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Perspective

Chronic Heroin Exposure and Long-Term Brain Function: A Testable Framework of Neuroprogressive Vulnerability

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Abstract

Chronic heroin exposure is associated with molecular and cellular neuroadaptations that may persist or reorganize after withdrawal. This Perspective proposes a testable framework for examining whether repeated exposure–withdrawal transitions are associated with progressively less complete recovery in cognition and everyday functioning after accounting for cumulative opioid exposure. The framework defines neuroprogressive vulnerability as susceptibility to a subsequent trajectory of worsening function or declining recovery capacity. Such trajectories are considered alongside stable impairment, improvement, and decline following discrete acquired injury. Experimental studies show that synaptic adaptations can depend on the pattern of morphine exposure and that specific heroin-associated adaptations can influence drug seeking. Human studies document brain alterations and changes during treatment or abstinence. Whether repeated heroin exposure–withdrawal transitions contribute to progressively poorer functional recovery in humans remains untested. Five complementary predictions address temporal exposure patterns, within-person recovery, pharmacological stabilization, molecular antecedents, and susceptibility to additional injury.

Keywords: heroin use disorder; molecular neuroadaptations; neuroprogression; neuroplasticity; exposure–withdrawal cycles; functional resilience; neuroinflammation; relapse; recovery; neurodegeneration

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1. Introduction

Heroin remains the most commonly used illicit opioid in Europe and accounts for a substantial share of the health burden associated with illicit drug use [1]. The affected population is also ageing. Between 2014 and 2024, both the mean age of clients entering specialist

treatment for heroin use and the proportion of older clients increased, while approximately 505,000 individuals received opioid agonist treatment in European Union Member States in 2024 [1]. These trends highlight the clinical relevance of investigating long-term brain outcomes in individuals with prolonged histories of heroin use and opioid exposure.

At the molecular and cellular levels, repeated μ-opioid receptor activation engages adaptive processes, including receptor desensitization and compensatory changes in downstream signaling, that contribute to tolerance, dependence, and withdrawal. These adaptations vary across neuronal populations and cannot be explained by a single regulatory mechanism [2]. At the circuit level, repeated exposure, withdrawal, and abstinence are associated with remodeling of reward- and relief-related networks, with neuronal and non-neuronal cellular environments influencing opioid responses [3]. Human studies further document altered prefrontal recruitment during inhibitory control [4] and widespread white matter microstructural abnormalities [5] in individuals with heroin use disorder (HUD). However, participants in these imaging investigations were receiving methadone or buprenorphine at assessment, limiting attribution of the observed differences specifically to prior heroin exposure rather than treatment or other associated factors.

Established neurobiological models provide complementary explanations for the development and maintenance of addiction. Allostatic accounts emphasize adaptations in reward and stress systems associated with the transition toward negative reinforcement [6,7]. Habit-based models describe the increasing contribution of habitual and compulsive mechanisms to drug seeking [8], whereas the impaired response inhibition and salience attribution model emphasizes altered prefrontal regulation and heightened processing of drug-related stimuli [9,10]. Evidence of prefrontal changes during abstinence and treatment further demonstrates that at least some addiction-associated brain alterations remain modifiable [11]. However, the conditions under which exposure-related neuroadaptations are followed by stable dysfunction, functional recovery, or progressively diminished recovery capacity remain insufficiently characterized. In particular, the relative contributions of cumulative exposure, its temporal organization, premorbid susceptibility, treatment, and additional injuries to long-term functional trajectories have not been adequately distinguished.

A review focused on chronic heroin use disorder found limited evidence concerning the long-term course of cognitive and neurological impairments after abstinence [12]. It called for longitudinal studies to clarify the contribution of pre-existing impairments and changes associated with heroin use.

This Perspective asks whether, in people with a history of heroin use, repeated transitions between opioid exposure and withdrawal are associated with progressively less complete recovery in cognition and everyday functioning across successive episodes after accounting for cumulative opioid exposure. We propose a framework in which molecular and cellular neuroadaptations, individual susceptibility, compensatory responses, treatment, and discrete acquired injuries may shape long-term functional outcomes. The framework distinguishes progressively poorer recovery from stable impairment, sustained improvement, and decline following a discrete injury. It identifies longitudinal observations and mechanistic studies that could support or weaken the proposed contribution of repeated exposure–withdrawal transitions.

2. Scope and Conceptual Definitions

2.1. Exposure, Vulnerability, Treatment, and Associated Injury

This Perspective focuses on molecular and cellular neuroadaptations associated with chronic heroin exposure and their potential relevance to persistent dysfunction, functional recovery, and neuroprogression. Studies of heroin exposure provide the most directly relevant evidence for the populations, models, and outcomes they examine. Experimental

studies with other opioids inform mechanistic plausibility, including whether the temporal pattern of exposure can alter neuroadaptations. Studies in broader opioid use disorder (OUD) populations provide clinical context for brain alterations and functional outcomes, with attribution to heroin depending on how exposure was characterized. Testing the heroin-specific neuroprogression hypothesis requires longitudinal evidence linking a documented history of heroin exposure and withdrawal to changes in functional recovery across successive episodes.

Interpreting brain alterations in HUD requires distinguishing exposure-related adaptations from pre-existing susceptibility, treatment-associated changes, and additional acquired injuries. Pre-existing susceptibility is illustrated by findings of impaired cognitive flexibility and inhibitory control in abstinent individuals with heroin addiction and their unaffected biological siblings relative to unrelated healthy controls [13]. Because siblings share genetic background and aspects of their early environment, these observations support a familial contribution without establishing its genetic or environmental origins. Accordingly, neurocognitive differences observed in HUD cannot be attributed exclusively to the consequences of heroin exposure. Individual susceptibility may also influence how exposure-related adaptations develop and how subsequent functional trajectories unfold, although these interactions require direct investigation.

Treatment represents another important source of variation. Participants in several human imaging studies of HUD were receiving methadone or buprenorphine at assessment [4,5], and longitudinal investigations have documented changes in brain measures during treatment [14–16]. Such findings cannot isolate the effects of prior heroin exposure from those of pharmacological treatment, abstinence, and other concurrent clinical changes. Additional acquired injury constitutes a distinct potential contributor to dysfunction. Todaro and colleagues reported lower hippocampal volume in individuals with OUD and a history of non-fatal overdose than in those without such a history [17].

However, the cross-sectional design cannot establish whether this difference resulted from overdose, preceded it, or reflected other characteristics associated with more severe substance use. Overdose-related hypoxic injury should therefore be considered a potential pathway to brain dysfunction rather than an inevitable consequence of overdose or a direct manifestation of exposure-related neuroadaptation. Within the proposed framework, exposure history, individual susceptibility, treatment, and additional injuries are considered distinct but potentially interacting influences whose independent contributions must be characterized before their combined effects can be meaningfully evaluated.

Polysubstance exposure complicates attribution of molecular, neuroimaging, and cognitive findings to heroin. Neuroimaging studies have included participants with histories of other substance use [18], and some exposure–outcome associations have been estimated across combined heroin and cocaine use disorder groups [5]. Prospective studies should document the amount, frequency, and timing of tobacco, alcohol, stimulant, and other opioid use, including whether use overlaps with heroin exposure or withdrawal. Repeated assessment would help distinguish co-exposures that precede a withdrawal episode from those that change during recovery. The analysis should specify whether the aim is to estimate a heroin-specific association or to characterize recovery under patterns of use that include multiple substances.

The literature was selected for a narrative Perspective. Studies were included to illustrate specific links in the proposed framework: how exposure patterns relate to neuroadaptation, whether molecular changes affect behavior, and what longitudinal human data show about functional change. Priority was given to heroin-specific studies with clearly described exposure conditions or assessment intervals. Studies involving other opioids or broader OUD populations were included where they addressed a relevant mechanism or provided

clinical context. During revision in November 2026, we conducted targeted searches in PubMed and Scopus and checked the publisher versions of selected articles. The searches focused on intermittent versus continuous heroin access, time-dependent changes during heroin abstinence, longitudinal brain and functional outcomes, and the interpretation of neuroaxonal injury biomarkers. We applied no prespecified restriction on publication dates.

2.2. Neuroadaptation and Persistent Dysfunction

For the purposes of this Perspective, neuroadaptation denotes molecular and cellular remodeling induced or modified by repeated opioid exposure, including changes in receptor signaling, gene expression, and synaptic and circuit organization [2,3,19]. The term does not imply either inevitable pathology or complete reversibility. Neuroadaptations may be maladaptive, compensatory, or functionally context-dependent, and their consequences may persist, reorganize, or resolve after exposure ceases. Whether a particular adaptation contributes to dysfunction depends on its functional effects, temporal persistence, and interactions with subsequent exposure and other biological processes. Importantly, the persistence of an addiction-related adaptation does not necessarily imply progressive impairment or neuronal injury.

Persistence refers to the continued presence of an alteration beyond a specified interval or clinical state, whereas reversibility denotes a change toward a previous or reference condition. Neither concept should be equated automatically with functional recovery, since molecular, structural, and behavioral outcomes may follow different temporal trajectories. Assessing persistence requires explicit consideration of time since last substance use, withdrawal status, treatment, and comorbidity, because state-dependent influences can contribute to apparently stable abnormalities. For example, whole-brain diffusion measures in individuals with heroin or cocaine use disorder have been associated with craving and recency of use [5]. Such cross-sectional associations do not establish the persistence of a specific alteration within individuals. Conversely, changes observed during treatment [14,15] demonstrate modifiability over the intervals examined but do not necessarily represent a return to a premorbid state, which is rarely documented in clinical samples.

Structural neuroimaging findings require particular interpretative caution. In a longitudinal study of extended-release naltrexone treatment for OUD, medial prefrontal and anterior cingulate cortical thickness decreased within approximately two weeks of the first injection, with greater thinning associated with greater reductions in opioid craving [16]. The temporal proximity of these changes to treatment initiation and their association with clinical improvement caution against interpreting cortical thinning as evidence of neuronal loss. More generally, the direction of a structural imaging change cannot independently establish whether it reflects injury, adaptive remodeling, recovery-related processes, or other biological influences. Similar limitations apply to diffusion imaging, where reduced fractional anisotropy or increased diffusivity may reflect different microstructural processes and cannot be interpreted as specific evidence of demyelination or axonal loss without additional validation [20]. Accordingly, molecular and neuroimaging alterations should be interpreted in relation to their temporal dynamics and functional correlates rather than assigned a pathological or restorative meaning on the basis of their direction alone.

