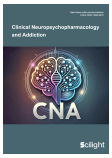
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Review

Stress-Driven Brain Remodeling in Opioid Use Disorder: Toward a Neuroprogressive Model

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Abstract: Background: Opioid use disorder (OUD) is classically understood through reward dysregulation, opponent processes, and allostatic adaptation, but these models only partly account for the persistent cognitive, affective, and stress-regulatory abnormalities observed in some individuals with long-standing OUD. Methods: This Perspective integrates human evidence from neuroendocrinology, neuroimaging, and neurocognitive research with mechanistic findings from preclinical opioid-exposure and withdrawal models. Throughout the revised framework, direct evidence in humans is distinguished from cross-species mechanistic inference. Results: Repeated opioid exposure induces neuroadaptations that initially compensate for persistent pharmacological perturbation. When exposure is prolonged and accompanied by recurrent intoxication-withdrawal cycling, these adaptations may become increasingly maladaptive and interact with repeated stress-system destabilization. Human studies document abnormalities in hypothalamic-pituitary-adrenal (HPA) axis regulation, brain structure and connectivity, and executive-cognitive functioning in OUD, whereas preclinical studies provide plausible mechanisms involving glucocorticoid and extrahypothalamic corticotropin-releasing factor (CRF) signaling, noradrenergic and dynorphin systems, synaptic plasticity, neuroimmune activation, and cellular stress. We propose a staged continuum from neuroadaptation to maladaptive brain remodeling and, potentially, neuroprogression. At the advanced end of this continuum, we describe a provisional neuroprogressive phenotype characterized by persistent multidomain dysfunction in stress regulation, cognitive-executive processing, affective regulation, and behavioral control beyond acute intoxication or withdrawal in a vulnerable subset of individuals with OUD. Conclusions: The proposed neuroprogressive model defines a testable hypothesis in which cumulative opioid exposure and recurrent withdrawal-related stress burden may contribute to persistent loss of adaptive capacity. Treatment-related stabilization and partial recovery are incorporated into the model, but disease-modifying effects of opioid agonist treatment remain to be demonstrated prospectively. Longitudinal multimodal studies are required to establish the existence, boundaries, prevalence, reversibility, and clinical utility of the proposed phenotype.

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Keywords: opioid use disorder; stress-system dysregulation; neuroadaptation; neuroprogression; brain remodeling; allostatic load

1. Introduction

1.1. From Reward Dysregulation to a Neuroprogressive Hypothesis

Opioid use disorder (OUD) has traditionally been conceptualized through the reinforcing actions of opioids within mesocorticolimbic reward circuitry and the progressive recruitment of motivational and habit systems. This framework remains fundamental for explaining acute reinforcement and the transition toward compulsive drug seeking [1–3]. The subsequent allostatic model substantially extended this account by showing how repeated drug exposure recruits brain stress and anti-reward systems, shifts behavior from positive toward negative reinforcement, and increases vulnerability to withdrawal-related dysphoria and stress-induced relapse [4–6].

These models nevertheless leave an important clinical question incompletely resolved. A subset of individuals with long-standing OUD exhibits persistent deficits in executive functioning, decision-making, cognitive flexibility, emotional regulation, and stress responsiveness that may remain detectable beyond acute intoxication or withdrawal [7–10]. Structural and functional neuroimaging studies likewise report abnormalities involving prefrontal, striatal, limbic, thalamic, and medial temporal systems, with some findings associated with duration or severity of opioid exposure [11–13]. These observations do not establish a progressive causal process: much of the available human literature is cross-sectional and is potentially influenced by premorbid vulnerability, polysubstance use, psychiatric and medical comorbidity, socioeconomic adversity, and treatment history. They do, however, justify asking whether transient neuroadaptation is sufficient to explain the longer-term phenotype of severe OUD.

The present Perspective addresses this question by focusing on a distinctive feature of opioid dependence: repeated alternation between opioid-induced stress dampening and withdrawal-related stress activation. Particularly with short-acting opioids, recurrent intoxication-withdrawal cycling may expose the organism to repeated neuroendocrine and extrahypothalamic stress-system perturbations superimposed on opioid-specific receptor, intracellular, and synaptic adaptations [14–16]. We therefore examine whether two partly separable forms of biological burden—repeated opioid-related neuroadaptation and recurrent stress-regulatory destabilization—may converge over time to reduce neural flexibility and resilience. This proposition extends, rather than replaces, established reward and allostatic models of addiction.

1.2. From Neuroadaptation to Neuroprogression: A Staged Conceptual Continuum

To avoid conflating adaptation with damage, we distinguish four conceptual levels. Neuroadaptation refers to molecular, cellular, synaptic, and circuit-level adjustments that arise in response to repeated opioid exposure and initially allow neural systems to function in the presence of persistent pharmacological perturbation. These processes include opioid-receptor and intracellular signaling adaptations, tolerance-related changes, altered synaptic plasticity, and opponent-process responses [3,17,18]. Neuroadaptation is not inherently pathological and may remain substantially reversible.

Maladaptive brain remodeling denotes the stage at which initially compensatory changes become increasingly persistent or functionally disadvantageous, contributing to impaired regulation of stress, reward, affect, or executive control. In OUD, such remodeling may involve abnormal glucocorticoid feedback, extrahypothalamic CRF and noradrenergic recruitment, dynorphin-mediated anti-reward signaling, altered synaptic plasticity, and changes in corticolimbic and frontostriatal organization [3,19]. Because current human evidence demonstrates biological reorganization more convincingly than irreversible tissue damage, the term remodeling is preferred to injury throughout this Perspective, except where direct evidence of injury is available.

Neuroprogression is used here in a more specific temporal sense: a hypothesized process through which repeated opioid-related and stress-related perturbations become cumulatively embedded across neuroendocrine, molecular, cellular, and network levels, producing increasingly persistent abnormalities and a progressive reduction in the capacity for flexible adaptation and recovery. This use is consistent with broader neuroprogressive frameworks in chronic psychiatric illness, while recognizing that the complete causal sequence has not been demonstrated longitudinally in human OUD [19–22]. Neuroprogression therefore describes a possible trajectory, not an inevitable outcome.

At the advanced end of this proposed continuum, we describe a provisional neuroprogressive phenotype characterized by persistent multidomain dysfunction in a subset of individuals with long-standing OUD. We use the term neuroprogressive cerebropathy only as a descriptive label for this putative brain-based clinical-functional

expression. Its conceptual role is distinct from that of neuroprogression: neuroprogression refers to the hypothesized temporal process through which abnormalities become increasingly persistent, whereas cerebropathy refers to the phenotype that might emerge if that process reaches a clinically meaningful level of multidomain dysfunction. A related heuristic use of the cerebropathy concept has recently been proposed in chronic cocaine exposure [23]. The term is not intended to define a new diagnostic entity and does not imply acute or subacute encephalopathy, dementia, inevitable neuronal loss, or equivalence with classical neurodegenerative disorders. Its existence, boundaries, prevalence, biological correlates, and clinical validity remain to be established prospectively. The distinctions among these concepts are summarized in Table 1.

Table 1. Operational distinctions among the central concepts used in this Perspective.

Concept	Working Definition in This Perspective	Interpretive Boundary/Evidentiary Status
Neuroadaptation	Molecular, cellular, synaptic, and circuit adjustments induced by repeated opioid exposure that support function in the presence of continued pharmacological perturbation	Established adaptive response. It is not inherently pathological and does not by itself imply tissue injury
Maladaptive brain remodeling	Persistent or functionally disadvantageous reorganization affecting stress, reward, affective, or executive regulation	Supported by convergent human and preclinical evidence, although its temporal and causal organization remains unproven. The term emphasizes altered organization rather than proven irreversible damage
Neuroprogression	A hypothesized temporal process in which opioid- and stress-related perturbations become cumulatively embedded, with increasing persistence and reduced capacity for adaptation or recovery	A trajectory hypothesis, not a fixed stage or inevitable outcome. It does not require progressive neuronal loss
Advanced neuroprogressive phenotype (“neuroprogressive cerebropathy”)	A provisional clinical-functional phenotype in a subset of individuals with long-standing OUD, characterized by persistent multidomain dysfunction outside acute intoxication or withdrawal	A research construct, not a diagnostic entity. The term “cerebropathy” is used descriptively to emphasize the multidomain, brain-based expression of the proposed phenotype; it does not imply acute encephalopathy, dementia, irreversible neuronal loss, or classical neurodegeneration

This formulation also makes heterogeneity and reversibility integral to the model. The proposed trajectory is likely to depend on cumulative opioid exposure and the recurrence of withdrawal, while treatment stability may substantially change the biological context in which these processes unfold. Trauma, polysubstance use, psychiatric or medical comorbidity, and age-related vulnerability may further influence persistence or recovery [9,10,24]. Longitudinal imaging studies indicate that at least some frontostriatal and white matter abnormalities can change during sustained abstinence or treatment, supporting partial biological recovery as a plausible component of the disease course [25,26]. The extent and determinants of recovery remain empirical questions central to testing the model.

