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Hypothesis

Maladaptive Brain-state Locking as a Lifespan Framework for Neurodevelopmental, Psychiatric, and Neurodegenerative Disorders: A Hypothesis

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Abstract

Neurodevelopmental, psychiatric, and neurodegenerative disorders are traditionally studied as distinct disease categories, yet they show overlapping disturbances in systems that regulate neural function and resilience. This article proposes maladaptive brain-state locking (MBSL) as a lifespan framework for examining whether otherwise distinct disorders may converge, in some contexts, on impaired biological-state reversibility. MBSL is defined as a failure of adaptive state-transition or recovery dynamics in which a maladaptive state becomes insufficiently reversible and the nervous system loses its normal capacity to terminate, recalibrate, or transition away from that state. Locking is therefore distinguished from persistence alone: an abnormal state maintained solely by a continuing pathological driver does not, by itself, constitute MBSL. Candidate operational features include abnormal persistence, impaired transition toward an adaptive state, delayed or incomplete recovery after perturbation reduction or removal, and history-dependent loss of flexibility. Lifespan timing, regional context, disease stage, severity, duration, and resilience are proposed to modify phenotypic consequences rather than assign disorder classes exclusively to specific age periods. Existing evidence is compatible with components of the hypothesis, but direct demonstration of MBSL will require longitudinal or perturbational evidence of impaired recovery or state-transition dynamics. Major limitations include etiological and pathological heterogeneity, nonspecific biomarkers, unresolved causality, and challenges in operationalizing multiscale state dynamics. If validated, the framework could support research focused on measurable reversibility, longitudinal monitoring, and interventions designed to restore adaptive state regulation rather than symptom improvement alone.

Introduction

Neurodevelopmental, psychiatric, and neurodegenerative disorders are commonly separated by age of onset, symptom profile, clinical specialty, and diagnostic framework. Neurodevelopmental disorders are usually linked to altered brain maturation, psychiatric disorders to disturbances in mood, cognition, perception, stress regulation, and behavior, and neurodegenerative disorders to progressive neural dysfunction and declining resilience.[1-3]

Despite these distinctions, these disorder groups show overlapping disturbances across several biological systems, including synaptic regulation, glial function, neuroimmune signaling, metabolic resilience, plasticity, repair, and circuit stability.[4,5] However, identifying shared mechanisms is not sufficient. It does not explain why some biological disturbances remain transient and recoverable, whereas others become persistent or self-reinforcing.

The central gap is therefore not only mechanistic overlap, but impaired state reversibility. The brain normally moves through changing biological states in response to development, learning, stress, injury, inflammation, adaptation, and aging.[2,6-10] These states can be beneficial when they are properly timed, regulated, and reversible. They become pathological when adaptive programs are stabilized in maladaptive forms that resist return to regulatory baselines.

This article introduces maladaptive brain-state locking (MBSL) as a lifespan hypothesis for understanding how distinct brain disorders may arise from failures in biological state regulation. In

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this framework, disease expression is shaped by the timing, duration, regional context, severity, and reversibility of locked brain states. Developmental timing is proposed to modify the consequences of MBSL rather than to assign specific disorder classes exclusively to particular age periods. Locking during early developmental windows may disproportionately affect circuit formation and maturation; during adolescence or adulthood, it may alter systems supporting emotion, cognition, perception, and stress regulation; and in later life, declining resilience and repair capacity may increase the consequences of persistent state dysregulation. These associations are illustrative rather than exclusive, because neurodevelopmental conditions persist across the lifespan, psychiatric disorders can emerge across multiple developmental periods, and neurodegenerative processes may begin years or decades before their clinical presentation. The hypothesis therefore shifts attention from the presence or persistence of shared biological abnormalities alone to the dynamic question of whether the brain has lost the capacity to transition efficiently away from a maladaptive state. In this framework, persistence is not synonymous with locking: a biological abnormality may remain present because its initiating driver persists, whereas MBSL specifically refers to impaired capacity for adaptive state transition, recovery, or recalibration. Accordingly, the objective of this article is to propose and critically evaluate MBSL as a testable lifespan hypothesis for understanding how impaired biological-state reversibility may contribute to divergent neurodevelopmental, psychiatric, and neurodegenerative phenotypes.

Hypothesis

MBSL is defined here as a failure of adaptive state-transition or recovery dynamics in which a maladaptive brain state becomes insufficiently reversible and the nervous system loses its normal capacity to efficiently terminate, recalibrate, or transition away from that state. The concept therefore extends beyond persistence or chronicity alone. Persistence describes how long an abnormal state remains present, whereas locking refers to impaired capacity for transition or recovery from that state. A persistent state maintained in proportion to an ongoing pathological driver is therefore not, by itself, evidence of MBSL. Likewise, a static biomarker abnormality, fixed structural lesion, progressive pathology, or persistent clinical symptom does not constitute locking unless accompanied by evidence of impaired biological state-transition or recovery dynamics. Normal brain-state transitions support plasticity, defense, repair, and functional remodeling; in disease, adaptive or compensatory programs may instead become mistimed, excessive, prolonged, or insufficiently reversible.

MBSL may overlap phenomenologically with concepts such as attractor-like dynamics, impaired homeostatic regulation, altered state transitions, and reduced network flexibility, but it is proposed here as a cross-scale framework centered specifically on maladaptive loss of state reversibility rather than on any single dynamical, homeostatic, or network-level mechanism.