2.3. Neuroprogression and Neurodegeneration

The concept of neuroprogression was developed in the context of bipolar disorder to describe the potentially cumulative biological and clinical consequences of recurrent episodes, with inflammatory, oxidative, and neurotrophic pathways proposed as contributing mechanisms [21]. However, its empirical status remains debated, and a meta-analysis of longitudinal studies did not identify consistent evidence of progressive cognitive decline

in bipolar disorder [22]. The concept is therefore adopted here as a hypothesis requiring empirical evaluation, rather than as an established characteristic of chronic psychiatric disorders or substance use disorders.

Within this framework, reduced functional resilience refers to greater functional disruption or poorer recovery following a defined perturbation. Neuroprogression refers to within-person worsening of function over time or progressively slower or less complete recovery following successive perturbations. Poor recovery that remains stable across episodes is consistent with reduced functional resilience. Neuroprogressive vulnerability refers to an antecedent susceptibility to developing a neuroprogressive trajectory. Neuroprogression is a longitudinal functional construct. Establishing its underlying mechanisms, including any contribution from neuronal degeneration, requires separate evidence.

Testing neuroprogression requires repeated within-individual assessments integrating exposure history, clinical course, and biological measures while accounting for ageing, treatment, comorbidity, and intervening injury. Two patterns would be consistent with the proposed construct: deterioration exceeding age-expected change, and progressively slower or less complete recovery following successive perturbations. Evaluation of the latter requires characterization of pre-perturbation function, the magnitude of acute impairment, subsequent recovery dynamics, and residual dysfunction at comparable follow-up intervals. Such trajectories must also be distinguished from worsening attributable primarily to increasingly severe perturbations or discrete acquired injuries. Cross-sectional associations between duration of substance use and brain abnormalities may motivate investigation but cannot establish progression. For example, associations between years of regular use and white matter measures were reported across combined heroin and cocaine use disorder groups rather than specifically within HUD [5]. Establishing that an observed neuroprogressive trajectory is mediated by exposure-related molecular neuroadaptations would require additional temporally informative mechanistic evidence.

Neurodegeneration is treated as a distinct pathological process involving progressive degeneration of neurons or their axons. It cannot be inferred from cognitive impairment, cortical thinning, diffusion abnormalities, or molecular overlap with pathways implicated in neurodegenerative disorders alone. Recent post-mortem proteomic findings in the hippocampus, putamen, and caudate nucleus of individuals with a history of heroin use identify candidate biological processes for further investigation [23]. However, the cases examined died of heroin overdose, and a single post-mortem assessment cannot establish the temporal development of a degenerative process or distinguish chronic exposure-related alterations from terminal events.

Neuropathological assessment can establish whether neuronal loss or axonal degeneration is present and characterize its anatomical distribution. A single post-mortem assessment leaves the timing and rate of tissue loss unresolved. In living cohorts, serial fluid and imaging measures may help characterize the course of injury. Neurofilament light chain, for example, is a marker of neuroaxonal injury across a range of acute and chronic conditions [24]. Interpreting such measures in people with a history of heroin use requires attention to the timing of overdose, other neurological insults, and changes in function. Attribution to chronic heroin exposure would require converging evidence of ongoing neuronal or axonal injury and a documented exposure history.

The proposed framework is therefore interpretative rather than diagnostic. It does not define a new nosological entity, establish validated disease stages, or presume an inevitable progression from neuroadaptation to neurodegeneration. Instead, it examines how exposure-related molecular remodeling, individual susceptibility, compensatory responses, treatment-related stabilization, and additional injuries may contribute to divergent functional trajectories, including recovery, persistent but stable dysfunction, injury-related

decline, and potentially progressive impairment. The working definitions of the principal constructs, the evidence required to evaluate them, and the findings that are insufficient on their own are summarized in Table 1.

Table 1. Working definitions and evidentiary requirements of the constructs used in this Perspective.

Construct	Working Definition	Evidence Required	Insufficient on Its Own
Neuroadaptation	Molecular and cellular remodeling induced or modified by repeated opioid exposure, with potentially maladaptive, compensatory, or context-dependent effects	Exposure-related changes in receptor signaling, gene expression, or synaptic and cellular organization, supported by appropriately characterized experimental or longitudinal evidence	Cross-sectional group differences without adequate exposure characterization
Persistence	Continued presence of a biological or functional alteration beyond a specified interval or clinical state	Repeated assessments documenting the alteration over time, with exposure, withdrawal, treatment, and relevant clinical conditions characterized	A single cross-sectional assessment or residual abnormality at one time point
Dysfunction	Measurable impairment in a specified functional domain. It may be transient, persistent, or progressive.	A functional assessment showing impairment relative to an appropriate reference or the individual's prior level of functioning.	A molecular or imaging alteration without a corresponding measure of functional impairment.
Reduced functional resilience	Greater functional disruption or poorer recovery following a defined perturbation.	Functional assessments before and after a defined perturbation, with its severity and the timing of assessments documented.	A single post-perturbation assessment or an isolated biomarker abnormality.
Neuroprogression	Longitudinal accumulation of dysfunction or progressively diminishing recovery capacity	Within-individual deterioration beyond age-expected change, or progressively slower or less complete recovery after successive perturbations, with relevant confounders addressed	Association with duration of use; persistent but stable impairment; isolated post-perturbation deficits
Neuroprogressive vulnerability	Susceptibility to a subsequent trajectory of worsening function or declining recovery capacity.	Prospective evidence that baseline or antecedent characteristics predict subsequent accumulating dysfunction or declining recovery capacity	Cross-sectional abnormalities; retrospective attribution of vulnerability from established impairment
Neurodegeneration	Progressive degeneration of neurons or their axons	Histopathological evidence of degeneration or validated in vivo markers with longitudinal evidence of progression	Cognitive impairment; cortical thinning; diffusion abnormalities; molecular pathway overlap alone

3. Molecular Neuroadaptations During Chronic Heroin Exposure

3.1. Exposure Patterns and Neuronal Excitability

Repeated μ-opioid receptor activation engages well-characterized cellular adaptations, including receptor desensitization and compensatory changes in downstream signaling [2,3].

Understanding the consequences of chronic heroin exposure, however, requires considering not only the cumulative extent of opioid exposure but also its temporal organization, because continuous and interrupted exposure may produce distinct molecular and cellular responses. Lefevre and colleagues demonstrated that continuous morphine administration and exposure interrupted by daily naloxone-precipitated withdrawal produced different, cell-type- and sex-dependent changes in excitatory and inhibitory transmission in the nucleus accumbens shell of mice [25]. Earlier experimental work also identified differences in mesolimbic dopaminergic and striatal transcriptional responses associated with interrupted versus continuous morphine exposure [26]. Although these paradigms do not directly reproduce the spontaneous withdrawal and variable exposure patterns characteristic of human heroin use, together they demonstrate that the temporal organization of opioid exposure can influence multiple neurobiological responses. Whether these differences persist or contribute to progressively reduced functional recovery remains to be established. Exposure duration alone may therefore provide an incomplete characterization of the biological consequences of repeated opioid exposure.

A direct comparison of heroin access schedules provides complementary behavioral evidence. In rats, intermittent access produced greater heroin intake and greater cue-induced heroin seeking on abstinence day 1 than continuous access within the daily sessions. The difference in seeking was no longer detected on day 21 [27]. Because total intake differed between groups, the study cannot isolate the contribution of access pattern at matched cumulative exposure. In a separate comparison of intermittent and continuous heroin access, Rakowski and colleagues found similar responding in progressive-ratio and conditioned reinforcement tests, but less elastic heroin demand after intermittent access in a behavioral economics task [28]. Together, these studies indicate that the behavioral differences associated with heroin access schedules depend on the outcome measured. Their relevance to cognitive and functional recovery across successive withdrawal episodes remains to be tested.

Future experiments could compare continuous opioid exposure, intermittent exposure followed by spontaneous withdrawal, and exposure interrupted by antagonist-precipitated withdrawal. Drug-free controls and an antagonist-only control would help distinguish effects of opioid exposure and withdrawal from those of the antagonist itself. Comparisons should match cumulative opioid administration where feasible and characterize achieved exposure, withdrawal severity, and physiological stress. In heroin-specific models, comparing self-administration with matched experimenter-administered exposure would help assess the contribution of behavioral context. Measuring both the candidate neuroadaptation and functional recovery after a subsequent standardized perturbation would test whether differences between exposure conditions extend to recovery.

Heroin-specific findings further indicate that neuronal excitability may be altered through mechanisms extending beyond synaptic receptor regulation. Anderson and colleagues found reduced nucleus accumbens levels of SCN1b, an auxiliary subunit of voltage-gated sodium channels, after heroin self-administration in male and female rats [29]. This reduction was absent after experimenter-administered heroin in the conditions tested. Experimental reduction of SCN1b increased the intrinsic excitability of medium spiny neurons. In the behavioral knockdown experiment, conducted in male rats, SCN1b reduction enhanced cue-induced reinstatement of heroin seeking without affecting acquisition of self-administration or extinction learning. Endogenous SCN1b levels returned to baseline following abstinence and extinction training, indicating that this exposure-associated molecular alteration was reversible under the conditions examined. However, the experimental reduction of SCN1b extended across behavioral phases, limiting conclusions about when altered expression contributed to subsequent seeking. These findings identify a mechanism

linking heroin-associated changes in neuronal excitability to relapse-related behavior, while illustrating that normalization of an individual molecular measure does not necessarily coincide with resolution of behavioral vulnerability. They do not establish that this adaptation contributes to accumulating brain dysfunction or neuroprogression.

The interval since last heroin exposure also matters when interpreting molecular and behavioral findings. After heroin self-administration in rats, cue-induced heroin seeking was greater on withdrawal day 30 than on day 1. Over the same interval, nucleus accumbens GDNF mRNA levels changed, while GDNF protein levels did not show a corresponding time-dependent change [30]. This divergence illustrates why transcript, protein, and behavioral outcomes should be assessed at comparable withdrawal intervals. The experiment addressed changes during a single period of abstinence. Whether repeated exposure–withdrawal transitions alter recovery across successive episodes remains a separate question.

3.2. Astrocyte–Synapse Remodeling and Glutamate Regulation

Heroin-associated neuroplasticity extends beyond neuronal adaptations to involve interactions between neurons and astrocytes. In a rat heroin self-administration model, Kruyer and colleagues identified two distinct forms of astrocytic plasticity during cue-induced heroin seeking: increased proximity of astrocytic processes to synapses and increased extrasynaptic expression of the glutamate transporter GLT-1 [31]. These responses occurred in different astrocyte subpopulations, with increased synaptic proximity preferentially involving dendrites of dopamine D2 receptor-expressing neurons. Experimental disruption of either response increased heroin seeking, indicating that both adaptations functioned to constrain rather than facilitate relapse-related behavior under the conditions examined.