1.3. Scope and Evidentiary Approach

This Perspective integrates evidence across stress neurobiology, addiction neuroscience, neuroendocrinology, neuroimmunology, neuroimaging, and neurocognition to evaluate whether chronic OUD may follow a trajectory from opioid-specific neuroadaptation toward maladaptive remodeling and, in a vulnerable subgroup, a persistent neuroprogressive phenotype. Particular emphasis is placed on opioid-specific neuroendocrine dynamics and recurrent intoxication-withdrawal cycling, because these constitute the most direct mechanistic basis for the stress-driven hypothesis advanced here. Human OUD findings are prioritized when available; preclinical opioid-exposure and withdrawal models are used to examine biological mechanisms that cannot currently be established directly in humans, and cross-substance evidence is treated as analogical rather than opioid-specific support.

Literature identification approach. This Perspective was developed through targeted narrative searches of PubMed/MEDLINE, supplemented by backward citation tracking from key reviews and primary studies and by screening the authors’ existing reference libraries. No lower publication-date limit was imposed, and searches were updated through July 2026. Literature identification focused on three interconnected domains: opioid exposure, withdrawal, and agonist treatment; neuroendocrine and extrahypothalamic stress regulation; and persistent molecular, neuroimaging, and neurocognitive alterations relevant to neuroadaptation and neuroprogression.

Priority was given to human OUD studies and longitudinal evidence, while recent high-quality reviews were used to contextualize established mechanisms and preclinical studies were retained when they directly addressed opioid exposure or withdrawal. Because the aim was hypothesis-generating narrative synthesis rather than systematic review, no PRISMA-based screening or meta-analytic selection procedure was applied.

The review evaluates whether recurrent intoxication-withdrawal stress adds a cumulative biological burden to opioid-specific neuroadaptation and whether their convergence may contribute to a neuroprogressive trajectory. It then considers how a putative neuroprogressive phenotype could be operationalized, distinguished from acute drug effects and major confounders, and tested for modification during stable treatment. OUD is not treated here as an established neurodegenerative disease, and cumulative brain dysfunction is not assumed to be inevitable. The framework is intended to generate longitudinal, multimodal tests of persistence, reversibility, staging, and treatment response.

2. Stress and Allostasis in Addiction: Essential Conceptual Background

2.1. Stress Regulation, Brain Stress Systems, and Allostasis

The hypothalamic-pituitary-adrenal (HPA) axis provides the principal endocrine response to stress. Hypothalamic corticotropin-releasing factor (CRF) and arginine vasopressin stimulate pituitary adrenocorticotropic hormone (ACTH) release, followed by adrenal cortisol secretion. Cortisol then acts through mineralocorticoid and glucocorticoid receptors to regulate the magnitude and termination of the response. This feedback operates within a circadian and ultradian architecture that is important for metabolic, cognitive, and emotional regulation [27–30]. The relevance of this system to addiction lies less in absolute cortisol concentrations than in the capacity to generate appropriately timed responses and to recover efficiently after challenge.

Stress regulation also depends on extrahypothalamic circuits that influence arousal, affective salience, and behavioral selection. CRF signaling within the central amygdala (CeA) and bed nucleus of the stria terminalis (BNST) interacts closely with locus coeruleus norepinephrine output, creating reciprocal pathways through which emotional and autonomic responses can be amplified during threat [6,31]. These systems have nonlinear effects on cortical function. Moderate catecholaminergic and glucocorticoid activation can support attention and adaptive responding, whereas sustained or excessive activation degrades prefrontal network function and favors more reactive forms of behavioral control [19,32,33]. This loss of regulatory precision becomes particularly relevant when stress responses are repeatedly coupled to drug exposure and withdrawal.

The dynorphin-kappa opioid receptor (KOR) system provides a complementary link between stress and reward. Stress-related dynorphin release can reduce mesolimbic dopamine signaling and increase dysphoric or aversive states, thereby contributing to the anti-reward processes that become prominent during dependence [34–36]. Endogenous resilience systems counterbalance this recruitment. Neuropeptide Y (NPY) and endocannabinoid signaling, for example, constrain excessive stress activation and support recovery after challenge [37,38]. Their importance in the present framework is functional: chronic addiction may involve both increased recruitment of stress-promoting pathways and reduced effectiveness of systems that normally restore regulatory stability.

These interactions are captured by the concepts of allostasis and allostatic load. Allostasis describes the adjustment of physiological systems to changing demands; repeated adjustment carries a biological cost when activation becomes frequent, prolonged, or poorly terminated [39,40]. In the brain, chronic stress can alter glucocorticoid signaling, synaptic plasticity, and the organization of circuits involved in emotion and executive control [19]. The resulting state is therefore better understood as reduced regulatory flexibility than as uniformly increased stress activity. This distinction is central to addiction, where tonic stress burden, phasic responses, and recovery dynamics may become dissociated as exposure becomes chronic.

2.2. Stress Recruitment Across the Addiction Cycle

Stress is mechanistically integrated into the addiction cycle. Psychosocial adversity increases craving and relapse vulnerability, while repeated drug exposure changes the sensitivity of stress and motivational systems. Contemporary models therefore describe addiction as a dynamic interaction between reward, stress, learning, and executive-control processes rather than as an isolated disturbance of mesolimbic reinforcement [3,41,42]. The three-stage framework of binge/intoxication, withdrawal/negative affect, and preoccupation/anticipation is useful because the contribution of stress changes across the course of addiction.

During binge/intoxication, behavior is still dominated by positive reinforcement and drug-associated learning. Reward-related signals within ventral striatal circuitry increase the motivational value of drug cues and strengthen associations between internal or environmental states and subsequent drug use [3,43]. Stress mediators can facilitate salience attribution and reinforcement learning, particularly when drug exposure occurs during

emotional or physiological arousal [44,45]. This principle is supported largely by cross-substance and experimental stress research and should not be assumed to imply a uniform endocrine response across drug classes. Opioids are especially relevant in this respect because acute mu-opioid receptor activation typically suppresses HPA-axis and noradrenergic stress signaling, a pharmacological feature considered specifically in Section 4.

With repeated exposure, withdrawal/negative affect becomes increasingly important. Recruitment of CRF, noradrenergic, and dynorphin systems within the extended amygdala contributes to dysphoria, anxiety-like states, and reduced reward sensitivity during drug discontinuation [6,34,46]. Drug taking consequently acquires greater value as a means of terminating or preventing an aversive internal state. This shift toward negative reinforcement is particularly relevant to opioids because withdrawal follows a period of pharmacological suppression of stress and arousal systems. Repeated transitions between these opposing states may therefore impose a distinctive regulatory burden that is not fully captured by models derived from substances that acutely activate the HPA axis.

During preoccupation/anticipation, stress-related vulnerability persists outside the immediate withdrawal state. Laboratory and ecological studies show that psychosocial stress and negative affect can increase craving and predict subsequent drug use, while conditioned cues retain the capacity to engage motivational circuitry after periods of abstinence [41,47]. At the same time, impaired prefrontal regulation reduces the ability to disengage from learned drug-related responses [3,7]. Relapse vulnerability therefore reflects the interaction of sensitized motivational responses with weakened regulatory control, rather than a single endocrine or subjective state.

This stage-dependent framework also clarifies the role of craving. Craving can accompany stress-system activation, cue exposure, or withdrawal, but it does not provide a complete measure of the underlying biological state. Stress-related alterations can remain detectable when subjective craving is modest, and relapse may occur through processes that are only partly represented in conscious urge ratings [41,48]. This distinction becomes important later in the review when neuroendocrine stabilization is considered as a treatment-relevant outcome that may not parallel craving reduction in a simple manner.

2.3. Stress, Behavioral Control, and the Transition to Compulsivity

Repeated drug use also changes the systems that govern action selection. As drug-related behaviors become extensively learned, control may shift toward dorsal striatal and stimulus-response mechanisms, while prefrontal systems that support flexible evaluation and inhibitory control become less effective [3,49]. Stress can facilitate this shift: glucocorticoid and noradrenergic activation biases behavior toward previously learned responses and reduces reliance on flexible goal-directed strategies, particularly when cognitive control is already compromised [33,50]. Habitual control should not be treated as a complete explanation of addiction, since persistent drug choice can also remain goal directed under negative affect; rather, it represents one mechanism through which stress and repeated learning may narrow the behavioral repertoire [51].

Clinically, these processes may be reflected in a gradual change in the function of opioid use. Early use is more strongly organized around reward and immediate relief. Established dependence increasingly links opioid taking to avoidance of withdrawal, control of dysphoric arousal, and restoration of a subjectively tolerable internal state. In later stages, cue reactivity and stress sensitivity coexist with reduced behavioral flexibility, allowing drug seeking to recur even when the individual recognizes its adverse consequences [41,46]. These processes remain heterogeneous across patients and can improve with sustained treatment, but they provide a coherent behavioral expression of progressively embedded stress-reward adaptations.