Throughout this article, "maladaptive state" refers to a biologically dysregulated state that may remain reversible, whereas "locked state" or "MBSL" is reserved for a maladaptive state that meets the proposed criteria for impaired state-transition or recovery dynamics.

Operationally, MBSL should be identified through abnormalities in state-transition or recovery dynamics rather than through persistence alone. Candidate signatures include prolonged or abnormal dwell time within a maladaptive state, reduced probability of transition toward an adaptive state, delayed or incomplete recovery after reduction or removal of the initiating perturbation, hysteresis in which recovery depends on the system's prior trajectory, persistence that is disproportionate to the remaining pathological driver, and reduced flexibility across repeated perturbation–recovery cycles. By the same logic, evidence of successful "unlocking" should require measurable restoration of at least one predefined state-dynamic property that was abnormal before intervention, such as normalization of dwell time, increased transition probability toward an adaptive state, faster or more complete recovery, reduced hysteresis, or restored state flexibility. Symptomatic improvement alone would not be sufficient to establish that a locked biological state has been reversed.

Conversely, an MBSL interpretation would be weakened if an abnormal state resolves with expected kinetics once the initiating perturbation is reduced or removed, if transition probabilities and recovery dynamics remain comparable to an appropriate reference state, or if persistence can be adequately explained by continued exposure to the pathological driver. Similarly, cross-sectional or static biomarker abnormalities without evidence of impaired reversibility, abnormal state persistence, or altered transition dynamics should not be considered sufficient evidence of locking. These criteria make the hypothesis falsifiable by requiring evidence not merely that an abnormal state exists, but that the capacity to exit or recover from that state is measurably impaired.

A schematic comparison of adaptive recovery and maladaptive state locking is shown in Figure 1.

Within this framework, "brain state" does not refer to a single molecular, cellular, or network variable. Rather, it denotes an integrated, time-dependent configuration of interacting biological processes across multiple levels of organization. At the molecular level, relevant states may involve signaling, transcriptional, metabolic, inflammatory, and stress-response programs; at the cellular level, they may involve neuronal, astrocytic, microglial, and other cell-state responses; at the local tissue and circuit levels, they may be expressed through synaptic balance, excitability, plasticity, repair, and regional cellular interactions; and at the organ or whole-brain network level, they may involve connectivity, oscillatory dynamics, network stability, and state-transition flexibility. Clinical and behavioral manifestations represent the human functional expression of these interacting biological states rather than a separate biological scale equivalent to the molecular or cellular levels. These levels are not assumed to form a rigid unidirectional cascade; instead, they can interact bidirectionally through feedback, such that circuit activity can influence cellular state regulation and cellular responses can in turn modify circuit activity.[11-13] MBSL therefore refers to impaired reversibility within this multiscale state-regulatory configuration, rather than persistence of any isolated molecular signal, cell state, biomarker, or network abnormality. The central hypothesis is therefore not that neurodevelopmental, psychiatric, and neurodegenerative disorders are biologically equivalent, but that otherwise distinct etiologies and pathological substrates may share

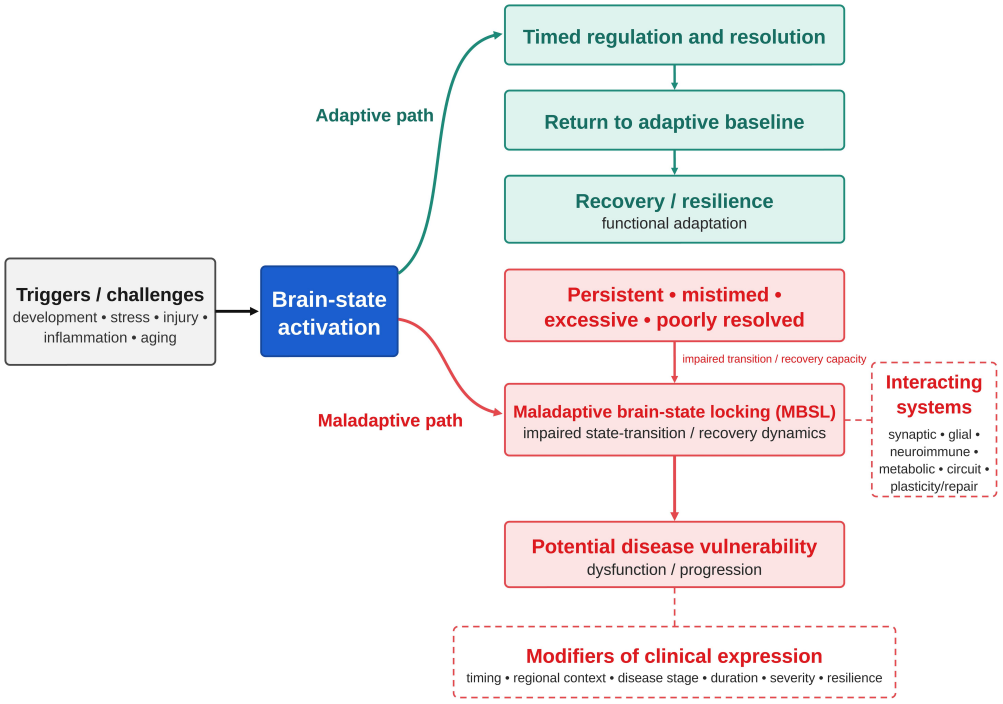


Fig. 1. The maladaptive brain-state locking model. This hypothesis-generating conceptual model illustrates the proposed divergence between adaptive recovery and maladaptive brain-state locking (MBSL) following brain-state activation. Adaptive responses may undergo appropriately timed regulation and resolution, return toward an adaptive baseline, and support recovery and resilience. In contrast, persistent, mistimed, excessive, or poorly resolved responses may become associated with impaired state-transition or recovery capacity and, in some contexts, progress toward MBSL. MBSL is defined here by impaired state-transition or recovery dynamics rather than persistence alone. Interacting synaptic, glial, neuroimmune, metabolic, circuit, and plasticity/repair systems may contribute to or reinforce these dynamics. Potential disease vulnerability and clinical expression are proposed to vary according to timing, regional context, disease stage, duration, severity, and resilience. Conceptual schematic diagram; no original experimental data.

