive change, and excessive drive produces excitotoxic or maladaptive change.

Table 5. Interventions to steer plasticity, by current maturity of evidence

Intervention	Principal indication	Evidence maturity
Task-specific intensive rehabilitation	Stroke; traumatic brain injury; spinal cord injury	Guideline-supported
Aerobic and combined exercise	Cognitive ageing; adjunct across indications	Multiple RCTs and meta-analyses
Constraint-induced movement therapy	Post-stroke upper limb	Multiple RCTs
Clinical hypnosis and mind-body techniques	Pain; anxiety; habit disorders; neuropsychological rehabilitation	Emerging; blinding and standardisation limited
Repetitive transcranial magnetic stimulation	Treatment-resistant depression; post-stroke motor	Guideline-supported (depression)
Paired vagus nerve stimulation	Chronic post-stroke upper limb	Pivotal RCT
Transcranial direct current stimulation	Motor and cognitive rehabilitation	RCTs; heterogeneous
Cognitive training	Cognitive ageing; post-stroke cognition	RCTs; limited far transfer
Sleep and dietary optimisation	Cognitive resilience	Observational and mechanistic; RCTs limited
Ketamine and rapid-acting antidepressants	Treatment-resistant depression	Multiple RCTs
Psychedelic-assisted therapy	Depression; post-traumatic stress disorder	Early-phase RCTs; blinding issues
Amantadine	Disorders of consciousness after traumatic brain injury	RCT-supported
Brain-computer interfaces	Post-stroke motor; severe motor impairment	Meta-analysis; heterogeneous
AI-guided personalised neuromodulation	Cross-indication	Emerging
Gene and epigenetic editing	Monogenic disease; experimental for plasticity	Preclinical except monogenic

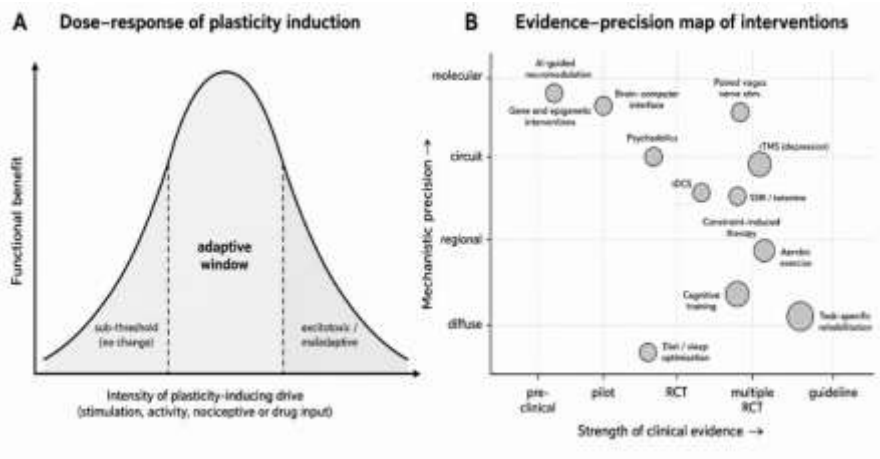

Figure 5. (A) Inverted-U dose-response relationship between the intensity of plasticity-inducing drive and functional benefit. (B) Evidence-precision map positioning current interventions by strength of clinical evidence and mechanistic precision; positions reflect the authors' appraisal of the cited literature and are intended as a heuristic.

Behavioural and rehabilitative approaches

Task-specific, repetitive, progressively challenging and attentionally engaged practice remains the best-validated method of steering plasticity, and is endorsed in stroke rehabilitation guidance alongside early organised interprofessional care72. The mechanistic requirements are explicit: practice must resemble the target function, engage the correct network, carry salience, and be delivered at sufficient intensity - passive or inattentive repetition is largely inert114,115. Constraint-induced movement therapy, which forces use of the affected limb, remains a well-studied instantiation, associated with

measurable increases in premotor and secondary somatosensory activation alongside functional gain116,117. Mirror therapy and graded motor imagery apply analogous logic to phantom limb pain104.