The general stress-recruitment model establishes the conceptual background for the opioid-specific mechanisms examined in the following sections. Its application to OUD requires attention to opioid pharmacology. Acute opioid exposure suppresses several components of the stress response, chronic receptor stimulation produces specific compensatory adaptations, and withdrawal reverses that suppression through marked neuroendocrine and extrahypothalamic activation. The resulting intoxication-withdrawal cycle is summarized in Figure 1. Repeated opioid neuroadaptation and recurrent withdrawal-related stress may then converge over time to favor maladaptive brain remodeling and, in a vulnerable subgroup, a neuroprogressive trajectory.

Repeated short-acting opioid exposure alternates acute MOR-mediated reward and stress dampening with falling opioid levels and withdrawal-related HPA-axis and central stress recruitment. Withdrawal-related negative affect may promote craving and re-use through negative reinforcement, re-establishing the cycle. Solid arrows depict the recurrent state sequence; dashed connections indicate the proposed cumulative contribution of repeated cycling to allostatic burden and reduced regulatory flexibility.

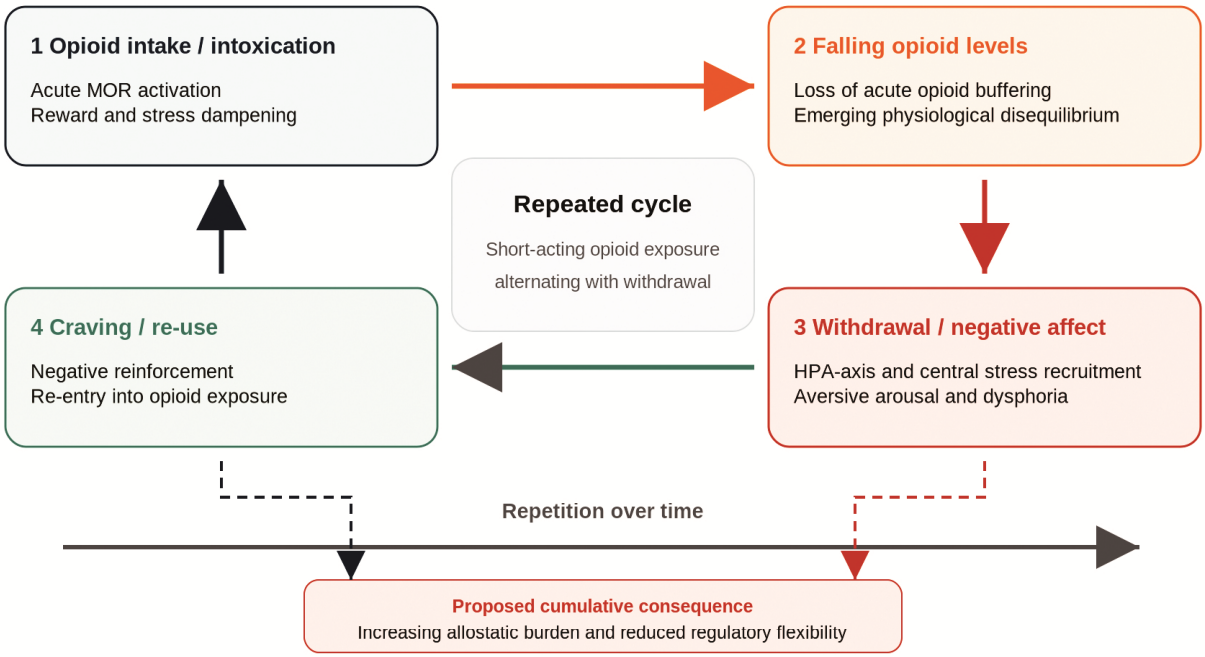


Figure 1. Opioid intoxication-withdrawal cycling and recurrent stress-system recruitment.

3. Opioid-Specific Molecular and Circuit-Level Neuroadaptations

3.1. Acute Opioid Action on Reward and Arousal Circuits

Opioid reinforcement is initiated primarily through mu-opioid receptor (MOR) signaling in circuits that regulate reward and arousal. In preclinical models, MOR activation on GABAergic interneurons in the ventral tegmental area disinhibits dopamine neurons and increases dopamine transmission in the nucleus accumbens, providing a well-established cellular mechanism for opioid reinforcement [52]. MOR activation also suppresses locus coeruleus firing and noradrenergic output, contributing to sedation, autonomic slowing, and rapid relief from arousal [53]. These effects may reinforce heroin use through reward as well as rapid relief of aversive internal states.

Repeated exposure changes the response to subsequent opioid administration. Acute modulation of neurotransmission is progressively accompanied by compensatory changes within opioid-sensitive neurons and connected circuits, establishing the substrate for tolerance and dependence [17,18]. This opioid-specific neuroadaptation can be considered separately from the neuroendocrine consequences of opioid exposure for analytical purposes, although the two processes interact throughout the development of dependence. The stress-related component is examined in Section 4.

3.2. Chronic MOR-Driven Neuroadaptation and Tolerance Mechanisms

Repeated MOR stimulation produces tolerance through receptor- and cell-specific changes in signaling. Experimental studies describe receptor phosphorylation and desensitization, altered receptor trafficking, and compensatory regulation of adenylyl cyclase, cAMP, PKA, and CREB pathways [17,18]. The expression of these adaptations varies across neuronal populations and opioid agonists, so clinical tolerance should not be reduced to a single molecular mechanism. Direct evidence for these intracellular processes in living patients with OUD remains limited; their mechanistic characterization derives predominantly from cellular and animal studies.

The locus coeruleus provides a particularly clear example of compensatory adaptation. Chronic opioid-mediated inhibition is followed by intracellular changes that become evident when agonist tone declines, producing increased noradrenergic activity during withdrawal [18,53]. This adaptation contributes to autonomic hyperarousal and strengthens the motivational significance of renewed opioid use. Parallel changes in opioid-sensitive reward systems reduce responsiveness to non-drug reinforcement and facilitate recruitment of anti-reward signaling as dependence becomes established [34]. These processes remain neuroadaptations in the strict sense: they alter the operating conditions of reward and arousal circuits without, by themselves, demonstrating irreversible neural injury.

3.3. Opioid-Evoked Synaptic Plasticity and Behavioral Control

Repeated opioid exposure also changes synaptic efficacy beyond canonical receptor tolerance. Preclinical work has documented persistent alterations in excitatory transmission and plasticity across circuits involved in

reward learning and behavioral inhibition [18]. Recent longitudinal experiments in heroin self-administering mice identified MOR-dependent weakening of a paraventricular thalamus-to-nucleus accumbens inhibitory circuit across the development of heroin seeking; experimentally restoring this circuit reduced reinstatement triggered by several relapse-related challenges [54]. These findings provide direct evidence that heroin may induce persistent, behaviorally relevant circuit plasticity, while their translation to human OUD remains to be established.

Human evidence for altered neural plasticity is less direct. In a TMS-EEG study, participants with heroin-related substance use disorder showed altered cortical responses to an rTMS plasticity paradigm relative to healthy controls [55]. Similar abnormalities were observed in the methamphetamine group, limiting opioid-specific interpretation; however, the study supports the presence of altered inducible cortical plasticity in people with heroin-related disorder. Clinically, OUD is also associated with impaired cognitive flexibility and inhibitory control, although cross-sectional human studies are not capable of determining how much of this impairment reflects opioid exposure, premorbid vulnerability, comorbidity, or other aspects of the addiction trajectory [9].

Direct opioid-related neuroadaptation and stress-system recruitment are therefore best understood as interacting processes rather than successive stages. Receptor tolerance and synaptic plasticity develop while repeated withdrawal begins to recruit neuroendocrine and extrahypothalamic stress systems. Their convergence may progressively reduce behavioral flexibility and increase reliance on opioid-mediated relief. In the framework developed here, opioid-specific neuroadaptation provides one component of the biological substrate, while recurrent stress-system destabilization provides a second potential source of cumulative burden. The following section examines this stress-related process in detail.

4. Opioid-Specific Neuroendocrine Dysregulation and Pathological Allostasis

4.1. Acute Opioid Suppression of Stress Signaling

Opioids have a distinctive acute neuroendocrine profile. In humans, mu-opioid receptor agonism generally suppresses hypothalamic-pituitary-adrenal (HPA) axis activity by reducing hypothalamic and pituitary drive, with subsequent decreases in ACTH and cortisol secretion [56–58]. This inhibitory effect has been documented after heroin and other opioid agonists and is consistent with the broader endocrine consequences of sustained exogenous opioid exposure [14,59–61]. The magnitude of suppression varies with compound, dose, opioid tolerance, and the endocrine state in which the drug is administered.

The acute endocrine response is clinically relevant because opioid administration can dampen stress-related affective and neural responses at the same time. In heroin-dependent participants, acute opioid exposure has been associated with lower salivary cortisol and reduced subjective stress, together with decreased amygdala reactivity [14,62]. These findings support a stress-relief component of opioid reinforcement: opioid effects can reduce physiological arousal and the aversive value of distress, increasing the reinforcing value of drug taking when stress or negative affect is prominent [53]. This interpretation complements reward-based accounts without requiring that stress suppression account for opioid reinforcement in every individual or phase of OUD.