vulnerability to failures of state regulation while differing in clinical expression according to timing, regional context, severity, duration, and reversibility.[14-16]

Candidate biological abnormalities relevant to the MBSL hypothesis may include persistent synaptic imbalance, altered excitatory-inhibitory regulation, prolonged glial reactivity, unresolved neuroimmune activation, metabolic stress, impaired plasticity, circuit instability, and maladaptive repair.[17-19] Synaptic remodeling, glial activation, inflammatory signaling, metabolic adaptation, and repair responses are protective when properly timed and resolved. Dysfunction may emerge when these programs fail to resolve, become self-reinforcing, or occur during vulnerable developmental or aging-related windows. These mechanistic layers and their proposed progression from adaptive regulation through potentially reversible maladaptation to candidate evidence of impaired state-transition or recovery dynamics are summarized in Table 1.[18-29]

Within the MBSL framework, lifespan timing is proposed as a modifier of phenotypic expression rather than as a categorical assignment of disorder type. Different developmental periods are characterized by distinct patterns of brain maturation, circuit organization, plasticity, and psychosocial functioning,[30-36] whereas aging is accompanied by cellular, immune, stress-response, and network changes that can alter resilience and recovery.[29,37-39] A comparable biological perturbation may therefore have different consequences depending on when it occurs. Experimental evidence supports this timing dependence: in mice, exposure to the same maternal immune stimulus during early versus late gestation produces distinct longitudinal neuroanatomical, transcriptional, and behavioral trajectories, demonstrating that the developmental window can modify the consequences of a common perturbation.[40] Age can similarly alter recovery from a comparable challenge; following experimental stroke, young and aged mice show markedly different pro-repair cellular responses, with aging associated with impaired angiogenic, oligodendrogenic, and myeloid-cell programs and poorer recovery.[41]

Regional and disease-stage contexts provide additional modifiers. Multiregion single-cell analysis of Alzheimer's disease has identified region- and cell-type-specific patterns of vulnerability and response despite shared underlying pathology, demonstrating that the biological consequences of disease processes depend strongly on anatomical context.[18] Disease stage can likewise change the functional expression of related pathology: in cognitively unimpaired older adults, amyloid-β deposition was associated with accelerated cortical neurophysiological activity, whereas the presence of medial temporal tau together with amyloid-β was associated with a shift toward slower activity and subsequent cognitive decline.[42] These observations do not establish MBSL itself,

Table 1. Mechanistic layers and candidate dynamic features relevant to maladaptive brain-state locking

Mechanistic layer	Adaptive state	Maladaptive but potentially reversible state	Candidate evidence of locking	Relevance across lifespan disorders	Example measurable features
Synaptic regulation	Synaptic remodeling supports learning, maturation, pruning, and experience-dependent plasticity	Synaptic balance becomes mistimed, excessive, deficient, or persistently altered but retains capacity for recalibration when the relevant perturbation is reduced or appropriate intervention is applied	Abnormally prolonged synaptic-state dwell time, reduced transition toward an adaptive synaptic configuration, or delayed or incomplete recalibration after reduction or removal of the initiating perturbation	May contribute to altered circuit maturation in neurodevelopmental disorders, cognitive and emotional dysregulation in psychiatric disorders, and synaptic vulnerability in neurodegenerative disorders	Excitatory–inhibitory balance, synaptic density, pruning markers, dendritic spine changes, synaptic protein expression[19,20]
Glial regulation	Microglia and astrocytes support synaptic refinement, metabolic coupling, tissue surveillance, and repair	Glial reactivity becomes prolonged or poorly resolved and may reinforce inflammatory or dysfunctional circuit states while remaining responsive to changes in biological context or intervention	Persistent glial-state abnormalities after attenuation of the initiating driver, delayed return toward homeostatic glial states, reduced transition probability between reactive and resolving states, or impaired recovery across repeated perturbation–resolution cycles	Is implicated in developmental pruning, stress-related circuit dysfunction, and aging-related neuroinflammatory vulnerability	Microglial activation states, astrocyte reactivity markers, complement signaling, cytokine profiles, glial transcriptomic signatures[21,22]
Neuroimmune signaling	Immune signaling supports defense, repair, synaptic homeostasis, and responses to injury	Inflammatory signaling becomes prolonged, mistimed, or self-reinforcing but may still resolve when the initiating perturbation is reduced or regulatory mechanisms recover	Failure of inflammatory resolution despite attenuation of the initiating driver, abnormal persistence of neuroimmune states, delayed recovery kinetics, or hysteresis across repeated inflammatory challenge–recovery cycles	Could influence neurodevelopmental vulnerability, psychiatric symptom fluctuation, and neurodegenerative progression	Cytokines, chemokines, complement proteins, immune-cell signatures, and CSF or blood inflammatory biomarkers[22,23]
Metabolic and mitochondrial regulation	Energy production, redox balance, and mitochondrial adaptation support neural resilience and recovery	Metabolic stress, oxidative burden, or mitochondrial dysfunction reduces resilience but may improve when energetic demand, inflammation, or other	Persistently impaired metabolic recovery, reduced metabolic flexibility, delayed restoration of energetic homeostasis after perturbation, or repeated failure to return toward an adaptive metabolic state	Is relevant to synaptic maturation, stress sensitivity, cognitive function, and aging-related loss of resilience	Mitochondrial function, oxidative-stress markers, metabolic profiling, lactate/glucose dynamics, cellular stress pathways[24,25]