Lifestyle modulators

Aerobic exercise is the most robust non-pharmacological enhancer of plasticity, increasing hippocampal volume, improving memory and executive function, promoting angiogenesis, and elevating BDNF through mechanisms including ketone-body-mediated epigenetic derepression of the BDNF locus118,119,120. Resistance training contributes complementary executive benefits, and combined regimens appear superior to either alone121. Sleep is not adjunctive but constitutive: it supports memory consolidation, synaptic downscaling and glymphatic clearance of metabolic waste, and its disruption impairs consolidation and is associated with accelerated cognitive decline122,123. Diet modulates the same substrate, with omega-3 fatty acids, polyphenols and antioxidant-rich patterns supporting synaptic health, and high-saturated-fat and high-sugar patterns promoting oxidative stress and neuroinflammation121.

Cognitive training produces reliable gains on trained tasks, but Cochrane-level synthesis indicates that far transfer to global cognition in healthy older adults remains modest and inconsistently demonstrated - a nuance frequently overstated in commercial contexts124. Social engagement and sustained intellectual activity contribute to reserve, though causal inference from observational cohorts is limited by reverse causation and confounding: individuals with better preserved cognition are more likely to remain socially and intellectually active, and prodromal disease may reduce engagement years before diagnosis125. Lifestyle interventions nonetheless retain a pragmatic advantage over device- and drug-based approaches, being low-cost, scalable, of favourable risk profile, and acting simultaneously on vascular, metabolic, inflammatory and neurotrophic determinants of plastic capacity121,122.

Mind-body and structured psychological interventions

Structured psychological techniques that manipulate attention, expectation and suggestibility occupy an intermediate position between behavioural training and neuromodulation. Clinical hypnosis is the most developed example: by modulating attentional control, interoceptive processing and prefrontal-limbic coupling, hypnotic procedures have been proposed to open a state in which maladaptive associative patterns can be destabilised and re-encoded, with reported applications in pain management, anxiety, habit disorders and neuropsychological rehabilitation9. Mindfulness-based stress reduction and cognitive-behavioural therapy operate on overlapping substrates, reshaping prefrontal-limbic circuits implicated in fear and threat processing. The mechanistic appeal of these approaches is that they supply the salience and attentional engagement that the plasticity rules described above identify as necessary, at negligible cost and with minimal adverse-effect burden. Their principal limitation is methodological: blinding is difficult, expectancy effects are intrinsic to the intervention, and standardisation of dose across practitioners remains incomplete9.

Neuromodulation

Paired vagus nerve stimulation represents the most compelling recent demonstration of intentionally timed plasticity induction: in a pivotal blinded device trial in chronic ischaemic stroke, active stimulation paired with upper-limb rehabilitation approximately doubled response rates relative to sham-paired rehabilitation71. The mechanistic rationale - precisely timed neuromodulator release coincident with movement, thereby tagging the desired synapses - is instructive for the field generally.

Non-invasive brain stimulation has a large but heterogeneous evidence base. Network meta-analysis in post-stroke upper-limb recovery suggests excitatory protocols are the most promising, with transcutaneous auricular vagus nerve stimulation requiring larger confirmatory trials126. Repetitive transcranial magnetic stimulation has the strongest indication-specific evidence in treatment-resistant depression, supported by evidence-based guidelines127; theta-burst protocols show benefit for upper-extremity recovery, with better response in patients retaining preserved cortical tissue128. Transcranial direct current stimulation remains promising but inconsistent, with efficacy modulated by cortical thickness, individual connectivity and montage. Three unresolved variables account for much of the observed heterogeneity: individual anatomy and induced electric field distribution; brain state at the moment of stimulation, which determines whether a given protocol potentiates or depresses; and the interval between stimulation and the paired behavioural task. Closed-loop designs that trigger stimulation on physiologically defined states, rather than on a fixed clock, represent the most credible route to reducing this variance129.