These findings have important implications for the proposed framework. Astrocytic remodeling cannot be interpreted uniformly as pathological, since compensatory responses may coexist with adaptations that facilitate drug seeking. The functional significance of a molecular or cellular change depends on its cellular localization, temporal context, and consequences for neural circuit function. Moreover, because these adaptations were observed following heroin self-administration and subsequent extinction training, their development cannot be attributed exclusively to drug exposure; withdrawal-related processes and extinction learning may also contribute. The findings therefore illustrate how exposure history and subsequent behavioral experience may shape compensatory neuroplasticity, without establishing whether these mechanisms influence long-term cognitive function or recovery capacity.

Complementary evidence implicates neuronal synaptic regulation in heroin-related behavioral vulnerability. Transcriptomic analysis of post-mortem human orbitofrontal cortex identified SHISA7 as a molecular feature associated with heroin use, while experimental overexpression of SHISA7 in the orbitofrontal cortex of male rats increased heroin seeking and impaired behavioral updating [19]. These findings provide translational evidence linking molecular changes in synaptic regulation to behavioral outcomes, although the human association and experimental manipulation do not establish a common temporal trajectory. Considered together, these studies illustrate that heroin-associated molecular and cellular adaptations may exert opposing influences on subsequent behavior. Their relevance to persistent functional impairment or neuroprogressive vulnerability remains to be established rather than inferred from their effects on drug seeking alone.

3.3. Adaptation of Stress Signaling

Stress-related signaling represents another potential mechanism linking repeated heroin exposure to subsequent behavioral vulnerability. In female rats, Schneider and

colleagues identified region-specific alterations in corticotropin-releasing factor (CRF) receptor expression following 16 days of escalating heroin administration [32]. CRF1 receptor expression increased in the nucleus accumbens and decreased in the ventral tegmental area, whereas CRF2 receptor expression decreased in the ventral tegmental area, dorsal hippocampus, and hypothalamus. In separate experiments, intracerebroventricular administration of CRF1 and CRF2 receptor antagonists produced brief reductions in heroin self-administration, supporting the involvement of both receptor systems in heroin-related behavior. These findings demonstrate that repeated heroin exposure is associated with anatomically differentiated adaptations in stress-related receptor expression, rather than a uniform change across brain regions.

The interpretation of these adaptations nevertheless requires distinguishing receptor abundance from signaling activity and behavioral function. The direction of receptor expression changes does not establish the corresponding level of CRF signaling or whether the observed responses are compensatory or maladaptive. Moreover, the receptor findings were obtained in female rats following non-contingent heroin administration, and the study did not directly compare continuous and interrupted exposure patterns or establish the persistence of receptor alterations during abstinence. Within the proposed framework, CRF-related remodeling therefore represents a candidate mechanism through which exposure history and subsequent stress-related perturbations might influence behavioral vulnerability. Whether repeated exposure–withdrawal transitions modify these adaptations, compromise functional recovery, or contribute to cumulative brain dysfunction remains to be directly investigated.

3.4. Neuroimmune Signaling and Cellular Stress

Using single-nucleus RNA sequencing of the human caudate and putamen, Phan and colleagues identified both shared and cell-type-specific transcriptional changes in OUD [33]. Interferon-response genes were upregulated across several glial populations, including astrocytes and oligodendrocytes. Other changes were more cell-type-specific, including increased expression of an NFKB1-associated gene module in astrocytes and a STAT3-associated module in oligodendrocyte precursor cells. DNA damage-related signatures were also detected in striatal neurons, and complementary findings were reported in rhesus macaques after chronic morphine exposure [33]. These results identify cell populations and pathways in which to test responses to a subsequent stressor. The human comparison included six OUD cases and six controls, and all OUD cases died of opioid overdose. The study therefore leaves open whether these changes persist beyond exposure or affect cellular recovery. The macaque findings support mechanistic plausibility for morphine exposure, while the relevance to heroin and to repeated exposure–withdrawal transitions remains to be tested.

In a separate post-mortem study of the human ventral midbrain, Wei and colleagues compared 45 donors with a history of opioid misuse and overdose with 50 opioid-free controls [34]. Single-nucleus RNA sequencing showed increased expression of immune response genes, including interferon-related genes, across microglia, astrocytes, and oligodendrocytes. Non-dopaminergic neurons showed lower expression of genes involved in synaptic signaling and plasticity. The glial findings are consistent with the interferon-related changes reported in the dorsal striatum [33]. Both studies examined tissue from donors who died of overdose, leaving the relative contributions of chronic exposure and terminal events unresolved.

In a post-mortem study of the dorsolateral prefrontal cortex in OUD, Mendez and colleagues identified alterations involving angiogenesis and cytokine signaling, including a gene network associated with astrocytes, endothelial cells, and microglia [35]. These find-

ings extend the discussion to the neurovascular compartment. Using bulk RNA sequencing, Seney and colleagues reported transcriptional changes involving neuroinflammation and synaptic remodeling in the dorsolateral prefrontal cortex and nucleus accumbens [36]. Whether these molecular changes persist beyond exposure or influence functional recovery remains to be tested.

Post-mortem proteomic investigations in individuals with a history of heroin use have similarly identified alterations involving proteins associated with mitochondrial function, metabolic regulation, and cellular stress responses [23]. These findings suggest potential biological pathways through which exposure-related alterations might influence cellular vulnerability to subsequent perturbations. However, the functional consequences of these proteomic differences remain uncertain, and their presence does not demonstrate impaired mitochondrial function or reduced cellular resilience. Importantly, both human datasets derive from individuals who died of overdose, complicating the distinction between adaptations associated with prolonged opioid exposure and changes related to terminal events. Within the proposed framework, the convergence of neuroimmune, DNA damage-related, and metabolic alterations provides a rationale for investigating whether exposure-associated molecular states modify responses to subsequent insults. It does not establish a sequential pathway from chronic heroin exposure to accumulating dysfunction or neurodegeneration.

3.5. Epigenetic Regulation and Subsequent Behavioral Vulnerability

Epigenetic regulation provides a potential mechanism through which molecular events occurring during active heroin exposure may influence subsequent behavioral vulnerability. In a rat heroin self-administration model, Anderson and colleagues demonstrated that histone deacetylase 5 (HDAC5) in the nucleus accumbens acts during the acquisition phase to constrain later relapse-associated behavior [37]. These effects were cell-type- and trigger-specific: HDAC5 activity in dopamine D1 receptor-expressing medium spiny neurons suppressed cue-induced heroin seeking, whereas its activity in D2 receptor-expressing neurons suppressed heroin-primed seeking. Cell-type-specific transcriptional analyses identified downregulation of genes involved in ion transport and neuronal excitability, accompanied by reduced intrinsic excitability in both neuronal populations. These findings link epigenetic regulation during active heroin use to subsequent behavioral responses through mechanisms involving neuronal excitability.

The functional significance of these adaptations is particularly relevant to the proposed framework. HDAC5-dependent regulation illustrates that molecular changes associated with heroin exposure may constrain rather than promote subsequent drug seeking. Its effects also depend on the neuronal population and behavioral trigger examined, arguing against a uniform interpretation of epigenetic remodeling as maladaptive. However, the demonstrated influence on relapse-related behavior does not establish that these mechanisms preserve cognitive function, protect against cellular injury, or prevent progressively diminished recovery capacity. Whether their behavioral effects persist independently of continued molecular regulation also requires further investigation.

Human post-mortem evidence also links heroin use to epigenetic differences. In the ventral striatum, Egervari and colleagues reported greater H3K27 acetylation and altered expression of genes involved in glutamatergic signaling in individuals with a history of heroin use [38]. These findings identify a candidate link between chromatin regulation and synaptic signaling in human tissue. The post-mortem comparison leaves open when these differences emerged, whether they persist during abstinence, and how they relate to functional recovery.

Evidence that sex modifies opioid-related neuroadaptations depends on the experimental design and outcome. In mice, synaptic responses to continuous and interrupted

morphine exposure varied by sex and cell type [25]. In the heroin access study by D'Ottavio and colleagues, cue-induced heroin seeking was greater in females than in males after intermittent access. This difference was not observed after continuous access [27]. In the heroin studies, SCN1b expression was assessed in both sexes, whereas the behavioral knockdown experiment was conducted in males [29]. The study of CRF receptor expression after repeated heroin exposure was conducted in females [32]. These designs support different inferences about sex differences. Future studies should report sex-specific estimates and, where adequately powered, test whether sex modifies the effect of exposure pattern on neuroadaptation or subsequent functional recovery.

Taken together, the evidence reviewed in this section supports a heterogeneous account of opioid-associated molecular and cellular remodeling, involving neuronal excitability, synaptic and astrocytic plasticity, stress-related signaling, neuroimmune and cellular stress responses, and epigenetic regulation (Table 2). Experimental findings indicate that some adaptations facilitate heroin seeking whereas others constrain it, and that the normalization of an individual molecular alteration may not coincide with the resolution of behavioral vulnerability [29,31,37]. Human molecular studies identify additional candidate pathways, although their functional and temporal significance remains incompletely established [19,23,33]. Within the proposed framework, the central question is which exposure-associated adaptations influence persistent behavioral vulnerability, which might modify susceptibility to subsequent insults, and which support stabilization or recovery. Establishing a contribution to neuroprogression would require demonstrating that specific molecular processes precede and influence accumulating dysfunction or progressively diminished recovery capacity, rather than inferring such effects from their presence or association with drug seeking alone.

Table 2. Selected molecular and cellular adaptations associated with opioid exposure, classified by experimental context, addiction-related phase, functional consequences, and evidence of reversibility.