Table 1. Mechanistic layers and candidate dynamic features relevant to maladaptive brain-state locking (*continued*)

Mechanistic layer	Adaptive state	Maladaptive but potentially reversible state	Candidate evidence of locking	Relevance across lifespan disorders	Example measurable features
		perturbations are corrected			
Circuit and network regulation	Circuits flexibly shift among states required for perception, cognition, emotion, sleep, and behavior	Network states become unstable, rigid, hyperactive, hypoactive, or poorly adaptable but retain measurable capacity for spontaneous or intervention-associated normalization	Abnormally prolonged network-state dwell time, reduced transition probability toward adaptive network configurations, impaired recovery after perturbation, reduced state flexibility, or hysteretic network dynamics	May contribute to sensory and cognitive alterations in development, mood and perception disturbances in psychiatric disorders, and network failure in neurodegeneration	Functional connectivity, EEG/MEG patterns, oscillatory activity, network excitability, neuroimaging-based state transitions[18,26]
Plasticity and repair*	Adaptive plasticity and repair restore function after stress, injury, inflammation, or developmental perturbation	Repair responses become incomplete, excessive, or chronically activated but retain some capacity for restoration or redirection	Persistent failure of repair or recalibration after the initiating challenge has subsided, delayed or incomplete functional recovery, or reduced responsiveness across repeated repair–recovery cycles	Shapes whether disrupted states remain reversible or progress toward persistent dysfunction	Plasticity markers, recovery trajectories, repair-associated transcriptional states, and responses to rehabilitation or neuromodulation[27,28]
Lifespan timing*	State transitions occur within age-appropriate developmental, adult, or aging-related contexts	A comparable disturbance produces context-dependent dysfunction whose expression varies with developmental timing, regional context, resilience, and disease stage	Timing-dependent differences in recovery kinetics, reversibility, transition probability, or state flexibility after comparable perturbations, rather than age-associated abnormality alone	Timing modifies the phenotypic consequences of state dysregulation rather than defining diagnostic category. Developmental-period disturbances may preferentially affect circuit formation and maturation, whereas later-life disturbances may interact with declining resilience and repair; these associations are illustrative and may overlap across the lifespan	Longitudinal biomarkers, disease-stage signatures, age-dependent omics profiles, and developmental or aging-related trajectory models[26,29]

Maladaptive abnormalities listed in this table should not be interpreted as evidence of MBSL by themselves. Candidate evidence of locking requires measurable impairment of state-transition or recovery dynamics interpreted within the relevant biological and temporal context. *Plasticity/repair and lifespan timing are cross-cutting dimensions rather than discrete biological systems. CSF, cerebrospinal fluid; EEG, electroencephalography; MEG, magnetoencephalography; MBSL, maladaptive brain-state locking.

but they directly support the narrower proposition that the consequences of biological disturbance are conditional on developmental timing, age-related resilience, regional context, and disease stage. Neurodevelopmental, psychiatric, and neurodegenerative manifestations should therefore be regarded as overlapping illustrative outcomes within the lifespan framework, not mutually exclusive age-defined categories. The lifespan timing logic of the hypothesis is summarized in Figure 2.

Unlike conventional shared-mechanism models, which identify biological features that appear across disorders, MBSL asks why states persist or resist recovery and how developmental timing, regional context, disease stage, and other modifiers alter their biological and clinical consequences.

Evaluation of the hypothesis

Existing evidence does not yet establish MBSL as a shared causal mechanism across neurodevelopmental, psychiatric, and neurodegenerative disorders. Rather, current findings identify biological abnormalities and dynamic disturbances that are compatible to varying degrees with components of the hypothesis and provide a basis for testing whether impaired state reversibility occurs in specific disease contexts.

For evaluation purposes, these processes are considered as interacting levels rather than as independent or equivalent forms of evidence. Molecular signaling, metabolic, inflammatory, and stress-response programs can shape neuronal and glial states; changes in those cellular states can influence synaptic balance, plasticity, excitability, and tissue repair; and these local effects can contribute to regional circuit and whole-brain network dynamics that are expressed clinically through changes in cognition, emotion, perception, behavior, and neurological function. Importantly, this sequence is conceptual rather than strictly linear: network activity, behavior, environmental exposure, and physiological state can also feed back onto cellular, metabolic, and immune regulation. The evaluation below therefore considers MBSL across linked molecular, cellular, tissue/circuit, network, and clinical levels while asking whether disturbances at any level exhibit the defining feature of impaired reversibility or state-transition failure.