Acute HPA suppression should therefore be treated as a state-dependent pharmacological effect. It does not imply chronically low stress-system activity in established OUD. Repeated exposure introduces tolerance, altered basal endocrine organization, and episodes of withdrawal-related activation, producing a neuroendocrine profile that becomes increasingly dependent on treatment status and recent opioid history [58,63].

4.2. Chronic Exposure and Withdrawal-Related Neuroendocrine Instability

Long-term opioid exposure may disrupt the temporal organization of HPA-axis function. Altered circadian profiles and abnormalities of basal cortisol regulation have been reported in chronic heroin users and in opioid-treated populations [57,64–66]. Clinically significant opioid-induced adrenal insufficiency also occurs in a subset of people exposed to long-term opioids [58,63]. Much of the adrenal-insufficiency literature derives from patients receiving prescribed opioids for chronic pain, so its prevalence and clinical expression should not be transferred directly to OUD. It nevertheless establishes that sustained opioid receptor stimulation may alter human HPA physiology beyond the immediate period of intoxication.

Withdrawal produces a different endocrine state. Human studies of spontaneous or antagonist-precipitated withdrawal have demonstrated ACTH and cortisol activation, although the magnitude and time course vary across study designs and treatment conditions [15,61,67–69]. HPA activation can precede overt somatic withdrawal signs, indicating that endocrine recruitment forms part of the withdrawal process itself [67]. More recent human data reinforce the close coupling between endocrine state and withdrawal severity. During a controlled buprenorphine taper, greater total daily cortisol was associated with more severe opioid withdrawal, while self-reported stress tracked both withdrawal and craving [70].

The central stress response to withdrawal is characterized most clearly in preclinical models. Morphine or heroin withdrawal recruits CRF signaling within the extended amygdala and alters noradrenergic activity in the CeA and BNST [16,71–73]. Dynorphin-KOR signaling contributes to withdrawal-related dysphoria and reward deficits, while local CRF and NPY systems influence the balance between stress amplification and recovery [16,74–76]. These experiments provide mechanistic resolution that is currently unavailable in living humans, and their relevance to human OUD should be interpreted as translational rather than direct evidence.

Repeated withdrawal is especially relevant to the present model because some stress-related adaptations outlast the acute syndrome in animals. Persistent abnormalities in endocrine responsivity and affective circuitry have been observed after chronic opioid exposure and withdrawal [77–81]. GR-dependent plasticity within the CeA provides one candidate mechanism for such persistence: corticosteroid signaling during withdrawal can recruit steroid receptor coactivator-1e and enhance CRF-related transcription, with subsequent effects on opioid-seeking behavior [82]. Other experimental studies identify enduring changes in amygdala circuitry after opioid withdrawal [16,83,84].

The human evidence does not yet establish that successive withdrawal episodes accumulate linearly to produce lasting neural damage. A narrower conclusion is supported: withdrawal repeatedly couples opioid deprivation to neuroendocrine and central stress activation, and experimental models show that some resulting adaptations persist beyond acute abstinence. This makes recurrent withdrawal a plausible source of cumulative stress burden and a testable component of the neuroprogressive hypothesis developed later in this Perspective.

4.3. GR/MR Dysregulation and Extrahypothalamic CRF Recruitment

The transition from episodic HPA activation to more persistent dysregulation is likely to depend on changes in corticosteroid feedback and region-specific stress circuitry. Mineralocorticoid receptors (MRs) contribute to basal HPA tone and response thresholds, whereas glucocorticoid receptors (GRs) become increasingly engaged as cortisol rises and participate in feedback termination and post-stress recovery [27,29,85]. Repeated exposure to atypical cortisol patterns may modify receptor sensitivity and downstream transcriptional responses, thereby reducing the fidelity with which future stress responses are initiated and terminated [19,86].

Direct evidence for GR/MR remodeling in human OUD remains limited. The mechanistic case relies mainly on opioid-withdrawal models and on broader stress biology. Chronic opioid exposure has been associated experimentally with changes in corticosteroid receptor signaling and with GR-dependent adaptations that influence withdrawal-related behavior [82,87,88]. These findings support a mechanism through which recurrent endocrine perturbation could become biologically embedded, but they do not establish a uniform receptor phenotype in people with OUD.

A parallel reorganization occurs within extrahypothalamic CRF systems. Experimental opioid studies describe region-specific changes in CRF activity or receptor signaling in the CeA, BNST, and dorsal raphe [71,89–91]. Glucocorticoid control of CRF is itself anatomically differentiated: negative feedback restrains hypothalamic CRF, whereas glucocorticoid signaling can enhance CRF expression within the amygdala under some conditions [92,93]. Repeated withdrawal could therefore produce distinct endocrine and limbic adaptations rather than a single global increase or decrease in stress-system activity.

Endogenous opioid tone adds another regulatory layer. Physiologically, opioid signaling constrains hypothalamic CRF and locus-coeruleus noradrenergic output; the ACTH and cortisol response elicited by naloxone or naltrexone provides a functional demonstration of this inhibitory tone in humans [56,94–96]. Chronic exogenous opioid exposure may reduce the effectiveness of this stress-buffering function through tolerance within opioid-sensitive circuits [53,97]. This mechanism remains inferential in OUD, but it offers a coherent explanation for why transient opioid-induced stress relief may coexist with vulnerability to stress when drug levels fall or external challenges occur.

Human laboratory findings are consistent with such state dependence. Individuals with OUD may retain acute opioid-induced cortisol suppression while showing altered endocrine or motivational responses to experimentally induced stress [62,98]. In buprenorphine-stabilized participants, combined noradrenergic and glucocorticoid stimulation shifted behavior toward opioid seeking as a function of basal cortisol level, demonstrating that tonic HPA activity can modify the behavioral impact of an acute stress challenge [99]. These data favor a model of dysregulated coordination among basal tone, pharmacological suppression, and stress-evoked responses.

4.4. Neuroendocrine Tolerance and the Pathological Stress Set Point

Neuroendocrine tolerance provides a useful framework for integrating these observations. The term describes an acquired change in stress-system regulation in which repeated drug-related perturbation alters basal tone, phasic

reactivity, or feedback control. This concept has been developed most extensively in alcohol and general addiction research [100,101]; its application to OUD is therefore partly analogical. Opioid-specific studies nevertheless show the constituent features required by the model: acute HPA suppression, withdrawal-related activation, altered basal cortisol in some cohorts, and treatment- or state-dependent responses to stress challenges [62,99,102,103].

The resulting phenotype should not be reduced to either hypercortisolism or hypocortisolism. Basal cortisol findings in OUD and during opioid agonist treatment are heterogeneous, and phasic responses depend on the challenge used, current opioid exposure, and clinical state [68,104–106]. Hair cortisol studies suggest that cumulative glucocorticoid exposure may be elevated in chronic heroin use and in some methadone-maintained samples, although psychopathology and perceived stress explain part of this variance [103,106]. The clinically relevant abnormality may therefore lie in reduced regulatory coherence: basal tone and acute responsivity no longer vary together in a consistently adaptive way.

General stress biology offers a second conceptual aid. The effects of glucocorticoids on neural function follow a nonlinear pattern in which transient, proportionate activation can support adaptation, whereas sustained or recurrent activation may impair synaptic and cognitive flexibility [19,107,108]. This inverted-U principle is not derived from opioid-specific data and is used here as a framework for interpreting repeated neuroendocrine perturbation. Applied to OUD, it predicts that the biological significance of stress exposure depends on its temporal pattern and on the capacity of the system to recover between episodes.

We use the term pathological stress set point to describe the proposed functional consequence of this loss of flexibility. It denotes a state in which stress regulation becomes increasingly organized around recurrent opioid-related perturbation, so that environmental challenges or falling opioid levels are handled with less stable endocrine and limbic responses. Such a state could facilitate negative reinforcement and stress-related drug seeking while increasing the biological burden imposed by subsequent withdrawal episodes [4,5,34]. The available human data support neuroendocrine dysregulation and state-dependent stress vulnerability; the progression from these abnormalities to a stable pathological set point remains a hypothesis that requires longitudinal testing.

This distinction sets the evidentiary boundary for the sections that follow. Neuroendocrine instability is directly observable in humans, whereas receptor-level remodeling and enduring circuit sensitization are supported more strongly by experimental models. Their convergence provides a biologically plausible route from repeated opioid exposure to persistent neural vulnerability, without presuming irreversible injury. The next section examines the cellular processes through which recurrent stress-system perturbation could contribute to more durable changes in brain function. The state-dependent neuroendocrine pattern and the distinction between human observations and mechanistic inference are summarized in Figure 2.