Adaptation	Model/Opioid	Phase Examined	Demonstrated Functional Effect	Reversibility Assessed	Ref.
Pattern-dependent excitatory and inhibitory synaptic plasticity, NAc shell	Mouse, both sexes/morphine	Continuous vs. interrupted exposure	Distinct cell-type- and sex-dependent synaptic phenotypes; behavioral consequences not established	Not assessed	[25]
Mesolimbic dopaminergic and striatal transcriptional adaptations	Mouse/morphine	Continuous vs. interrupted exposure	Exposure-pattern-dependent molecular and dopaminergic responses; long-term functional consequences uncertain	Not established	[26]

Table 2. *Cont.*

Adaptation	Model/Opioid	Phase Examined	Demonstrated Functional Effect	Reversibility Assessed	Ref.
Reduced SCN1b expression and increased MSN excitability	Rat/heroin (SCN1b expression assessed in both sexes, behavioral knockdown tested in males only)	Self-administration, abstinence and reinstatement	Experimental SCN1b reduction increased MSN intrinsic excitability and, in male rats, enhanced cue-induced reinstatement of heroin seeking.	Endogenous SCN1b returned to baseline after abstinence and extinction	[29]
Astrocytic process proximity and extrasynaptic GLT-1, NAc core	Rat/heroin	Extinction and cue-induced seeking	Cue-associated astrocytic responses constrain heroin seeking	Transient cue-induced responses; long-term reversibility not established	[31]
SHISA7-associated synaptic regulation, OFC	Human post-mortem; male rat/heroin	Human exposure history; experimental heroin seeking	Experimental SHISA7 overexpression increases seeking and impairs behavioral updating	Not assessed	[19]
Region-specific CRF1 and CRF2 receptor expression	Female rat/heroin	Repeated escalating exposure	Receptor alterations observed; antagonists transiently reduce self-administration in separate experiments	Not assessed	[32]
Interferon-response and DNA damage-related molecular signatures	Human post-mortem; rhesus macaque/opioids, including morphine	OUD at death; experimental chronic exposure	Cell-type-specific transcriptional alterations; consequences for recovery not established	Not assessed	[33]
Mitochondrial-and metabolism-associated proteins	Human post-mortem/heroin	Exposure history, assessed at death	Proteomic differences; functional consequences not established	Not assessable longitudinally	[23]
HDAC5-dependent transcriptional regulation and MSN excitability	Rat/heroin	Acquisition and subsequent relapse-related testing	Suppresses cue-induced seeking in D1-MSNs and heroin-primed seeking in D2-MSNs	Long-term reversibility not established	[37]

Note. None of the studies summarized in this table directly tested whether the reported adaptation contributes to progressively slower or less complete functional recovery across successive perturbations. The "Demonstrated functional effect" column reports the outcomes assessed in each study, including effects on neuronal excitability or heroin seeking where measured. Abbreviations: NAc, nucleus accumbens; MSN, medium spiny neuron; OFC, orbitofrontal cortex; CRF, corticotropin-releasing factor; HDAC5, histone deacetylase 5; GLT-1, glutamate transporter 1; OUD, opioid use disorder.

4. Human Evidence of Brain Alterations and Their Longitudinal Modifiability

4.1. Neurocognitive Findings and Their Temporal Interpretation

Human studies document neurocognitive and functional abnormalities in HUD, particularly in processes relevant to behavioral regulation. Altered prefrontal recruitment during

inhibitory control has been associated with task performance in individuals with HUD [4]. However, deficits in cognitive flexibility and inhibitory control observed in both abstinent individuals with heroin addiction and their unaffected biological siblings suggest that part of this neurocognitive profile may reflect familial susceptibility rather than acquired dysfunction alone [13]. These findings emphasize the need to consider premorbid vulnerability alongside exposure history when interpreting cognitive abnormalities in HUD.

A meta-analysis of 61 studies found that neuropsychological differences between individuals with OUD and healthy controls varied across domains, with the largest difference in complex psychomotor performance [39]. Across studies, longer abstinence was associated with smaller group differences in this domain. This between-study association provides context for the longitudinal findings below. Estimating recovery requires repeated measurements within individuals.

Longitudinal evidence indicates that cognitive performance can change following cessation of opioid use. Kaur and colleagues assessed 50 men with OUD at baseline and after two and eight weeks of abstinence [40]. Attention, concentration, and verbal and nonverbal memory improved during the first two weeks, whereas significant improvement in executive functioning was observed only at eight weeks. Baseline performance in selected cognitive domains was also associated with exposure characteristics, including duration and frequency of use. These observations demonstrate domain-specific temporal changes during early abstinence, but do not establish whether cognitive performance returns to premorbid levels or whether the observed improvements persist over longer intervals.

Cognitive performance can also change during opioid agonist treatment. In a study of 17 opioid-dependent participants assessed at baseline and after two months of methadone maintenance, performance improved on measures of verbal learning and memory, visuospatial memory, and psychomotor speed [41]. The study documents within-person change during treatment. The contribution of methadone itself remains uncertain. In a separate observational study, participants receiving methadone or buprenorphine were assessed up to 12–17 months after treatment initiation. Several cognitive differences relative to healthy controls remained evident, although performance on one working-memory task improved in the buprenorphine group [42].

The interpretation of these findings requires consideration of withdrawal-related effects, repeated testing, treatment conditions, and other time-varying clinical factors. Improvements during abstinence may reflect resolution of transient impairment, broader functional recovery, practice effects, or a combination of these processes. Moreover, results obtained in a broader OUD population cannot be attributed specifically to heroin exposure. Within the proposed framework, neurocognitive performance represents a relevant functional outcome whose persistence, improvement, or deterioration must be established through repeated assessment under adequately characterized conditions. Although these longitudinal observations support the modifiability of cognitive functioning, they do not demonstrate neuroprogression or progressively diminished recovery capacity following successive perturbations.

4.2. Structural and Functional Brain Organization

Human neuroimaging studies extend the characterization of opioid-associated brain alterations beyond cognitive performance. In a multimodal comparison of methadone-treated individuals with OUD and healthy controls (103 versus 105 participants for structural imaging; 74 versus 100 for resting-state functional imaging), Mehta and colleagues identified regionally heterogeneous structural and functional differences [18]. Smaller regional volumes were observed in the bilateral thalamus, right caudate and orbitofrontal cortex, and right medial temporal lobe, whereas larger volumes were identified in the brainstem,

bilateral cerebellum, left medial temporal lobe, left insula, and right dorsal posterior cingulate cortex. Increased intrinsic functional connectivity was also reported in several regions, including the thalamus, right medial temporal lobe, cerebellum, and brainstem.

The coexistence of smaller and larger regional volumes, including opposing findings across medial temporal regions, argues against interpreting these observations as evidence of uniform tissue loss. Neither regional volume nor functional connectivity was significantly associated with OUD duration in the study. Moreover, participants with OUD differed from controls in age, sex distribution, smoking prevalence, and histories of other substance use, and all were receiving methadone at assessment. These findings therefore document distributed structural and functional differences without establishing their temporal development or distinguishing the contributions of premorbid characteristics, prior opioid exposure, comorbidity, and treatment. The absence of significant associations with OUD duration does not exclude exposure-related effects, but provides no direct evidence of progressive structural deterioration.

White matter investigations provide complementary evidence of altered brain microstructure. Gaudreault and colleagues reported widespread diffusion MRI abnormalities in individuals with heroin and cocaine use disorders, with selected measures associated with duration of regular substance use across the combined clinical groups [5]. These findings are compatible with possible cumulative exposure-related contributions but cannot demonstrate heroin-specific progressive change because of the cross-sectional design and mixed substance-use sample. As discussed in Section 2.2, diffusion measures are sensitive to tissue microstructural properties but do not directly identify a specific cellular lesion, such as demyelination or axonal loss, without additional validation [20].

Evidence potentially related to discrete acquired injury is more anatomically specific. Todaro and colleagues reported lower hippocampal volume in individuals with OUD who had experienced non-fatal overdose than in those without such a history [17]. Given the vulnerability of the hippocampus to hypoxic injury, this association provides a rationale for considering overdose-related insults separately from exposure-associated neuroadaptations. However, its cross-sectional nature cannot establish whether the volumetric difference resulted from overdose, preceded it, or reflected other characteristics associated with more severe opioid use. Within the proposed framework, these observations support distinguishing distributed exposure-associated brain alterations from possible consequences of discrete injury, while neither establishes a neuroprogressive trajectory without longitudinal evidence.

4.3. Longitudinal Change During Treatment and Abstinence

Longitudinal neuroimaging provides evidence that brain measures associated with HUD can change within individuals during treatment and abstinence. Increased anterior prefrontal recruitment during inhibitory control and changes in frontal white matter diffusion measures consistent with partial normalization have been reported after approximately 15 weeks of inpatient treatment [14,15]. These findings demonstrate modifiability over the intervals examined but do not establish restoration of premorbid brain organization. Moreover, the contributions of pharmacological treatment, reduced illicit opioid exposure, psychosocial interventions, and the structured inpatient environment cannot be reliably separated. Changes in diffusion measures should therefore not be interpreted as direct evidence of tissue repair, just as the direction of structural changes alone does not identify their underlying cellular processes [16,20].

Wang and colleagues acquired MRI scans in 20 participants with heroin dependence at three days and one month of abstinence and included 20 healthy controls [43]. A superior frontal gray matter difference relative to controls was detected at three days but was no

longer statistically significant at one month. Differences in other regions, including the middle frontal and cingulate gyri, remained detectable. The loss of statistical significance in the superior frontal comparison alone does not establish within-person normalization.

In a separate longitudinal study, 61 of 108 participants with heroin addiction completed repeat MRI after eight months of abstinence. Among those who completed follow-up, bilateral superior frontal cortical thickness increased, Trail Making Test Part A completion time decreased, and craving declined [44]. These findings document changes in brain measures and task performance during one period of sustained abstinence. The incomplete follow-up limits generalizability, and the study does not establish whether recovery changes across successive withdrawal episodes.

Longer observation periods provide additional evidence of heterogeneity in clinical trajectories. In a cohort of 53 individuals with HUD undergoing eight months of abstinence in rehabilitation centres, baseline multimodal neuroimaging combined with clinical variables was used to classify subsequent craving reduction, with high accuracy in the discovery sample [45]. External validation, however, involved 21 individuals with methamphetamine use disorder rather than an independent HUD cohort, and predictive accuracy was substantially lower. These findings suggest that baseline neuroimaging characteristics may contain information relevant to subsequent changes in craving, but their generalizability and clinical predictive value remain uncertain. Importantly, predicting craving reduction is not equivalent to predicting cognitive deterioration, diminished recovery capacity, or neuroprogression.

Collectively, these studies provide evidence of longitudinal modifiability more directly than of progressive brain deterioration. Improvement during treatment does not establish complete functional or biological recovery, whereas residual abnormalities do not necessarily imply continued worsening. Within the proposed framework, an unresolved question is whether repeated exposure–withdrawal transitions or other perturbations are associated with progressively slower or less complete recovery, independently of cumulative exposure, treatment conditions, baseline susceptibility, and intervening injury. Addressing this question requires repeated assessment of functional trajectories across adequately characterized clinical states, rather than inferring neuroprogression from improvement or persistence observed over a single treatment or abstinence interval. Table 3 summarizes selected human studies and the inferences supported by their designs.