The evidence can therefore be considered at three distinct levels. First, shared disease-associated features such as synaptic dysfunction, glial reactivity, neuroimmune activation, metabolic disturbance, or network abnormalities demonstrate biological overlap across disorders but do not by themselves establish a shared causal mechanism or MBSL. Second, findings of prolonged activation, failed resolution, reduced resilience, impaired plasticity, or altered state dynamics are more directly compatible with impaired state regulation, but still do not demonstrate locking unless reduced reversibility is shown. Third, direct evidence for MBSL would require longitudinal or perturbational demonstration of abnormal recovery or transition dynamics, such as delayed or incomplete recovery, reduced transition probability, abnormal dwell time, hysteresis, persistence after attenuation of the initiating driver, or restoration of predefined state dynamics after intervention. This hierarchy distinguishes shared biological features from shared causal mechanisms and from the more specific dynamic state-transition failure proposed by MBSL.

Synaptic and circuit-level findings are central to this framework. Excitatory-inhibitory imbalance, altered synaptic remodeling, disrupted pruning, impaired plasticity, and network instability have been implicated across neurodevelopmental, psychiatric, and neurodegenerative disorders.[43-45] During normal development and learning, synaptic remodeling and circuit adaptation refine neural function. When mistimed, excessive, deficient, or persistent, these processes may contribute to long-term instability in sensory processing, cognition, mood regulation, and neural resilience.[44,46] These findings establish disease-associated abnormalities in synaptic and circuit regulation and are compatible with impaired recalibration in some contexts; however, they do not by themselves demonstrate MBSL without longitudinal or perturbational evidence that recovery or state-transition dynamics are impaired.

Glial and neuroimmune findings provide an additional set of disease-associated observations relevant to the hypothesis. Microglia, astrocytes, complement signaling, cytokines, and inflammatory mediators shape synaptic pruning, tissue surveillance, metabolic support, injury responses, and repair.[23,47,48] These functions are essential during development and remain important throughout adulthood and aging. Prolonged glial reactivity or unresolved neuroimmune activation may sustain inflammatory tone, alter synaptic function, disrupt metabolic support, or impair circuit homeostasis.[28,49-52] Such persistence is compatible with impaired state regulation, particularly when protective responses fail to resolve within an appropriate temporal window, but persistent glial or inflammatory activity alone does not establish a locked state or a common causal mechanism across disorders.

Metabolic and mitochondrial findings represent another biological domain potentially relevant to impaired state regulation. Neural function depends on energy regulation, mitochondrial performance, redox balance, and cellular stress adaptation.[53,54] Energy imbalance, oxidative stress, mitochondrial dysfunction, and impaired metabolic flexibility can reduce the brain's capacity to recover from inflammatory, excitotoxic, developmental, or aging-related challenges.[54,55] These observations are compatible with reduced biological resilience and recovery capacity, particularly in neurodegenerative contexts, and may also influence developmental and psychiatric trajectories through effects on synaptic maturation, stress sensitivity, and circuit function.[43,53] However, metabolic dysfunction itself should not be interpreted as evidence of MBSL unless accompanied by demonstrable abnormalities in reversibility or state-transition dynamics.

Plasticity and repair mechanisms help determine whether a disrupted state remains reversible. Adaptive recovery requires synaptic modification, glial regulation, metabolic restoration, and circuit recalibration after stress, injury, or developmental perturbation.[27,28] When repair responses are incomplete, excessive, or chronically activated, they may contribute to persistent dysfunction or failed recalibration; however, direct evidence of MBSL would additionally require demonstration that recovery or transition away from that state is measurably impaired.

Taken together, the current literature establishes substantial biological overlap across disorder categories and identifies several phenomena compatible with impaired state regulation, including persistence, failed resolution, reduced resilience, and altered recovery. These observations provide a rationale for testing MBSL but should not be interpreted as direct evidence of a shared state-