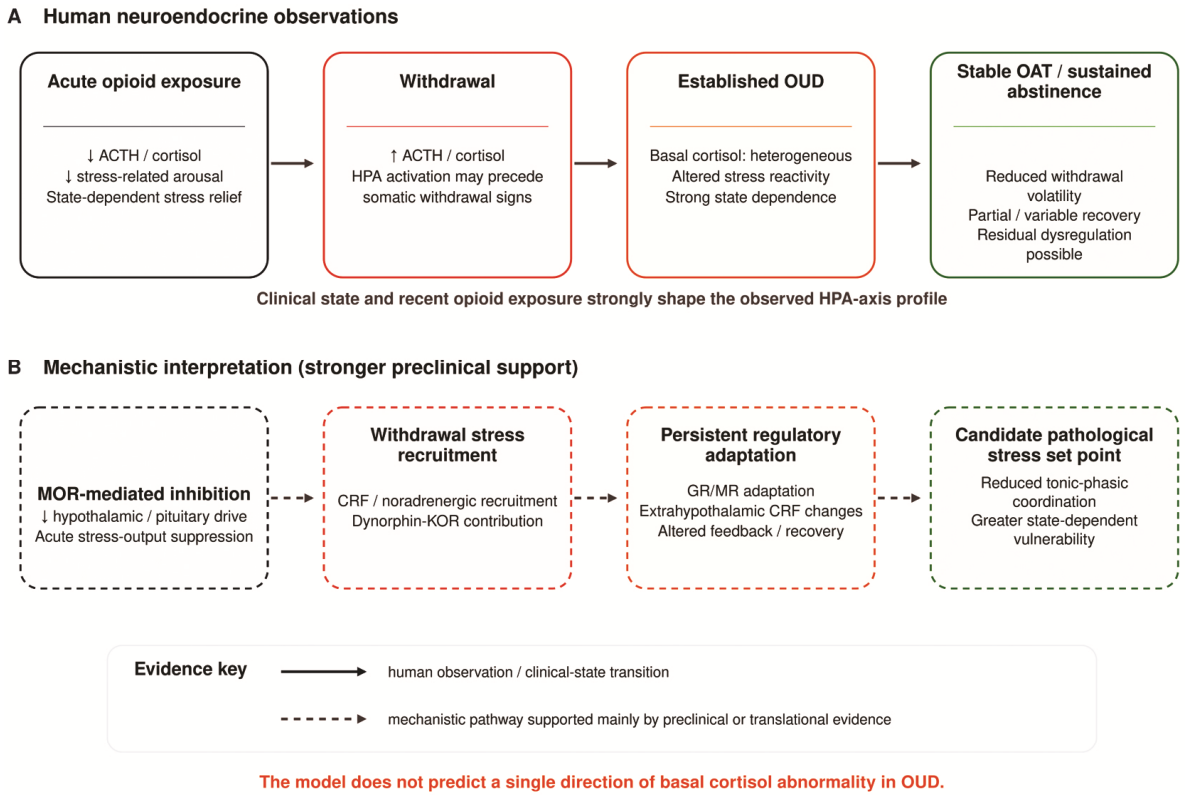


Figure 2. Opioid-specific neuroendocrine dynamics across clinical states. Abbreviation: OAT: Opioid agonist treatment.

Panel A summarizes human observations across acute opioid exposure, withdrawal, established OUD, and stable OAT or sustained abstinence. Acute opioid exposure generally suppresses ACTH and cortisol and dampens stress-related arousal; withdrawal activates the HPA axis; established OUD shows heterogeneous basal and phasic patterns; stable treatment or abstinence may reduce withdrawal volatility while residual dysregulation persists in some patients. Panel B separates the mechanistic interpretation—MOR-mediated inhibition, withdrawal recruitment of CRF, noradrenergic and dynorphin-KOR systems, corticosteroid and extrahypothalamic adaptation, and a candidate pathological stress set point—which is supported more strongly by preclinical and translational evidence. The model does not assume a single direction of basal cortisol abnormality.

5. Potential Cellular and Molecular Mechanisms of Stress-Related Neural Vulnerability

5.1. Stress-Related Synaptic and Glutamatergic Vulnerability

Chronic stress alters synaptic architecture most consistently in the medial prefrontal cortex and hippocampus, where glucocorticoid signaling interacts with excitatory transmission and activity-dependent plasticity. Experimental studies show dendritic retraction and changes in spine density after prolonged stress exposure, with corresponding deficits in working memory and behavioral flexibility [32,109–111]. These effects are region specific and at least partly reversible after stress cessation, which argues for remodeling of neural architecture rather than uniform neurodegeneration [19,112].

Glucocorticoids influence glutamate release, NMDA-receptor signaling, and calcium-dependent synaptic processes, providing a plausible route through which recurrent endocrine activation may alter circuit stability [19]. Opioid exposure adds a second source of plasticity within corticostriatal and corticolimbic pathways. In heroin self-administration models, altered astrocyte-synapse proximity and dendritic spine morphology persist during extinction and are responsive to N-acetylcysteine, indicating that opioid-associated glutamatergic remodeling remains biologically modifiable [113,114]. Such findings support persistent synaptic vulnerability after opioid exposure, although their direct contribution to long-term cognitive impairment in human OUD remains uncertain.

The relevance of these mechanisms to the present model therefore lies in convergence. Recurrent withdrawal-related stress responses may interact with opioid-evoked synaptic plasticity in the same regulatory circuits. This interaction provides a plausible route to reduced regulatory flexibility and impaired recovery without requiring neuronal loss. Direct longitudinal evidence linking cumulative withdrawal burden to progressive synaptic change in humans is still lacking, so this step of the model should be considered mechanistically plausible rather than established.

5.2. Neuroimmune and Glial Mechanisms

Neuroimmune signaling provides another pathway through which opioid exposure and stress physiology may influence neural function. Human evidence is strongest at the peripheral level. Individuals with heroin use disorder show altered serum cytokine and inflammatory-protein profiles compared with healthy controls, while a recent longitudinal study found that cytokine patterns were associated with treatment-related changes in frontal and corticolimbic white-matter microstructure [26,115]. These findings indicate a relationship between immune state and neural recovery, although peripheral cytokines should not be taken as direct measures of microglial activity.

Preclinical studies provide more direct evidence that opioids modify glial function. Microglia and astrocytes participate in synaptic maintenance and glutamate regulation, and chronic opioid exposure or withdrawal may shift these functions toward inflammatory or maladaptive states [116]. TLR4-related signaling has been proposed as one component of this response, though its importance for human OUD remains unresolved. The available evidence therefore supports neuroimmune dysregulation as a potential amplifier of opioid-related neural vulnerability rather than a demonstrated causal pathway to progressive brain damage.

A stage-sensitive interpretation is particularly important. Immune profiles appear to vary across active use, withdrawal, and treatment, and longitudinal data suggest that some abnormalities may diminish as clinical stability improves [26]. Neuroimmune changes may therefore contribute both to biological burden during unstable phases and to measurable recovery during treatment.

5.3. Oxidative, Mitochondrial, and Genomic Stress

Oxidative and metabolic stress are plausible downstream consequences of repeated endocrine, excitatory, and inflammatory activation. Glucocorticoids influence mitochondrial energy production and calcium handling, while excessive excitatory signaling increases energetic demand within neurons [19]. Evidence specific to OUD is more limited than for synaptic or neuroendocrine mechanisms, and available findings should be interpreted accordingly.

One translational study provides direct evidence of genomic stress in opioid-exposed brain tissue. Increased DNA damage was observed in postmortem prefrontal cortex and nucleus accumbens from individuals with OUD; in parallel, heroin self-administration produced similar changes in mice, with persistent prefrontal DNA damage during abstinence. N-acetylcysteine reduced both DNA damage and subsequent heroin seeking in the animal model [117]. The human component was cross-sectional and based on postmortem tissue; however, the combined design strengthens the biological plausibility of oxidative or genomic stress as part of the opioid-related burden.

Mitochondrial adaptations are also evident in preclinical withdrawal models. Astrocytic mu-opioid receptor signaling has been linked to persistent changes in oxidative phosphorylation after morphine withdrawal, suggesting that metabolic responses may remain altered beyond the acute abstinence period [118]. Other experimental work shows marked regional heterogeneity in redox responses to chronic morphine exposure and does not support a uniformly neurotoxic effect [119]. This variability is important for the present framework: mitochondrial and oxidative mechanisms may increase vulnerability in selected circuits, but they should not be presented as evidence of generalized opioid-induced neurodegeneration.

5.4. Epigenetic Persistence, Biological Aging, and Resilience

Repeated stress exposure may leave persistent transcriptional effects through DNA methylation, histone modification, and glucocorticoid-sensitive gene regulation. Stress research has established that prior adversity modifies subsequent glucocorticoid transcriptional responses, with FKBP5 providing a well-characterized example of environmentally sensitive regulation [86,120]. These findings establish a general mechanism of biological embedding, while opioid-specific human evidence is beginning to define related molecular signatures.

Postmortem analyses of dorsolateral prefrontal cortical neurons from opioid overdose cases have identified widespread alterations in H3K27 acetylation and substantial interindividual heterogeneity in regulatory changes [121]. More recent analyses of brain methylation datasets have reported epigenetic age acceleration in brain tissue from opioid overdose cases, whereas comparable acceleration was not detected in datasets involving short-term medically administered opioids [122]. Cross-species RNA sequencing has also identified sex-specific nucleus accumbens transcriptional signatures in postmortem OUD that overlap with molecular patterns observed across experimentally defined stages of opioid exposure and withdrawal in rodents [123]. These findings do not establish accelerated aging or a uniform molecular trajectory as features of OUD itself. Overdose-related hypoxia, polysubstance exposure, medical comorbidity, and other factors may contribute to the observed signals. They nevertheless provide evidence that severe opioid exposure is associated with persistent molecular signatures relevant to the neuroprogressive hypothesis.