Table 3. Selected human studies of brain and functional outcomes in heroin and opioid use disorders.

Study	Population and Clinical Context	Design and Follow-Up	Main Finding	Inference Supported
Kaur et al. [40]	50 men with OUD assessed during early abstinence	Longitudinal, baseline and 2 and 8 weeks	Attention and memory improved early, with later improvement in executive performance.	Cognitive performance can change over early abstinence. The contribution of repeated testing remains uncertain.
Mehta et al. [18]	Methadone-treated participants with OUD and healthy controls. Structural MRI: 103 and 105. Resting-state fMRI: 74 and 100.	Cross-sectional	Regional differences in brain volume and resting-state connectivity.	Documents between-group differences at assessment. Their onset and course remain unresolved.

Table 3. *Cont.*

Study	Population and Clinical Context	Design and Follow-Up	Main Finding	Inference Supported
Yang et al. [44]	Participants with heroin addiction during sustained abstinence. 61 of 108 completed repeat MRI.	Longitudinal, 8 months	Superior frontal cortical thickness increased, Trail Making Test Part A completion time decreased, and craving declined.	Documents change during one abstinence period among participants who completed follow-up.
Wen et al. [45]	53 participants with HUD in the development cohort. External validation involved 21 participants with methamphetamine use disorder.	Longitudinal, 8 months in the HUD cohort	Baseline imaging and clinical measures classified subsequent craving reduction, with lower accuracy in the external cohort.	Supports further study of craving prediction. Performance in an independent HUD cohort remains unknown.

Abbreviations: fMRI, functional magnetic resonance imaging. HUD, heroin use disorder. MRI, magnetic resonance imaging. OUD, opioid use disorder.

4.4. Molecular Findings and Longer-Term Brain Health

Post-mortem studies provide access to molecular processes that cannot be directly characterized through conventional neuroimaging. Heroin-associated proteomic differences and cell-type-specific transcriptional alterations identified in OUD implicate pathways involved in synaptic regulation, neuroimmune signaling, and cellular stress responses [23,33]. However, their interpretation is constrained by the circumstances of death, potential polysubstance exposure, limited sample sizes, and the absence of longitudinal measurements linking molecular changes to the emergence or progression of functional impairment. In particular, both human datasets include individuals who died of opioid overdose, complicating the separation of chronic exposure-related adaptations from terminal events. These findings therefore identify candidate mechanisms rather than establishing their persistence, functional consequences, or temporal contribution to progressive brain dysfunction.

In the Million Veteran Program, a clinical diagnosis of opioid use disorder (OUD) was associated with a higher incidence of all-cause dementia in participants of European ancestry (HR 1.56, 95% CI 1.39–1.76) and African ancestry (HR 1.27, 95% CI 1.02–1.59) [46]. The cohort was predominantly male, and the available data did not adequately characterize opioid identity, route, or duration of use. The Mendelian randomization analysis addressed a separate question by examining genetically predicted liability to OUD. In a separate longitudinal imaging analysis of 229 opioid-naïve participants, polygenic liability to OUD showed no statistically significant association with structural brain change [46]. These findings motivate investigation of long-term brain health in people with OUD. Assessing whether cumulative heroin exposure contributes to progressive neuronal injury would require direct characterization of heroin exposure and longitudinal evidence specific to that outcome.

4.5. Strength of Evidence Across Study Designs

The strength of the evidence depends on the question and the study design. Cross-sectional human studies document group differences at a given time, and post-mortem studies can identify molecular and cell-type-specific differences at death. Epidemiological studies estimate associations with long-term outcomes. Longitudinal studies quantify within-person change over the observed interval, which may reflect improvement, stable

impairment, or deterioration. Controlled animal studies can isolate effects of exposure conditions, and targeted manipulations can test whether a candidate adaptation contributes to a specific outcome in that model. The evidence reviewed here supports opioid-associated neuroadaptation and the capacity for some human functional and brain measures to change over time. Establishing neuroprogression attributable to chronic heroin exposure would require repeated within-person assessments linked to a documented history of exposure and withdrawal.

5. An Integrated Neuroprogressive Vulnerability Model

5.1. Structure of the Model

The proposed framework distinguishes exposure-related molecular and cellular adaptations, factors that modify their long-term consequences, and discrete acquired injuries that may contribute independently or interact with pre-existing vulnerability (Figure 1). These components are proposed to shape divergent functional trajectories rather than a predetermined sequence of progressive deterioration.

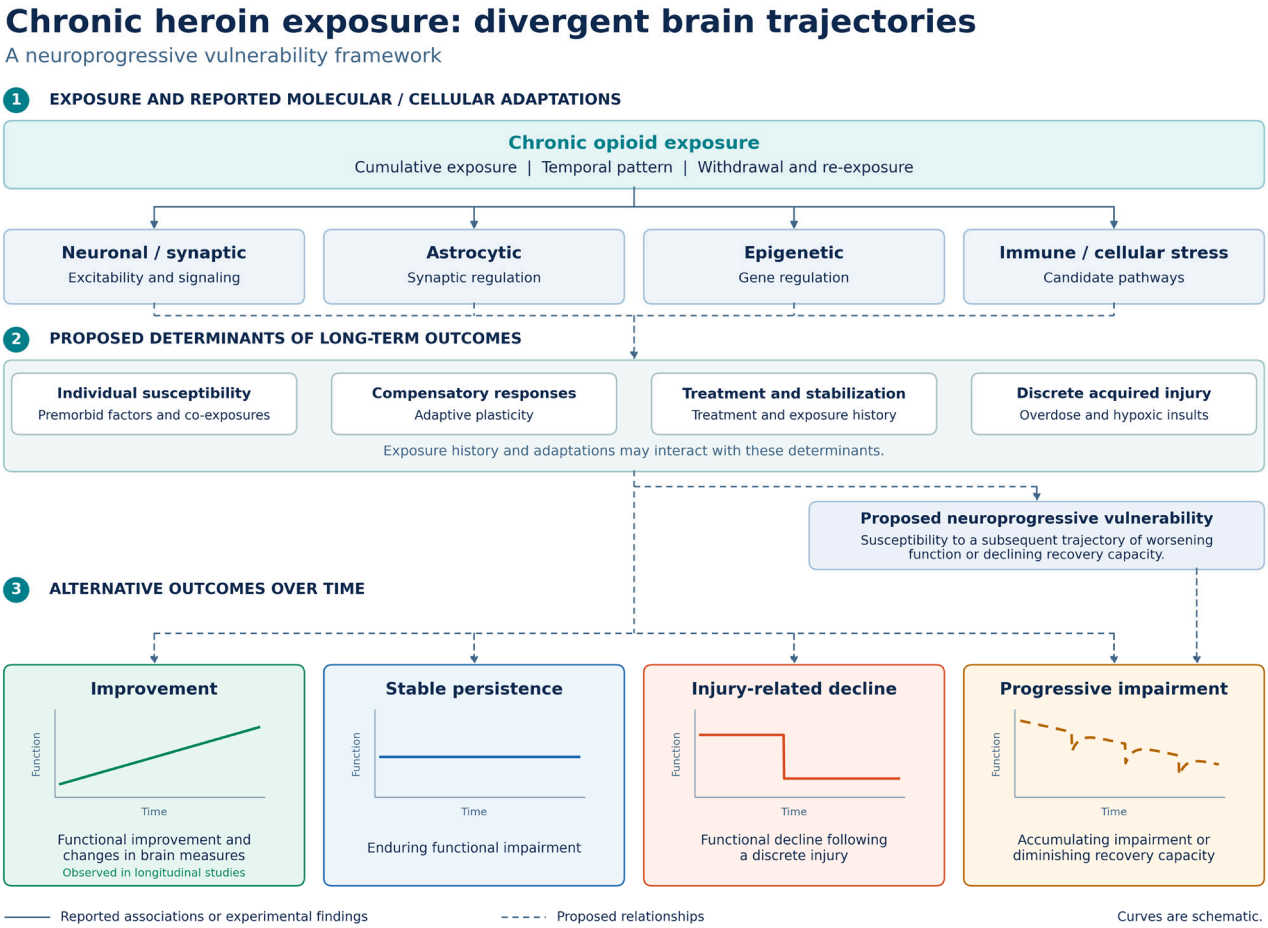

Figure 1. Conceptual framework for long-term brain and functional outcomes following chronic heroin exposure. The four colored curves illustrate alternative functional trajectories that may arise from interacting determinants. The dashed curve represents the hypothesized trajectory of progressive impairment. Solid connecting lines indicate reported associations or experimental findings, and dashed connecting lines indicate proposed relationships. Neuroprogressive vulnerability denotes susceptibility to a subsequent trajectory of worsening function or declining recovery capacity.

Exposure-related neuroadaptations comprise molecular and cellular remodeling induced or modified by repeated opioid exposure, with changes that may persist, reorganize,

or resolve after exposure ceases. These include alterations in neuronal excitability, synaptic organization, astrocyte–synapse interactions, and stress-receptor expression [25,29,31,32,37]. Such adaptations are not necessarily pathological: their functional consequences may be maladaptive, compensatory, or context-dependent.

Neuroprogressive vulnerability refers to an antecedent susceptibility to developing a neuroprogressive functional trajectory. The framework proposes that this susceptibility may depend on the interaction between individual characteristics, prior neuroadaptations, and the temporal pattern of opioid exposure. Whether these factors predict progressively slower or less complete functional recovery remains to be tested in people with HUD.

Individual susceptibility encompasses familial and premorbid characteristics that may influence both the development of substance use disorder and subsequent functional outcomes [13]. The temporal pattern of opioid exposure describes how exposure is distributed over time, including interruptions, withdrawal and re-exposure, and periods of treatment-related stabilization. Section 5.2 distinguishes this pattern from cumulative opioid exposure. Compensatory cellular responses and treatment-related changes may further modify functional trajectories, potentially supporting stabilization or recovery.

Discrete acquired injuries, particularly those associated with overdose-related hypoxia, represent an additional pathway to persistent brain dysfunction [17]. Their consequences may occur independently of exposure-related neuroadaptations or may be amplified by pre-existing biological vulnerability. The latter possibility constitutes a proposed interaction requiring direct investigation rather than an established mechanism.