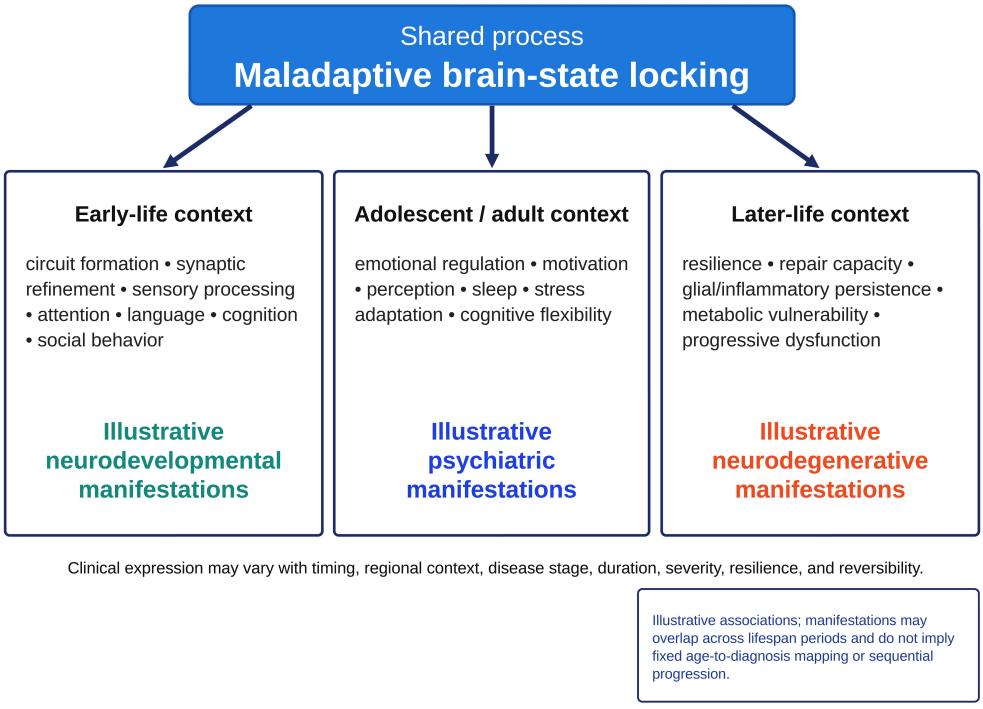


Fig. 2. Lifespan context of maladaptive brain-state locking. This hypothesis-generating conceptual model illustrates how lifespan context may modify the phenotypic consequences of MBSL. Early-life, adolescent/adult, and later-life contexts are shown as illustrative examples rather than exclusive age-to-diagnosis mappings. Early-life MBSL may disproportionately affect circuit formation, synaptic refinement, and other developmental processes; adolescent/adult MBSL may alter systems involved in emotional regulation, motivation, perception, sleep, stress adaptation, and cognitive flexibility; and later-life MBSL may interact with declining resilience, repair capacity, glial or inflammatory persistence, metabolic vulnerability, and progressive dysfunction. Neurodevelopmental, psychiatric, and neurodegenerative manifestations are therefore presented as illustrative and potentially overlapping outcomes rather than mutually exclusive categories. Clinical expression is proposed to vary with timing, regional context, disease stage, duration, severity, resilience, and reversibility. The model should not be interpreted as an empirically established sequential lifespan disease trajectory or as implying fixed progression from one disorder category to another. Conceptual schematic diagram; no original experimental data. MBSL, maladaptive brain-state locking.

locking mechanism. Direct support will require longitudinal or perturbational studies showing predefined abnormalities of reversibility or transition dynamics and determining whether those abnormalities can be modified experimentally or therapeutically.

Future directions

Future research should test MBSL as a measurable, dynamic, and potentially reversible biological process. This requires determining whether specific brain states become persistent before, during, or after clinical worsening.

Key operational predictions, falsification criteria, and experimental tests of the MBSL hypothesis are summarized in Table 2.[3,14,56-70]

Longitudinal studies will be essential. Rather than measuring disease at a single endpoint, researchers should track how biological state signatures change over time and whether specific patterns become stabilized before functional decline, symptom worsening, or treatment resistance.[35,71-73] Such studies could help distinguish transient adaptive responses and persistent but still reversible maladaptive states from states showing measurable impairment of recovery or transition dynamics.

Multimodal biomarkers will be necessary. Neuroimaging, electrophysiology, blood and cerebrospinal fluid biomarkers, single-cell and spatial omics, metabolic profiling, and digital behavioral measures could help identify candidate state-dynamic signatures relevant to MBSL across biological levels.[66,72,74,75] The goal is to define patterns of state persistence, reversibility, and transition failure that differ across disease stage and lifespan context.

Experimental models should directly test reversibility. Organoids, assembloids, animal models, and patient-derived cellular systems can be used to test whether predefined abnormalities of state-transition or recovery dynamics can be shifted toward adaptive regulation.[62,75-77] These models may help determine whether candidate abnormalities of state-transition or recovery dynamics emerge in response to genetic risk, environmental stress, injury, inflammation, aging-related vulnerability, or interactions among these factors.

Artificial intelligence-based modeling may help integrate complex data across biological scales. Multimodal models could identify state-transition patterns that are difficult to detect through isolated measurements or cross-sectional analysis.[66,67,78,79] These models could also help predict loss of reversibility and identify

Table 2. Operational predictions, falsification criteria, and future tests of maladaptive brain-state locking