The same framework should retain room for recovery. Neural resilience depends on trophic and homeostatic systems that support synaptic maintenance after stress. BDNF and FGF2 signaling, together with endocannabinoid regulation, are among the mechanisms implicated in restoring adaptive plasticity [124,125]. Chronic stress may weaken these protective responses, whereas treatment, abstinence, and environmental stabilization may allow partial restoration. Neuroprogression is therefore better modeled as a changing balance between cumulative biological burden and residual capacity for repair.

5.5. From Cellular Vulnerability to Brain Remodeling

Taken together, the evidence supports several biologically plausible routes by which repeated opioid exposure and recurrent stress-system activation may become more persistent at the cellular level. The strength of evidence differs substantially across mechanisms: human data are available for inflammatory biomarkers, postmortem genomic changes, and selected epigenetic signatures, whereas much of the causal work on synaptic, glial, and mitochondrial mechanisms remains preclinical. These processes may converge on the efficiency and adaptability of corticolimbic and frontostriatal circuits, providing a mechanistic basis for the structural and functional findings considered in the following section. Their contribution to a longitudinal neuroprogressive trajectory in human OUD remains a hypothesis to be tested.

6. Structural, Network, and Neurocognitive Alterations in OUD

6.1. Structural Alterations and Evidence of Partial Recovery

Human neuroimaging provides the most direct evidence that OUD is associated with alterations in brain systems relevant to the proposed neuroprogressive framework. The available studies nevertheless remain heterogeneous with respect to opioid exposure, treatment status, abstinence duration, and co-occurring conditions.

Most structural findings are cross-sectional, so they establish anatomical differences associated with OUD more securely than they establish when those differences developed or which biological process produced them.

Early structural MRI studies reported lower gray matter volume in prefrontal, cingulate, temporal, and insular regions in individuals with heroin dependence [126,127]. Duration of heroin use has also been associated with greater regional abnormalities, including prefrontal and insular reductions [128]. Such correlations are compatible with cumulative exposure, although they cannot separate acquired change from premorbid vulnerability or other time-dependent influences. More recent work has refined this picture. Ceceli and colleagues identified smaller ventromedial prefrontal and nucleus accumbens/putamen volumes in heroin use disorder [12], while a multimodal MRI study of methadone-treated individuals with OUD found structural and resting-state connectivity differences in the thalamus, medial temporal lobe, brainstem, and cerebellum [11]. The latter findings also varied by sex in the medial prefrontal cortex, underscoring that OUD is not associated with a uniform pattern of cortical volume loss.

Alterations involving amygdala-centered systems extend the structural phenotype beyond the prefrontal-striatal axis. In prescription opioid dependence, lower bilateral amygdala volume occurred together with reduced anisotropy in major amygdala pathways and altered functional connectivity of amygdala, anterior insula, and nucleus accumbens seeds; longer opioid exposure was associated with larger connectivity differences [129]. White matter abnormalities have likewise been detected in heroin use disorder, including impaired prefrontal-habenular microstructure [130]. Importantly, the association of this tract abnormality with earlier age of drug-use onset leaves open the possibility that some imaging differences partly reflect vulnerability preceding chronic exposure rather than its consequence.

Longitudinal findings provide an important counterweight to a simple degeneration model. During approximately 15 weeks of inpatient medication treatment, individuals with heroin use disorder showed increased fractional anisotropy and reduced diffusivity in frontal white matter pathways, with the magnitude of microstructural change related to improvement in baseline craving [131]. An independent eight-month abstinence study reported increased superior frontal cortical thickness and strengthening of frontolimbic resting-state connectivity alongside improved cognitive performance and lower craving [132]. These observations support substantial structural plasticity during recovery and suggest that at least part of the OUD-associated imaging phenotype is dynamic rather than fixed.

The anatomical distribution of these findings is compatible with the stress-remodeling hypothesis developed in earlier sections. Prefrontal and medial temporal regions are also sensitive to prolonged stress exposure in non-addicted populations, where structural differences and partial reversibility have been reported [133–135]. This overlap strengthens biological plausibility, though it has to be conceived as analogical evidence: regional convergence does not demonstrate that glucocorticoid or stress-system dysregulation caused the structural abnormalities observed in OUD.

6.2. Functional and Network-Level Dysregulation

Functional abnormalities in OUD are most consistently evident when motivational salience and regulatory control are challenged. In heroin use disorder, drug cues engage nucleus accumbens and prefrontal regions more strongly than neutral or non-drug stimuli, while activity in ventromedial and dorsolateral prefrontal regions relates to craving and the capacity to regulate cue responses [136]. Withdrawal history also appears relevant: greater mesocorticolimbic cue reactivity has been observed in individuals with OUD who had experienced withdrawal, linking a clinically defined exposure variable to subsequent neural responsivity [137]. These studies support an association between the addiction course and altered salience processing without establishing that withdrawal itself is the sole cause of the observed network phenotype.

Resting-state studies similarly point to disrupted integration among prefrontal, limbic, and striatal systems [138,139]. The 2024 multimodal study by Mehta et al. identified increased intrinsic connectivity in several of the same regions showing volumetric differences, including the thalamus and medial temporal lobe [11]. At the task level, successful reappraisal of heroin cues recruits frontal control regions and is associated with lower cue-induced craving, indicating that regulatory circuitry remains functionally recruitable even in established OUD [136]. This residual capacity is clinically relevant because it argues against viewing frontostriatal dysfunction as a simple loss of function.

Recent longitudinal evidence further shows that cue-related network abnormalities can change during treatment. After approximately 15 weeks of inpatient treatment, drug-biased synchronization in the orbitofrontal cortex declined in individuals with heroin use disorder, and the reduction tracked improvement in craving [140]. Together with the structural recovery findings above, these data favor a model of altered network calibration with variable persistence and recovery. They are consistent with maladaptive remodeling, while leaving the direction

and relative contribution of opioid exposure, repeated withdrawal, treatment, and pre-existing circuit characteristics largely unresolved.

6.3. Persistent Neurocognitive Dysfunction

The functional relevance of these brain alterations is supported by neuropsychological evidence. Meta-analytic data indicate mild generalized cognitive dysfunction in OUD, with the largest impairment in complex psychomotor performance and smaller effects across several executive and memory domains [13]. The same meta-analysis also found that mean raw scores frequently remained within normative ranges. Thus, cognitive impairment is common at the group level but should not be treated as an invariant feature of OUD.

Recent studies provide more specific evidence for deficits in self-regulatory cognition. Individuals with OUD showed reduced metacognitive sensitivity during a perceptual decision task, accompanied by altered activation in rostrolateral prefrontal and orbitofrontal-striatal systems; exploratory analyses suggested greater impairment with more recent illicit opioid use [141]. In a longitudinal cohort entering opioid maintenance treatment, cognitive flexibility was impaired in approximately two thirds of participants, whereas verbal fluency improved over one year and more complex executive measures changed little [8]. A separate 2025 study of individuals with heroin use disorder receiving prolonged methadone maintenance found persistent difficulties in inhibitory control and self-reported executive functioning, particularly among those with a history of relapse [142].

These findings support persistence of selected executive deficits beyond acute intoxication or withdrawal, but they do not establish irreversible cognitive decline. Treatment exposure, psychiatric comorbidity, prior educational and cognitive characteristics, and continued use of other substances contribute to substantial between-person variability. The most defensible interpretation is therefore that long-standing OUD is associated with a higher probability of persistent inefficiency in executive-control systems, with recovery differing across cognitive domains and individuals.

6.4. Stress Hypersensitivity as a Candidate Persistent Phenotype

Stress hypersensitivity is especially relevant to the present model because it links the neuroendocrine abnormalities described earlier with behavior outside the laboratory. Human studies in opioid-dependent populations show enhanced subjective or endocrine responses to stress and associations between stress exposure, craving, and relapse-related behavior [47,62,143]. More recently, experimentally induced noradrenergic and glucocorticoid activation increased the relative reinforcing value of opioids in buprenorphine-stabilized participants with OUD, with the effect moderated by basal cortisol levels [99]. This finding demonstrates that stress-system state remains behaviorally relevant even during pharmacological stabilization.

Whether this pattern constitutes an acquired trait of OUD remains less certain. Persistent stress vulnerability is biologically compatible with repeated HPA-axis disruption and extrahypothalamic stress recruitment, yet longitudinal human studies capable of establishing its emergence across the addiction course are still limited. Trauma exposure and pre-existing affective vulnerability may generate similar phenotypes. We therefore use stress hypersensitivity here as a candidate marker of persistent dysregulation rather than as an established consequence of chronic opioid exposure.