Pharmacological approaches

Plasticity-targeted pharmacology has moved beyond monoaminergic augmentation. Ketamine and related rapid-acting agents produce prefrontal synaptogenesis and functional improvement within hours, via mechanisms converging on TrkB and mechanistic target of rapamycin signalling130. Serotonergic psychedelics have been shown to bind TrkB directly and to promote dendritic spine formation and cortical plasticity, providing a mechanistic rationale for the plasticity-window model of psychedelic-assisted therapy, although questions of blinding, expectancy, durability and safety remain substantial131. Amantadine accelerates functional recovery in severe disorders of consciousness after traumatic brain injury and remains among the better-evidenced pharmacological adjuncts in neurorehabilitation132. Selective serotonin reuptake inhibitors, cholinesterase inhibitors and ion-channel modulators are used with varying and often indication-specific evidence. Direct TrkB agonists and neurogenesis-promoting compounds remain largely preclinical, the central formulation and delivery difficulty being achievement of regional specificity without excitotoxicity.

Technological frontiers

Brain-computer interfaces translate neural activity into device commands and provide contingent, closed-loop feedback that can itself drive reorganisation; meta-analysis supports benefit for post-stroke motor rehabilitation, and long-term communication has been sustained in locked-in syndrome133,134,135. Cost, technical complexity, calibration burden and attrition remain limiting136. Gene-based approaches have achieved decisive success in monogenic neurological disease, most notably gene replacement in spinal muscular atrophy, establishing feasibility while remaining distant from application to acquired plasticity disorders137. Epigenetic editing offers a conceptually attractive route to reopening constrained plasticity, but is preclinical138. Artificial intelligence is being applied to earlier diagnosis, prediction of individual treatment response, and closed-loop optimisation of stimulation parameters from real-time electrophysiology, moving neuromodulation from fixed protocols toward state-dependent personalisation139,129,140.

In neurosurgical practice, slow-growing intrinsic tumours permit progressive functional redistribution across cortical and subcortical networks, particularly in language and motor systems, such that eloquent-appearing structures may no longer be functionally eloquent141. Knowledge of normative anatomy is therefore insufficient; discordance between imaging and bedside deficit should raise suspicion of compensatory reorganisation, and individualised preoperative functional mapping with intraoperative direct cortical stimulation is required to exploit the expanded resection window safely142,143.

Measurement, evidence quality and ethics

Biomarker non-equivalence

A pervasive interpretive error is treating plasticity biomarkers as interchangeable. Transcranial magnetic stimulation indices of cortical excitability, functional and diffusion magnetic resonance imaging, electroencephalographic measures and serum BDNF interrogate different levels of biological organisation on different timescales; a patient may show increased excitability, reduced functional connectivity and unchanged serum BDNF while improving clinically, without contradiction144,145. Systematic frameworks for measuring plasticity in humans, including explicit specification of which construct a given assay indexes, are needed before biomarkers can legitimately guide treatment selection146. Candidate fluid and imaging markers - serum BDNF, synaptic vesicle glycoprotein 2A as an in vivo index of synaptic density, and network connectivity signatures - are promising but not yet standardised for cost, reproducibility or clinical decision thresholds147,148,149.

Methodological limitations

Six limitations recur across the literature and constrain translation (Table 6): protocol heterogeneity that precludes meaningful pooling; small samples with correspondingly low power; short follow-up that leaves durability and the need for maintenance dosing unresolved; population specificity, since findings in young healthy volunteers, older adults and clinical cohorts do not transfer freely; reliance on narrow outcome sets; and difficulty disentangling causation from confounding in observational cohort studies of lifestyle and reserve125. The preclinical-clinical gap is compounded by over-reliance on a small number of animal models with limited construct validity, prompting interest in computational and in silico alternatives150. Publication and reporting bias are additionally likely to be substantial in a field where positive neuromodulation and cognitive-training results attract disproportionate attention, and the absence of universal prospective registration for device and behavioural trials makes the magnitude of this bias difficult to estimate. Effect sizes reported in small early trials frequently fail to replicate at scale, so forward-looking reviews should weight replication and multi-centre confirmation more heavily than mechanistic elegance125.