Prediction	Experimental or clinical approach	Expected finding if prediction is supported	Key limitation	Translational implication
Candidate MBSL-associated dynamic abnormalities precede or accompany clinical worsening	Longitudinal cohorts with repeated neuroimaging, electrophysiology, fluid biomarkers, digital behavioral measures, and clinical assessments	Predefined abnormalities of recovery or transition dynamics emerge before or alongside functional decline, symptom worsening, treatment resistance, or progression	Longitudinal studies are expensive, slow, and vulnerable to cohort heterogeneity, missing data, and uncertainty regarding causal direction	Earlier identification of transition failure or declining reversibility before more persistent dysfunction develops[56,57]
MBSL is characterized by abnormal temporal dynamics rather than by a static abnormality alone	Repeated multimodal measurements across disease stages, perturbation–recovery intervals, and treatment windows	Candidate state signatures show abnormal dwell time, delayed recovery, reduced transition probability, hysteresis, or progressive loss of reversibility over time	Static biomarkers or cross-sectional differences may be misinterpreted as evidence of locking without temporal validation	More precise disease staging and longitudinal monitoring of reversibility[58-60]
MBSL should not be inferred when persistence is fully explained by an ongoing driver and normal recovery occurs after that driver is removed	Controlled perturbation–withdrawal studies or natural experiments measuring recovery kinetics and state transitions before, during, and after attenuation of the initiating perturbation	States interpreted as MBSL show delayed, incomplete, or history-dependent recovery after driver attenuation; expected recovery after driver removal would argue against a locking interpretation	The initiating driver may be incompletely measurable or impossible to remove cleanly in human disease	Prevents chronicity or biomarker persistence from being misclassified as MBSL and provides an explicit falsification criterion
Distinct disorder groups may show partially overlapping state-regulatory abnormalities without sharing an identical causal mechanism	Cross-disorder comparison of neurodevelopmental, psychiatric, and neurodegenerative cohorts using harmonized longitudinal biomarkers and state-dynamic measures	Some abnormalities of recovery, flexibility, or transition dynamics overlap across diagnoses, while their timing, magnitude, regional distribution, and causal role differ	Shared biomarkers may be nonspecific and may reflect downstream consequences rather than a shared mechanism	A biology-based complement to diagnostic labels without collapsing etiologically distinct disorders[3,14,61]
Predefined MBSL-associated dynamic abnormalities can be modified under targeted perturbation or intervention	Organoid, assembloid, animal, and patient-derived cellular models exposed to defined genetic, inflammatory, metabolic, environmental, or aging-related perturbations, followed by perturbation withdrawal or targeted intervention	At least one predefined abnormal dynamic feature—such as dwell time, recovery kinetics, transition probability, hysteresis, or state flexibility—moves measurably toward an adaptive range after intervention	Model systems may not reproduce the multiscale and lifespan complexity of human disease, and improvement in one state feature may not indicate system-wide recovery	Experimental development of state-redirection strategies and objective measures of reversibility[62]
Greater impairment of reversibility is associated with treatment resistance or progression	Clinical studies comparing responders, nonresponders, remitting cases, and progressive cases using repeated biological, functional, and clinical measurements	Treatment-resistant or progressive cases show longer maladaptive-state dwell times, slower recovery, lower transition probability toward adaptive states, or reduced flexibility compared with reversible or remitting cases	Treatment response is influenced by adherence, comorbidity, environment, treatment exposure, socioeconomic factors, and baseline	Improved stratification by dynamic reversibility rather than symptom severity alone[63-65]

Table 2. Operational predictions, falsification criteria, and future tests of maladaptive brain-state locking (*continued*)

Prediction	Experimental or clinical approach	Expected finding if prediction is supported	Key limitation	Translational implication
			disease severity	
Computational models can identify candidate state-transition and reversibility patterns not evident from isolated measurements	Multimodal machine-learning models integrating imaging, omics, electrophysiology, biomarkers, and behavioral data	Models reproducibly identify transition patterns, recovery trajectories, reversibility windows, or progression-associated dynamic signatures that generalize across independent datasets	Risk of overfitting, poor generalizability, data leakage, limited interpretability, and dependence on heterogeneous training data	Prediction of intervention windows and individualized longitudinal monitoring[66,67]
Lifespan timing and biological context modify the consequences of comparable state-regulatory disturbances	Lifespan studies comparing developmental, adult, and aging-related trajectories, ideally using comparable perturbations or harmonized dynamic measures across age groups	Comparable disturbances are associated with different recovery trajectories, regional effects, or phenotypic consequences according to developmental timing, age-related resilience, regional context, and disease stage	Age, diagnosis, medication exposure, comorbidity, environmental history, and cohort effects may confound interpretation	Context-sensitive risk stratification and timing of intervention rather than fixed age-to-diagnosis mapping[68]
Successful biological state unlocking restores a predefined abnormal state-dynamic feature rather than clinical symptoms alone	Prospective intervention studies measuring biological state dynamics before, during, and after treatment, rehabilitation, neuromodulation, or behavioral intervention, with the relevant dynamic endpoint predefined before analysis	Clinical improvement is accompanied by measurable normalization of at least one previously abnormal feature, such as shorter maladaptive-state dwell time, increased transition probability toward an adaptive state, faster or more complete recovery, reduced hysteresis, or restored state flexibility	Clinical symptoms and biological state dynamics may improve independently or on different timescales, complicating causal interpretation	Development of outcome measures that distinguish symptomatic response from biological state unlocking and track restoration of adaptive regulation[69,70]

MBSL, maladaptive brain-state locking.

windows in which intervention may be most effective.

Implications for intervention timing and modality

Within the MBSL framework, intervention timing would depend on the degree to which a maladaptive state remains reversible rather than on diagnosis alone. During an early or still-reversible phase, the primary goal would be to reduce or remove the initiating perturbation where possible and support normal adaptive resolution before state-transition dynamics become persistently impaired. During emerging stabilization, intervention would aim to prevent further consolidation by targeting the biological processes sustaining abnormal state persistence. Once a locked state is established but remains partially reversible, treatment would need to restore the specific impaired dynamic property, such as recovery capacity, transition probability, or state flexibility. More strongly stabilized or multisystem states may require sequential or combination approaches because dysregulation at molecular, cellular, circuit, and network levels may reinforce one another. These stages are conceptual rather than validated clinical categories and should be tested prospectively rather than used as current treatment classifications.

Intervention modality would likewise depend on the dominant biological processes contributing to the impaired state dynamics in a particular context. Candidate approaches could include inflammatory-resolution strategies when unresolved neuroimmune activation is prominent, glial-state modulation when persistent astrocytic or microglial responses contribute to dysregulation, metabolic support when impaired energetic or mitochondrial recovery constrains resilience, synaptic rebalancing when excitatory-inhibitory or plasticity abnormalities predominate, neuromodulation when maladaptive circuit or network dynamics are measurable, and behavioral or environmental interventions when experience-dependent regulation remains modifiable.[80-83] These modalities should not be interpreted as MBSL-specific therapies; rather, the framework predicts that their relevance would depend on whether they measurably restore the predefined state-dynamic abnormality associated with a given case or model.