Figure 1 summarizes how exposure-related neuroadaptations, individual susceptibility, compensatory responses, treatment, and discrete acquired injuries may contribute to four alternative trajectories: functional improvement, stable impairment, injury-related decline, and progressive impairment. The central hypothesis concerns progressively slower or less complete recovery across successive episodes and its association with prior exposure–withdrawal transitions after accounting for cumulative opioid exposure.

5.2. Temporal Organization of Exposure as a Candidate Determinant

The central hypothesis is that repeated opioid exposure–withdrawal transitions are associated with progressively less complete functional recovery across successive episodes in people with a history of heroin use, beyond what can be explained by cumulative opioid exposure. Whether the temporal pattern of exposure contributes to this trajectory remains to be tested.

Experimental evidence demonstrates that temporal exposure patterns can produce distinct synaptic adaptations. Lefevre and colleagues showed that continuous morphine administration and exposure interrupted by daily naloxone-precipitated withdrawal induced different, cell-type- and sex-dependent synaptic phenotypes in the nucleus accumbens shell of mice [25]. Although precipitated withdrawal does not reproduce the spontaneous withdrawal associated with intermittent heroin use, these findings establish that exposure pattern can influence synaptic remodeling. Whether such differences contribute to persistent dysfunction or progressively diminished recovery capacity remains unknown. Region-specific changes in CRF receptor expression following heroin exposure [32] further identify stress-related signaling as a potential mechanism through which repeated exposure–withdrawal transitions might influence subsequent vulnerability. However, these findings were obtained in female rats, concern receptor expression rather than signaling activity, and do not directly establish an effect of exposure pattern.

Two implications follow. First, cumulative opioid exposure and its temporal pattern should be characterized separately. Cumulative exposure should be estimated from the duration of use, the amount and overall frequency of use, and the identity of the opioids

involved. Temporal pattern describes how that exposure is distributed over time, including the frequency of interruptions, the duration and severity of withdrawal, the intervals before re-exposure, and periods of stabilization. Route of administration, polysubstance use, treatment history, and overdose should also be documented. Prospective studies should compare a model that includes these temporal measures with a model that adequately characterizes cumulative exposure, and evaluate their incremental predictive value in an independent sample. Estimates of cumulative opioid exposure may be less accurate than prospectively documented withdrawal histories, particularly when the amount or composition of illicit opioids is uncertain. If temporal measures improve prediction, some of the gain may reflect exposure information missed by the cumulative measure.

Second, the temporal pattern of opioid exposure raises two distinct questions. A prognostic analysis would test whether adding temporal exposure measures to a model of cumulative opioid exposure improves prediction of later cognitive and everyday functioning. A causal analysis would ask whether a specified intervention that reduces the frequency of exposure–withdrawal transitions improves subsequent functional recovery. Comparisons involving sustained opioid agonist treatment and intermittent illicit heroin use should document treatment continuity, opioid exposure, and the timing and severity of withdrawal episodes.

5.3. Cellular Resilience and Additional Insults

A further component of the framework concerns the potential interaction between exposure-related molecular remodeling and additional insults capable of producing brain injury. Interferon-response, DNA-damage, and neurodegeneration-related transcriptional signatures identified in the human striatum [33], together with alterations in mitochondrial and metabolic proteins in post-mortem heroin samples [23], identify candidate pathways through which chronic opioid exposure might influence cellular stress responses and susceptibility to subsequent insults. However, these findings do not establish impaired cellular resilience or progressive tissue injury. Both human datasets derive from individuals who died of overdose, limiting the ability to distinguish adaptations associated with prolonged opioid exposure from changes related to terminal events.

In this framework, cellular resilience denotes the capacity of a defined cell population to maintain or regain function after a standardized stressor. Experimental studies could measure mitochondrial respiratory reserve before and after an oxidative challenge or track the resolution of DNA damage at prespecified intervals after a defined insult. Synaptic homeostasis could also be assessed by measuring the extent and time course of recovery of excitatory synaptic transmission towards its baseline level after a standardized perturbation. Baseline, early post-challenge, and later measurements would help distinguish greater initial damage from slower or incomplete recovery. Comparing these responses across opioid exposure histories would test whether prior exposure alters the cellular response to a subsequent insult.

Overdose-associated hypoxic injury represents a distinct potential contributor to persistent brain dysfunction. Lower hippocampal volume has been reported in individuals with OUD and a history of non-fatal overdose compared with those without such a history [17]. Although this association supports considering overdose history when investigating long-term brain outcomes, its cross-sectional nature does not establish that the volumetric difference resulted from the overdose itself rather than preceding vulnerability, greater substance-use severity, or other associated factors.

The framework distinguishes independent or additive effects of exposure-related adaptations and acquired injury from a genuine interaction between them. An additional insult may contribute to dysfunction independently of prior molecular remodeling, whereas a bio-

logically vulnerable state might amplify its consequences. Only the latter possibility would support the proposed multi-hit mechanism. Testing this hypothesis requires longitudinal evidence that pre-existing exposure-related characteristics modify the association between a subsequent documented insult and functional outcomes, with appropriate consideration of confounding and the scale on which interaction is assessed. Statistical interaction would support this possibility but would not, by itself, establish a causal biological mechanism. The proposed relationship between neuroadaptation, diminished cellular resilience, and increased susceptibility to injury therefore remains a testable hypothesis rather than an established consequence of chronic heroin exposure.

5.4. Susceptibility, Compensation, and the Measurement of Resilience

Individual susceptibility influences both the emergence of addiction-related neuroadaptations and the interpretation of subsequent functional outcomes. Shared deficits in cognitive flexibility and inhibitory control among abstinent individuals with heroin addiction and their unaffected biological siblings suggest that some functionally relevant characteristics may precede substance exposure or reflect shared familial influences [13]. Such findings complicate the attribution of observed impairment exclusively to acquired neurobiological changes and underscore the importance of distinguishing premorbid vulnerability from exposure-related dysfunction.

The functional interpretation of a neuroadaptation depends on the outcome measured, the cell population involved, and the phase in which it is examined. Astrocytic responses involving GLT-1 and cell-type-specific HDAC5 signaling can be considered compensatory with respect to the forms of heroin seeking they constrain in experimental models [31,37]. By contrast, experimental reduction of SCN1b enhanced cue-induced heroin seeking, supporting a maladaptive interpretation for that behavioral outcome [29]. The classification remains context-dependent when the effect varies across cell populations or relapse triggers, as illustrated by HDAC5 [37]. Where studies document molecular changes without testing their functional consequences, the functional role remains undetermined. Whether adaptations that constrain heroin seeking also preserve cognitive function or improve recovery after a later perturbation requires separate testing.

Reduced functional resilience can remain stable over time. A person may recover poorly after successive withdrawal episodes yet show a similar degree of recovery after each one. The longitudinal pattern relevant to the central hypothesis is progressively slower or less complete recovery within the same person across comparable episodes. Section 6.2 outlines how repeated assessments could distinguish these patterns.

5.5. Divergent Trajectories, Relation to Existing Models, and Conditions for Revision

The interaction of exposure-related neuroadaptations, individual susceptibility, compensatory processes, treatment, and additional injuries may give rise to divergent long-term functional trajectories. These include persistent but stable dysfunction, partial recovery or compensatory reorganization, abrupt deterioration associated with discrete injury, and, potentially in a subgroup, accumulating impairment or progressively diminished recovery capacity (Figure 1). These trajectories represent alternative conceptual outcomes rather than sequential or validated clinical stages. Longitudinal improvements observed during treatment and abstinence [14,15,40] support the inclusion of functional modifiability, whereas epidemiological associations between OUD and incident dementia [46] motivate investigation of adverse long-term outcomes without establishing a progressive or neurodegenerative process attributable to heroin exposure.

Allostatic models emphasize changes in reward and stress systems that contribute to negative reinforcement [6,7]. Habit-based models describe the increasing role of habitual

and compulsive control in drug seeking [8]. The impaired response inhibition and salience attribution model explains how altered prefrontal control and heightened salience of drug-related cues contribute to continued use [9,10]. This Perspective asks how functional recovery changes within the same person across successive episodes of opioid exposure and withdrawal. Its central hypothesis is that, among people with a history of heroin use, a greater burden of prior exposure–withdrawal transitions is associated with progressively slower or less complete recovery in cognition and everyday functioning, beyond what can be explained by cumulative opioid exposure.

The predictions test distinct aspects of the framework. Where the data allow episode order to be distinguished from elapsed follow-up time, a sufficiently precise estimate that excludes a prespecified, clinically meaningful worsening of recovery across successive episodes would weaken the primary prediction. If recovery worsens but shows little association with measured exposure–withdrawal history beyond cumulative opioid exposure, that result would weaken the proposed role of repeated transitions while leaving the observed functional trajectory to be explained. Stable impairment, sustained improvement, and abrupt decline following a discrete injury represent other trajectories that longitudinal studies should distinguish from progressively poorer recovery.

5.6. Limitations of the Evidence and Proposed Framework

The evidence reviewed here supports individual links in the framework. Whether repeated heroin exposure–withdrawal transitions contribute to progressively poorer functional recovery remains unresolved. Findings from other opioids and from controlled animal models have limited transferability to heroin use in humans. In clinical cohorts, errors in estimating cumulative exposure or reconstructing withdrawal and re-exposure can make it difficult to separate the contributions of cumulative exposure and temporal pattern. Recovery estimates also depend on which episodes are documented and which participants survive and remain in follow-up. Section 6.2 describes how the proposed cohort would ascertain withdrawal episodes and address loss to follow-up and death. These limitations should guide the interpretation of both positive and null findings.

6. Therapeutic Implications and Testable Predictions

6.1. Treatment Continuity and the Hypothesis of Neurobiological Stabilization

Sustained opioid agonist treatment may reduce the frequency or severity of exposure–withdrawal transitions. Experimental studies showing distinct synaptic adaptations after continuous and interrupted morphine exposure provide a rationale for testing whether greater physiological stability influences neuroadaptation and functional recovery [25]. Longitudinal studies during inpatient treatment have documented changes in prefrontal recruitment and frontal white matter measures [14,15]. The contributions of medication, reduced illicit opioid use, and the treatment setting remain difficult to separate. Testing this pathway would require direct measures of withdrawal burden, candidate neuroadaptations, and subsequent functional recovery.

A second potential pathway concerns exposure to overdose-related injury. Studies of treatment retention, overdose, and mortality underscore the clinical importance of treatment continuity [47–49]. The association between non-fatal overdose history and lower hippocampal volume provides a rationale for examining brain outcomes along this pathway [17]. Whether treatment continuity reduces overdose-related brain injury or improves long-term functional recovery through either pathway remains to be established.