Overall, human structural, functional, and neurocognitive studies support the presence of clinically relevant brain alterations in OUD and provide emerging evidence that some abnormalities persist during treatment or abstinence. The same literature also documents partial recovery. This combination is central to the present framework: it supports a dynamic process of maladaptive remodeling more readily than a fixed degenerative lesion. The evidence does not yet demonstrate a continuous causal sequence from repeated intoxication-withdrawal stress to progressive brain dysfunction. It instead provides the human phenotypic substrate against which that hypothesis can be tested. The next section formalizes this distinction by separating neuroadaptation, neuroprogression, and the proposed advanced neuroprogressive phenotype.

7. From Neuroadaptation to Neuroprogression: A Testable Model

The evidence reviewed so far identifies a set of biological changes extending beyond acute opioid pharmacology. Repeated exposure produces well-established neuroadaptations, while human studies document persistent differences in stress regulation, brain structure, network function, and cognition in at least some individuals with OUD. What remains uncertain is whether these findings form a temporally ordered process in which recurrent opioid-related and stress-related perturbations become progressively embedded. The present section defines that hypothesis and considers the possible clinical-functional phenotype at its advanced end. Figure 3 summarizes the proposed architecture and distinguishes observed phenomena from hypothesized temporal and causal transitions.

The model distinguishes two partly interacting burdens: repeated opioid-driven neuroadaptation and recurrent intoxication-withdrawal stress. Their convergence is proposed to contribute to maladaptive brain remodeling and, over time, neuroprogression in a vulnerable subgroup. Solid-bordered boxes summarize observed exposures, clinical states, modifiers, or recovery phenomena; dashed-bordered boxes and arrows identify interpretive constructs or temporal-causal links that remain inferential or are supported more strongly by preclinical and translational evidence. Alternative contributors and trajectory modifiers are shown explicitly. The recovery pathway allows stabilization and partial biological recovery during stable OAT or sustained abstinence, so progression is neither inevitable nor assumed to be irreversible. In this framework, "cerebropathy" is used only as a descriptive term for the putative advanced clinical-functional phenotype and does not define a separate disease entity.

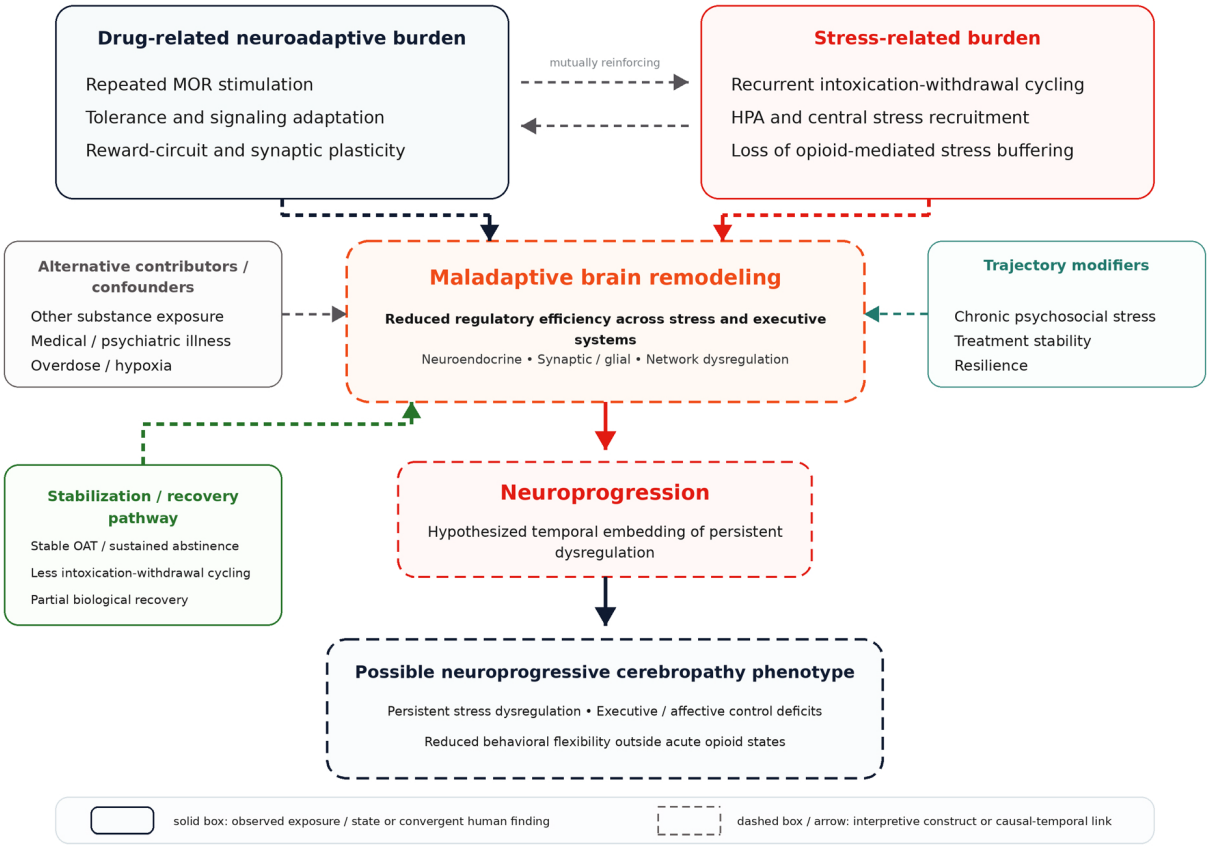


Figure 3. Proposed neuroprogressive model in opioid use disorder, including a putative advanced cerebropathy phenotype.

7.1. Neuroadaptation, Maladaptive Remodeling, and Neuroprogression

Neuroadaptation is the most firmly established level of this continuum. Repeated opioid exposure changes receptor responsiveness, intracellular signaling, synaptic plasticity, and the operating state of reward and arousal circuits. These responses support tolerance and dependence and may initially serve compensatory functions that preserve neural activity in the presence of the drug [3,17,18]. Their presence therefore does not, by itself, imply progressive brain pathology.

Maladaptive remodeling describes a subsequent functional condition in which compensatory changes become persistent enough to reduce regulatory efficiency. The preceding sections identified several candidate manifestations: impaired HPA-axis coordination, recruitment of extrahypothalamic stress signaling, altered synaptic regulation, and reduced efficiency of prefrontal-limbic control. Human imaging and neurocognitive studies show that corresponding abnormalities may remain detectable outside acute intoxication and withdrawal, although their origin is often uncertain [8,11,19]. Remodeling is therefore used here as a descriptive term for durable biological reorganization, without assuming irreversible tissue loss.

Neuroprogression adds a temporal proposition. It refers to the hypothesis that recurrent perturbations accumulate across the course of OUD and gradually reduce the capacity of neural systems to return to a flexible operating range. Recent conceptual work has extended neuroprogressive models to substance use disorders and has emphasized the potential value of staging approaches that distinguish biological burden from diagnostic status

alone [20,21]. In this Perspective, neuroprogression remains an inferred trajectory because the required longitudinal human evidence linking early neuroadaptation to later multidomain dysfunction is not yet available.

At the advanced end of this trajectory, the model allows for a provisional neuroprogressive phenotype characterized by persistent dysfunction across stress regulation and higher-order behavioral control after acute opioid effects have resolved. This putative brain-based expression is referred to descriptively in this Perspective as neuroprogressive cerebropathy, without implying a separate diagnostic entity, consistent with a related heuristic use in chronic cocaine exposure [23].

7.2. Repeated Intoxication-Withdrawal Cycling as Cumulative Stress Burden

The distinctive contribution of the present model concerns the repeated alternation between opioid-induced stress dampening and withdrawal-related stress activation. Human studies demonstrate HPA-axis activation during spontaneous or precipitated withdrawal, and endocrine changes may precede prominent somatic manifestations [15,67,68]. In unstable patterns of use, these transitions recur over months or years. The biological significance of such repetition has received far less attention than the motivational significance of withdrawal.

Preclinical findings provide a plausible mechanism for cumulative effects. Repeated or prolonged opioid withdrawal is associated with persistent changes in glucocorticoid and CRF-related signaling, altered stress responsivity, and adaptations within amygdala-centered circuitry that outlast the immediate withdrawal episode [79–82]. These studies establish that withdrawal leaves measurable biological traces in experimental systems. They do not establish the same temporal sequence in humans, where exposure patterns and competing sources of stress are considerably more complex.

The cumulative-stress hypothesis currently rests on converging evidence while direct longitudinal proof is lacking. Nevertheless, human OUD is associated with abnormal basal and stress-evoked endocrine activity, persistent stress-related behavior, and brain alterations that may remain detectable during treatment or abstinence [62,99,106]. The proposed interpretation is that recurrent withdrawal-related activation may add a repeated stress burden to opioid-driven neuroadaptation. Its contribution is expected to vary with the instability of opioid exposure and the frequency of withdrawal states. Continuous deterioration is not implied, and stable agonist treatment provides a biologically different exposure condition that is considered in Section 8.