Table 6. Methodological limitations and proposed remedies

Limitation	Consequence	Proposed remedy
Protocol heterogeneity	Pooling and meta-analysis unreliable	Consensus reporting and parameter standards
Small samples	Low power; inflated effect estimates	Multi-centre consortia; prospective registration
Short follow-up	Durability and maintenance needs unknown	Minimum 12-month outcomes; maintenance-dose arms
Population specificity	Poor transfer across age and diagnosis	Stratified enrolment; explicit generalisability limits
Narrow outcome sets	Incomplete picture of plastic change	Multimodal outcomes across biological and behavioural levels
Confounding in cohort studies	Causal overclaiming for lifestyle factors	Longitudinal designs; triangulation methods

Ethical and societal considerations

Four issues require concurrent attention. First, equity: advanced imaging, devices and personalised protocols are costly, and without deliberate policy intervention will widen rather than narrow outcome disparities. Second, neural data privacy: plasticity research increasingly aggregates imaging, genetic and behavioural data of unusual intimacy, requiring encryption, de-identification, explicit governance and clear limits on secondary and commercial use151,152. Third,

autonomy and informed consent: the novelty and complexity of neurotechnology strain conventional single-point consent, favouring staged, iterative models with independent ethical oversight153. Fourth, the therapy-enhancement boundary: interventions that restore function attract broad support, whereas the same tools deployed to augment memory or attention in healthy individuals raise questions of fairness, coercion in educational, occupational and military settings, and social stratification154. These require anticipatory rather than reactive governance.

Future directions

Four priorities follow from this synthesis. Standardisation of reporting, specifying stimulation and training parameters, timing relative to injury, outcome domains and minimum follow-up, would convert a fragmented literature into a poolable one. Stratification should be tested prospectively, with trials evaluating biomarker- and genotype-based responder prediction rather than treating heterogeneous populations as uniform. Combination and timing deserve priority, because plasticity mechanisms interact across levels and single-modality interventions are unlikely to be optimal; the most promising designs pair a permissive intervention with a behaviourally specific one, precisely timed, the paired-stimulation paradigm being the current proof of principle. Longitudinal scale is required, since only multi-centre cohorts with years of follow-up can establish whether induced plasticity is durable and whether early intervention alters trajectories of decline. Two cross-cutting requirements underpin all four: interdisciplinary integration spanning cellular neuroscience, pharmaceutical sciences, rehabilitation medicine, engineering, data science and bioethics; and cost-conscious design built in from the outset, since an evidence base assembled exclusively around high-cost technologies will produce recommendations that most health systems cannot implement.

CONCLUSION

Neuroplasticity is a lifelong, mechanistically tractable and clinically relevant property of the nervous system, resting on interdependent synaptic, structural, neurogenic and network-level processes, supported by glial, vascular and matrix environments, and modulated across the lifespan by age, hormones, experience and behaviour. Its most important clinical feature, however, is its neutrality: it constructs skills and recoveries with the same machinery that constructs chronic pain, addiction and compulsive behaviour. Interventions capable of steering this process now span task-specific rehabilitation, exercise and lifestyle optimisation, structured psychological techniques including clinical hypnosis, paired and non-invasive neuromodulation, plasticity-promoting pharmacology, and emerging brain-computer and artificial-intelligence-guided technologies, but they differ widely in the maturity of their supporting evidence. Progress is currently limited less by mechanistic ignorance than by methodological heterogeneity, biomarker non-equivalence, short follow-up and unresolved ethical questions concerning access, neural data privacy and the therapy-enhancement boundary. The decisive question for the coming decade is therefore not whether plasticity can be induced, which is largely settled, but whether it can be reliably, safely, equitably and durably steered toward outcomes that patients value.

ABBREVIATIONS:

AI: artificial intelligence; AMPA: alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid; BCI: brain-computer interface; BDNF: brain-derived neurotrophic factor; CREB: cyclic adenosine monophosphate response element-binding protein; EEG: electroencephalography; fMRI: functional magnetic resonance imaging; LTD: long-term depression; LTP: long-term potentiation; MRI: magnetic resonance imaging; NMDA: N-methyl-D-aspartate; RCT: randomised controlled trial; rTMS: repetitive transcranial magnetic stimulation; SGZ: subgranular zone; SV2A: synaptic vesicle glycoprotein 2A; SVZ: subventricular zone; tDCS: transcranial direct current stimulation; TBI: traumatic brain injury; TMS: transcranial magnetic stimulation; TrkB: tropomyosin receptor kinase B; VNS: vagus nerve stimulation.

CONFLICT OF INTEREST:

The authors declare no conflict of interest.

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