6.2. Cognitive and Functional Outcomes as Longitudinal Endpoints

A central implication of the framework is that craving and substance use should be assessed alongside cognitive performance and everyday functioning, as these domains may follow distinct trajectories. Behavioral stabilization may precede cognitive improvement, while cognitive or functional impairment may persist despite otherwise favorable treatment outcomes. Importantly, the persistence of addiction-related behaviors and the course of cognitive dysfunction should not be treated as interchangeable indicators of long-term brain consequences.

Repeated assessments of attention, memory, executive function, and everyday functioning are necessary to distinguish transient state-dependent effects, stable impairment, functional recovery, and progressive deterioration. The domain-specific timing of cognitive improvement during early opioid abstinence [40] illustrates the importance of assessment intervals. Longitudinal studies should document recent substance exposure, withdrawal symptoms, treatment status, medication dose and timing, sleep, psychiatric symptoms, and concurrent sedating medications. Practice effects should be addressed through appropriate comparison groups, alternate test forms, or reliable-change methods, since repeated testing may otherwise be misinterpreted as genuine improvement.

A prospective cohort of people with heroin use disorder could combine scheduled assessments with additional visits after naturally occurring withdrawal episodes. At each scheduled visit, participants should be asked systematically about withdrawal episodes since the previous visit. The protocol should define which episodes trigger an additional assessment and examine whether episode severity or the delay from onset to detection changes over follow-up. It should prespecify a primary cognitive domain, such as executive function, and assess everyday functioning separately. Scheduled visits would provide pre-episode measurements and help estimate changes between episodes. Post-episode visits should capture the magnitude of acute impairment and quantify the residual deficit relative to pre-episode function at a prespecified follow-up interval. This primary endpoint measures the completeness of recovery at that interval. Where post-episode assessments are sufficiently frequent, time to regain a prespecified proportion of pre-episode function could be examined as a secondary outcome. Within-person analyses should distinguish deterioration between episodes, larger acute declines, and less complete recovery after episodes of comparable severity. Separating changes associated with episode order from those associated with elapsed time requires sufficient variation in the spacing of episodes across participants. The protocol should account for practice effects, measurement reliability, and floor or ceiling effects.

For example, an index episode could begin on the first day that withdrawal following a reduction or cessation of opioid use meets prespecified criteria. In this example, the early recovery window extends from withdrawal onset to a scheduled assessment 14 days later. The protocol should prespecify the assessment interval based on the expected time course of recovery in the domain selected, because cognitive domains can improve at different rates during abstinence [40]. If opioid use resumes on day 7, the timing of resumed use would be recorded and the day-14 assessment would still be attempted. A new withdrawal episode or a major treatment change during the window would likewise be documented, and the original assessment date would be retained. The next primary recovery window could open only with a qualifying withdrawal episode that begins after the preceding window has closed. The day-14 residual deficit would quantify how far functioning remains below the pre-episode level, reflecting the course observed during the window, including any intervening events. If the scheduled assessment is missed, the residual deficit for that window is treated as missing, with any intervening events recorded separately.

Prognostic and causal analyses address different questions. Temporal exposure measures may improve prediction even if their causal effect on recovery remains uncertain. Prior functional impairment may affect subsequent treatment continuity, return to opioid use, withdrawal, and overdose, which can in turn affect later functioning. Across successive episodes, functioning after one episode may influence the likelihood or severity of the next. This creates the potential for time-varying confounding affected by prior exposure. Estimating a causal effect in this setting would require methods that account for this feedback between exposure and functioning. For causal analyses, the effect of interest should be specified before selecting adjustment variables. For example, an overdose that occurs after the exposure of interest may lie on a pathway to later impairment. Adjusting for it can remove part of the total effect under investigation. Studies should assess whether loss to follow-up is related to prior instability or impairment, and account for death as an event that precludes subsequent assessment of recovery. Analyses restricted to participants who remain alive and under observation may give a more favorable picture of recovery.

Persistent impairment alone would not substantiate neuroprogression. Evidence consistent with a neuroprogressive trajectory would require within-individual deterioration beyond measurement variability, practice effects, and age-expected change, or progressively slower or less complete recovery following successive perturbations under adequately characterized conditions. Conversely, sustained functional improvement would support recovery within the affected domains without necessarily implying normalization of the underlying molecular adaptations. Experimental findings showing that molecular normalization and persistent behavioral vulnerability may follow different temporal courses [29] illustrate the need to investigate these outcomes separately. Establishing that changes in functional recovery are specifically mediated by exposure-related molecular neuroadaptations would require additional mechanistic evidence.

6.3. Mechanistic Targets and Their Translational Limits

Two lines of experimental evidence illustrate different steps in the proposed link between exposure history and functional recovery. In mice, continuous morphine exposure and exposure interrupted by precipitated withdrawal produced distinct synaptic adaptations in the nucleus accumbens shell [25]. This finding supports the sensitivity of synaptic plasticity to exposure pattern. In rats with a history of heroin self-administration, astrocytic responses involving glutamate transporter GLT-1 helped limit cue-induced heroin seeking [31]. Whether either adaptation influences functional recovery after a subsequent perturbation remains open. A mechanistic test would establish whether a defined exposure pattern produces the candidate adaptation before the next perturbation, then determine whether selectively modifying that adaptation changes the rate or completeness of recovery. For the astrocytic pathway, recovery and heroin seeking should be measured separately to determine whether the adaptation influences both outcomes.

The therapeutic significance of these mechanisms depends on the biological process and functional outcome being targeted. Interventions that modify heroin seeking or relapse-related behavior do not necessarily prevent cognitive impairment, enhance functional recovery, or reduce susceptibility to cellular injury. These outcomes should therefore be investigated separately rather than treated as interchangeable indicators of neurobiological improvement. Moreover, the compensatory character of certain adaptations introduces an important mechanistic distinction. Astrocytic and epigenetic responses that constrain heroin seeking in experimental models [31,37] illustrate why molecular alterations cannot be classified uniformly as pathological or considered appropriate targets for suppression. Their functional effects must be established in the relevant cellular population, neu-

ral circuit, and phase of the addiction trajectory before therapeutic manipulation can be meaningfully interpreted.

Within the proposed framework, identifying a candidate therapeutic target for neuroprogressive vulnerability would require evidence extending beyond the modulation of drug-seeking behavior. Specifically, interventions should be evaluated for their ability to modify exposure-related molecular adaptations and determine whether these changes are associated with preserved function or improved recovery following subsequent perturbations. Establishing a causal contribution would require mechanistic manipulation and temporally informative assessment of both biological and functional outcomes. Similarly, peripheral biomarkers should not be interpreted as indicators of heroin-associated brain progression without validation against relevant central processes and longitudinal functional trajectories. At present, these molecular findings identify potential mechanisms for investigation rather than established interventions capable of preventing neuroprogressive dysfunction.

6.4. Predictions That Could Support or Challenge the Model

The proposed framework generates five complementary predictions addressing the contribution of exposure history, the longitudinal dynamics of functional recovery, pharmacological stabilization, molecular antecedents, and susceptibility to additional injury. Each prediction requires distinct measurements and can be challenged independently. Together, they provide a basis for distinguishing neuroprogressive vulnerability from persistent but stable dysfunction and injury-related decline. Figure 2 summarizes findings that would support or weaken each prediction. The proposed study designs are described below.

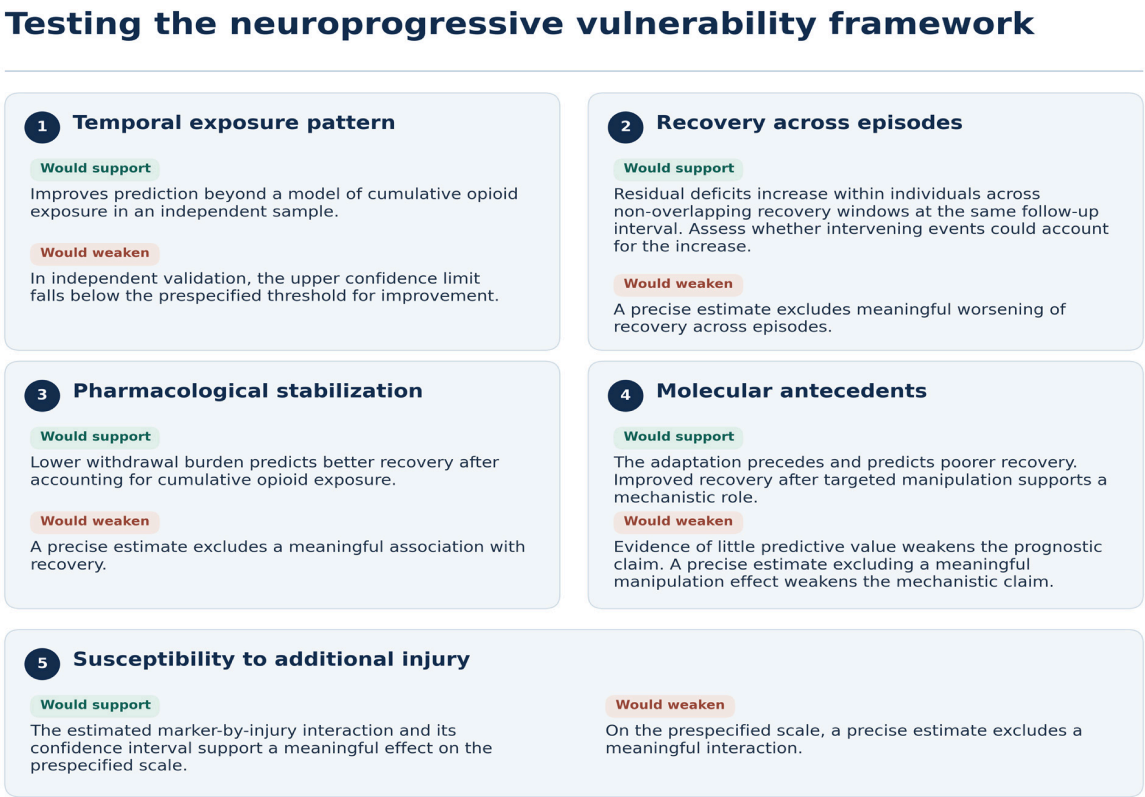

Figure 2. Five testable predictions of the neuroprogressive vulnerability framework and findings that would support or weaken each prediction. Prediction 1 provides a feasible initial test of incremental predictive value, while Prediction 2 provides the most direct clinical test of the central hypothesis. Section 6.4 describes the proposed study designs and measurements.