A therapeutic test of MBSL should therefore distinguish symptomatic improvement from biological state unlocking. The rel-

evant state-dynamic abnormality should be defined before intervention and measured longitudinally alongside clinical outcomes. Evidence of unlocking would require restoration of the impaired dynamic property, such as shorter maladaptive-state dwell time, increased transition probability toward an adaptive state, improved recovery kinetics, reduced hysteresis, or greater state flexibility, rather than symptom improvement alone. Clinical improvement without corresponding normalization of the predefined dynamic abnormality would indicate therapeutic benefit but would not, by itself, demonstrate reversal of MBSL. Conversely, concordant improvement in clinical function and state dynamics would provide stronger evidence that an intervention has modified the proposed locking process. Importantly, no biomarker, therapeutic target, intervention window, or treatment strategy has yet been validated specifically for MBSL; these implications therefore represent hypotheses for future experimental and clinical testing rather than recommendations for current clinical practice.

Together, these approaches provide a roadmap for testing the state-locking hypothesis across experimental, computational, and clinical settings (Table 2).

Limitations

A principal limitation of the MBSL framework is the substantial etiological and pathological heterogeneity within and across neurodevelopmental, psychiatric, and neurodegenerative disorders. Neurodevelopmental disorders may arise from highly penetrant genetic variants, altered developmental programs, or structural abnormalities, whereas neurodegenerative disorders can involve progressive cellular loss, protein aggregation, region-specific degeneration, and other established neuropathological changes.[84-88] Psychiatric disorders also have biological substrates, including molecular, cellular, circuit, and network abnormalities, but these do not necessarily correspond to the same degree or type of fixed macroscopic structural or degenerative pathology. MBSL therefore does not imply biological equivalence among these disorder groups or propose that they arise from a single shared lesion or causal mechanism. The proposed commonality is narrower: otherwise distinct etiologies and pathological substrates may, in some contexts, converge on impaired state regulation or reduced reversibility. Fixed structural lesions, genetic abnormalities, proteinopathy, or neurodegeneration may initiate, constrain, or reinforce dynamic state dysregulation, but these pathologies are not themselves synonymous with MBSL unless impaired state-transition or recovery dynamics can also be demonstrated.

A second limitation is the nonspecificity of many candidate biological markers. Inflammation, synaptic dysfunction, glial activation, oxidative stress, and metabolic disturbance occur across numerous conditions and may reflect causes, consequences, compensatory responses, or amplifiers of disease rather than MBSL itself.[89,90] Their presence alone therefore cannot establish that a locked state exists. Even when similar abnormalities recur across diagnostic categories, shared or static biomarkers do not demonstrate a shared causal mechanism or impaired reversibility. MBSL must instead be evaluated through dynamic evidence showing abnormal recovery, persistence, or state-transition behavior over time.

Measurement presents a further limitation. MBSL is not represented by a single validated biomarker, pathway, lesion, or measurement platform. Its proposed operationalization requires distinguishing transient adaptive activation, persistence driven by a continuing perturbation, and genuine impairment of state-transition or recovery dynamics. This will likely require longitudinal designs, multimodal biomarkers, repeated functional measurements, and disease-stage-specific analysis. Cross-sectional studies can identify associations but generally cannot determine whether a biological state is locked, reversible, or causally involved. In addition, candidate measures may operate at different spatial and temporal scales, making harmonization across molecular, cellular, circuit, network, and clinical levels challenging.

Causality remains another major limitation. A persistent inflammatory, glial, metabolic, synaptic, or network state may contribute causally to disease progression in one context but represent a downstream consequence or compensatory response in another. In neurodevelopmental disorders, altered state regulation may influence circuit formation early in life; in psychiatric disorders, state dynamics may fluctuate with stress, sleep, hormonal state, environment, treatment, or experience[91]; and in neurodegenerative disorders, impaired state regulation may emerge after cumulative cellular injury or proteinopathic burden is already established.[59,92] Current evidence therefore does not establish MBSL as a universal upstream cause. Longitudinal and perturbational studies will be required to determine whether impaired reversibility precedes pathology, emerges as a secondary consequence, or participates in feedback loops that subsequently sustain disease.

These limitations define the current boundary of the hypothesis. MBSL should therefore be regarded as a testable framework rather than an established cross-disorder mechanism, and its validity will depend on demonstrating reproducible abnormalities of reversibility or state-transition dynamics that cannot be explained solely by persistent external drivers, fixed pathology, nonspecific biomarkers, or cross-sectional disease associations.

Conclusions

MBSL is proposed as a testable lifespan hypothesis for examining whether clinically and biologically distinct brain disorders may, in some contexts, converge on impaired state-transition or recovery dynamics. Its central concept is that persistence becomes mechanistically meaningful when the capacity to leave, recalibrate, or recover from a maladaptive state is measurably impaired. MBSL therefore does not equate chronicity with locking or imply that neurodevelopmental, psychiatric, and neurodegenerative disorders share a single pathology or causal mechanism.

Current evidence is compatible with components of this framework but does not yet establish MBSL as a general cross-disorder mechanism. Direct validation will require longitudinal or perturbational evidence demonstrating impaired reversibility or altered state-transition dynamics. If validated, MBSL could provide a complementary framework for studying disease in terms of measurable reversibility, recovery dynamics, and state-transition control alongside existing diagnostic and mechanistic approaches.

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Author contributions

MMN is the sole author of the manuscript.

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