Temporal exposure measures should add predictive value beyond cumulative opioid exposure. In a prospective cohort of people with heroin use disorder, a model that characterizes cumulative exposure should be compared with an otherwise identical model that also includes the temporal measures defined in Section 5.2. Both models should account for baseline function and the same relevant clinical characteristics. Incremental predictive value for prespecified cognitive and everyday functioning outcomes should be assessed in an independent sample. A sensitivity analysis should repeat the same model comparison in participants or observation periods with better-characterized exposure histories, using prespecified criteria for documentation quality. Where available, pharmacy dispensing records or toxicology results can corroborate specific aspects of exposure. The analysis should report how much temporal exposure patterns vary in this subset relative to the full sample, because a narrower range could reduce the observed predictive gain.

Experimental studies of interrupted morphine exposure provide a rationale for testing this prediction [25,26]. For a continuous cognitive outcome, a study could prespecify the percentage reduction in root mean squared prediction error (RMSE) relative to the cumulative-exposure model and define the smallest improvement considered meaningful. Both models should be evaluated on the same observations in the independent validation sample. The confidence interval for the improvement should account for repeated observations within participants, where applicable. Prediction 1 would be weakened if the upper confidence limit were below the prespecified threshold for meaningful improvement. If the interval still includes a meaningful improvement, the result remains inconclusive.

Recovery may become less complete across successive exposure–withdrawal episodes. In a longitudinal cohort of people with heroin use disorder, the primary analysis should test whether the residual functional deficit at a prespecified interval after withdrawal onset increases within individuals across successive index episodes. Available fixed-interval assessments would be included regardless of intervening events. Studies should report the type and frequency of intervening events and the number of missed assessments by index episode order. If residual deficits increase across successive windows, differences in intervening events should be examined as a possible explanation. A secondary descriptive analysis could summarize recovery in uninterrupted windows, recognizing that these may preferentially represent more stable clinical courses. Pre-episode function, the magnitude of acute impairment, and withdrawal severity should be recorded to distinguish poorer recovery from larger acute declines. The primary within-person analysis should distinguish changes in recovery across successive episodes from changes associated with time since enrolment. Age at enrolment can be examined as a potential modifier of the within-person trajectory. The number of documented episodes may reflect both how often withdrawal occurs and how consistently episodes are captured. Withdrawal episodes that begin during an open recovery window are recorded as intervening events and contribute to the documented exposure history. They do not open a new primary window, so the number of index episodes may be lower than the total number of documented withdrawal episodes, especially in participants with closely spaced episodes. Studies should therefore report how many episodes were observed per participant and examine whether estimates are sensitive to incomplete episode ascertainment.

A separate analysis should assess whether a greater burden of prior exposure–withdrawal transitions is associated with worsening recovery beyond cumulative opioid exposure, taking account of ageing, treatment, and intervening injury. Candidate predictors should be prespecified and measured before the index withdrawal episode whose recovery is being assessed. Secondary analyses should distinguish predictors of poorer recovery after an episode from predictors of progressively less complete recovery across successive episodes. A pre-episode characteristic may already reflect prior opioid exposure, treatment,

or injury. Establishing that it was present before opioid exposure would require measurements obtained before exposure began. Any candidate susceptibility profile identified in these analyses would require independent validation. The framework currently has no validated markers of susceptibility. Studies should report how much the distributions of elapsed follow-up time overlap across episode orders. Where the data allow episode order to be distinguished from elapsed time, a sufficiently precise estimate that excludes a prespecified, clinically meaningful increase in residual deficit across episodes would weaken the primary prediction.

Lower withdrawal burden is expected to be associated with better subsequent functional recovery after accounting for cumulative opioid exposure. If repeated exposure–withdrawal transitions contribute to long-term vulnerability, treatment conditions that reduce physiological instability may be associated with different functional trajectories from conditions characterized by recurrent withdrawal, even after accounting for cumulative opioid exposure. This prediction should be evaluated by characterizing treatment continuity, pharmacokinetic profiles, withdrawal symptoms, and concomitant substance use rather than assuming that particular medications produce constant receptor activation. Comparisons involving longer-acting opioid agonist regimens may be informative, but differences in pharmacodynamics, clinical severity, treatment setting, and exposure history must be addressed. Supervised diacetylmorphine administration cannot be equated with continuous opioid exposure solely because it occurs under controlled conditions, given its rapid metabolism and administration-dependent concentration profiles [50]. If indices of physiological stabilization do not predict subsequent trajectories independently of other exposure characteristics, the proposed contribution of stabilization would be weakened. No neuroprotective effect of any specific treatment is presumed.

Molecular alterations should predict subsequent functional trajectories rather than merely accompany impairment. If exposure-related molecular adaptations contribute to reduced recovery capacity, relevant biological changes should precede and predict subsequent functional deterioration or incomplete recovery. Human post-mortem transcriptomic and proteomic studies identify candidate pathways involving cellular stress, mitochondrial function, and neuroimmune signaling [23,33], but cannot establish their temporal relationship with functional outcomes and are constrained by overdose-related circumstances. Experimental models with controlled exposure histories and repeated molecular and functional assessments are therefore needed to determine whether candidate alterations precede adverse trajectories and whether their manipulation modifies subsequent recovery. Longitudinal human studies using appropriately validated biomarkers may provide complementary evidence. Associations restricted to terminal tissue or concurrent with established impairment would be insufficient to establish a mechanistic contribution to neuroprogression.

Pre-existing neuroadaptations should modify susceptibility to additional injury if a multi-hit mechanism operates. The association between non-fatal overdose history and lower hippocampal volume [17] motivates investigation of whether exposure-related biological characteristics influence the consequences of subsequent hypoxic insults. This hypothesis requires measurements obtained before a documented injury, followed by assessment of its functional and biological consequences. Evidence of effect modification, beyond the independent contributions of exposure history and injury, would support the proposed interaction, although causal interpretation would require control of confounding and consideration of the scale of interaction. Studies should report the estimated interaction, its confidence interval, and the scale on which it was evaluated. A sufficiently precise estimate that excludes a prespecified, meaningful interaction would weaken the multi-hit hypothesis for the markers, injury, and outcome studied. An imprecise estimate would

leave the question unresolved. Controlled experiments could provide complementary evidence by testing whether prior opioid exposure modifies the functional response to a standardized insult.

Prediction 1 is prognostic and tests whether temporal exposure measures add predictive value beyond cumulative opioid exposure. Prediction 2 is descriptive and associational: it characterizes within-person changes in recovery across episodes and examines their relationship with prior exposure–withdrawal history. Prediction 3 is associational and tests whether lower withdrawal burden is linked to better subsequent functional recovery after accounting for cumulative opioid exposure. A causal test of Prediction 3 would require a defined intervention and an appropriate study design. Prediction 4 has a prognostic component in longitudinal human studies and a causal component in experiments that manipulate the candidate adaptation. Prediction 5 examines effect modification on a prespecified scale by testing whether the association between injury and subsequent functioning varies with a characteristic measured before injury.

A feasible first step is to establish whether temporal exposure measures improve prediction beyond cumulative opioid exposure (Prediction 1). Repeated within-person assessment of recovery after documented withdrawal episodes is the most direct clinical test of the central hypothesis (Prediction 2), although it requires more intensive follow-up. Studies of treatment continuity and withdrawal burden could address pharmacological stabilization alongside these efforts (Prediction 3). In parallel, controlled experiments can test whether candidate molecular adaptations precede and influence recovery (Prediction 4). Testing whether pre-existing adaptations modify the consequences of a subsequent injury requires measurements obtained before the injury and is a longer-term priority for human studies (Prediction 5).

6.5. What Is Already Defensible in Clinical Practice

Although the neuroprogressive vulnerability hypothesis remains untested, several clinical considerations are supported by existing evidence and do not depend on its confirmation. First, overdose history should be systematically documented, including the occurrence of non-fatal events, given their potential association with hypoxic brain injury and the reported relationship between previous overdose and lower hippocampal volume [17]. This association does not establish that overdose caused the observed structural differences, but it supports considering such events when interpreting cognitive and neuroimaging findings. The clinical importance of preventing overdose is independently supported by evidence concerning treatment continuity and overdose-related risk [48,49].

Second, cognitive assessment should be interpreted in relation to the clinical state in which it is performed. Domain-specific improvements observed during early opioid abstinence [40] indicate that a single assessment conducted during withdrawal or shortly after cessation may not reliably characterize longer-term cognitive functioning. When clinically appropriate, repeated evaluation under adequately documented conditions may help distinguish transient impairment from more persistent difficulties. Treatment status, recent substance exposure, withdrawal symptoms, and medications with potential cognitive effects should therefore be considered when interpreting performance.

Finally, cognitive impairment represents a clinically relevant dimension of heroin use disorder, irrespective of whether it reflects premorbid susceptibility, exposure-related neuroadaptation, treatment effects, or additional injury [4,13,40]. Difficulties involving attention, memory, and executive functioning may influence patients' ability to engage with and follow treatment, although the extent of these effects requires individual assessment. Recognizing such difficulties can inform clinical evaluation and the adaptation of care to individual functional needs without presuming progressive deterioration. These

considerations are justified by existing clinical evidence and do not require acceptance of the proposed neuroprogressive mechanism.

7. Conclusions

Experimental studies show that the temporal pattern of morphine exposure can shape synaptic and dopaminergic adaptations [25,26] and that specific heroin-associated adaptations can influence drug seeking [29,31,37]. Human studies document brain alterations and changes in cognition or brain measures during treatment and abstinence [5,14,15,19,23,33,40]. The central hypothesis remains untested in humans: repeated heroin exposure–withdrawal transitions may be associated with progressively less complete functional recovery across successive episodes after accounting for cumulative opioid exposure. Testing this hypothesis requires longitudinal within-person assessments that distinguish worsening recovery from larger acute declines and discrete acquired injuries. Establishing a molecular contribution would additionally require evidence that candidate adaptations precede and influence subsequent recovery.

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Abbreviations

The following abbreviations are used in this manuscript:

Abbreviation	Definition
CRF	Corticotropin-releasing factor
CRF1	Corticotropin-releasing factor receptor 1
CRF2	Corticotropin-releasing factor receptor 2
GLT-1	Glutamate transporter 1
HDAC5	Histone deacetylase 5
HUD	Heroin use disorder
MSN	Medium spiny neuron
NAc	Nucleus accumbens
OFC	Orbitofrontal cortex
OUD	Opioid use disorder
SCN1b	Sodium voltage-gated channel beta subunit 1

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