This distinction also helps separate the proposed model from a generic toxicity account. Neuroprogression, if present, would arise from the interaction between direct opioid-related adaptation and repeated disruption of stress regulation. Either pathway may predominate in a given individual, and both remain susceptible to influences that precede opioid use. The model therefore predicts heterogeneity in biological burden even among patients with comparable diagnostic severity.

7.3. Candidate Features for Prospective Operationalization of the Neuroprogressive Phenotype

The phenotype proposed here has not been validated and should not be treated as a set of diagnostic or staging criteria. At present, no validated duration of clinical stability, threshold for stress-system dysregulation, or neuropsychological cutoff exists for this purpose. The features outlined below should therefore be regarded as candidate dimensions for prospective operationalization.

Exposure history is one such dimension. Studies should document long-standing OUD and characterize the course of opioid use in sufficient detail to estimate cumulative instability, particularly recurrent withdrawal. Duration of opioid use alone is unlikely to be adequate because patients with similar years of exposure may have experienced markedly different patterns of intoxication, withdrawal, treatment, and abstinence. Withdrawal burden should consequently be treated as an exposure variable and quantified prospectively whenever possible.

Persistence outside acute opioid states is a second candidate feature. Future studies should assess patients after acute intoxication and withdrawal have resolved, ideally during a clinically stable treatment or abstinence interval, with repeated assessment when feasible. The duration of stability required before an abnormality can be considered persistent remains unknown. A plausible research phenotype would combine persistent stress-regulatory dysfunction with impairment in at least one higher-order domain relevant to adaptive control, such as executive cognition, affective regulation, or behavioral flexibility. Existing neuropsychological studies indicate that such deficits may remain detectable in some treated patients, while between-person variability remains substantial [8,9,142].

Biological measures may strengthen phenotypic characterization, but none is currently suitable as a defining criterion. Neuroendocrine indices may capture persistent stress-system dysregulation, whereas structural or functional imaging may identify associated network abnormalities. No available biomarker is sufficiently specific to define the proposed phenotype, and a normal biomarker result should not be interpreted as excluding clinically

significant dysfunction. This approach is consistent with recent proposals for biologically informed staging in SUDs, which emphasize multidimensional characterization over a single disease marker [20,21].

Attribution will also require careful characterization of alternative contributors. Other substance exposure, major neurologic or medical illness, and independent psychiatric syndromes may produce overlapping cognitive or affective findings. These factors are better treated as potential contributors or modifiers than as automatic exclusion criteria, because comorbidity is part of the clinical reality of long-standing OUD. The proposed phenotype will become scientifically useful only if prospective studies establish temporal coherence, reproducibility, and clinically relevant prediction.

7.4. Boundaries with Neurodegeneration and Alternative Explanations

Neuroprogression should be kept distinct from classical neurodegeneration. OUD has not been shown to produce a disease-specific proteinopathy, a stereotyped pattern of neuronal loss, or a progressive clinicopathologic sequence comparable with Alzheimer disease, Parkinson disease, or frontotemporal dementia. The human literature instead shows regional structural and functional differences with variable persistence, accompanied in some longitudinal studies by measurable recovery [25,131,132]. These features are more compatible with dynamic remodeling than with an established degenerative disease process.

Several neurologic complications associated with opioid use must also remain conceptually separate. Toxic leukoencephalopathy and hypoxic-ischemic injury after overdose represent defined forms of brain injury with mechanisms and clinical presentations that differ from the gradual phenotype proposed here [144]. Epidemiologic associations between regular opioid exposure and later cognitive decline or dementia are potentially relevant, but they should not be used as direct evidence for OUD-related neuroprogression when the studied populations include chronic pain, older age, or other sources of vascular and medical risk [24,145].

Premorbid vulnerability presents a different challenge. Executive inefficiency, heightened stress reactivity, trauma-related symptoms, and psychiatric comorbidity may precede opioid dependence and increase the likelihood of developing severe OUD. Cross-sectional studies are not capable of determining whether a brain or cognitive abnormality was present before addiction, emerged during chronic exposure, or reflects both processes. This limitation applies directly to the proposed neuroprogressive phenotype and argues for prospective designs beginning early in the course of OUD.

The proposed construct is therefore deliberately narrower than a claim of opioid-induced neurodegeneration. It describes persistent loss of adaptive efficiency that may arise through several interacting mechanisms and may be amplified by the course of addiction. Its scientific value will depend on whether it identifies a reproducible subgroup with a distinct longitudinal trajectory or clinically useful pattern of treatment response.

7.5. Reversibility, Resilience, and Disease-Course Modifiers

A neuroprogressive model of OUD should accommodate recovery. Longitudinal human studies show changes in frontal cortical thickness, white matter microstructure, and cue-related network function during sustained abstinence or treatment [25,131,132,140]. These findings indicate that persistent abnormalities are not uniformly fixed and that substantial plasticity remains present even after prolonged opioid exposure. Neuroprogression is therefore better conceptualized as increasing probability of persistent dysregulation than as an irreversible downward course.

The balance between persistence and recovery is likely to reflect the interaction of accumulated exposure with pre-existing vulnerability and the stability achieved after treatment engagement. Trauma or continued polysubstance use may maintain stress burden, while medical illness and aging may reduce neural reserve. Conversely, sustained withdrawal prevention and reduction of environmental instability create conditions in which recovery may occur. Current evidence does not allow these influences to be ranked or converted into a validated risk score.

This formulation yields testable predictions. A genuine neuroprogressive phenotype should show greater persistence with increasing cumulative instability, should remain measurable after acute opioid effects have resolved, and should predict clinically relevant outcomes beyond conventional measures of OUD severity. Improvement during sustained treatment would be compatible with trajectory modification, although it would not establish a disease-modifying effect by itself. These questions place opioid agonist treatment in a particularly informative position: its ability to reduce recurrent withdrawal and stabilize opioid exposure permits examination of whether stress-system stabilization is accompanied by recovery in the biological and functional domains proposed here.

8. Opioid Agonist Treatment as a Potential Stress-System Stabilizing Intervention

Opioid agonist treatment (OAT) changes the temporal pattern of opioid exposure that characterizes active heroin use. Sustained treatment with methadone or buprenorphine reduces withdrawal and illicit opioid use and limits repeated transitions between short-acting opioid effects and withdrawal-related stress activation. In the model proposed here, this change in exposure pattern is relevant because recurrent withdrawal is a candidate source of cumulative stress burden [146,147]. The therapeutic hypothesis is therefore specific: OAT may reduce stress-system volatility by decreasing the frequency and intensity of opioid deprivation states.

The available endocrine evidence does not establish a uniform normalization of the HPA axis during OAT. Basal cortisol concentrations, challenge responses, and longer-term glucocorticoid measures vary across studies and patient groups [65,106,148]. In this section, stress-system stabilization refers to a reduction in recurrent physiological destabilization rather than restoration of every endocrine measure to control values. This distinction is important because the proposed trajectory-modifying effect of OAT remains a mechanistic hypothesis rather than a demonstrated neuroprotective action.

8.1. Pharmacologic Stabilization and Neuroendocrine Regulation

Methadone has been studied most extensively in relation to opioid-dependent HPA-axis function. Acute methadone exposure suppresses ACTH and cortisol, whereas findings during maintenance treatment are heterogeneous, with reports of altered basal activity and abnormal responses to endocrine challenges [60,65,104,105]. These data argue against a single endocrine signature of methadone maintenance. They are compatible, however, with the possibility that stable agonist exposure reduces the repeated suppression-withdrawal oscillation associated with uncontrolled short-acting opioid use [147,149].

Residual stress dysregulation may remain clinically relevant during otherwise stable methadone treatment. A recent real-world stress-task study found higher baseline physiological arousal and altered stress reactivity in methadone-treated participants compared with healthy controls; the largest responses were observed in the pre-dose group [150]. Because the study was cross-sectional, an inter-dose causal effect cannot be established. It nevertheless illustrates that maintenance treatment and physiological stability are not equivalent states and that within-treatment variation deserves direct study.

Buprenorphine provides a complementary model because its partial MOR agonism produces prolonged receptor occupancy with a different pharmacodynamic profile from methadone. Experimental administration has attenuated psychosocial stress responses in healthy participants [151], while human laboratory work shows that acute noradrenergic and glucocorticoid activation may still increase opioid-seeking behavior during buprenorphine stabilization [99]. Recent clinical data in young men with heroin-related OUD also showed a lower cortisol/DHEA-S ratio in buprenorphine-maintained participants than in recently admitted patients, although the small cross-sectional design and associations with coping and social support preclude attribution to medication alone [152]. Together, these findings suggest partial regulation rather than complete normalization of stress physiology.

Diacetylmorphine offers a more specialized comparison. Controlled studies in patients receiving pharmaceutical heroin show acute reductions in ACTH, cortisol, and craving after diacetylmorphine administration [14,102]. These findings establish a marked acute stress-dampening effect, but they do not demonstrate superior long-term restoration of HPA regulation. Heroin-assisted treatment is also reserved for selected patients with severe OUD in treatment systems where injectable OAT is legally and organizationally available. Regulatory requirements, delivery infrastructure, and political acceptance vary substantially across jurisdictions [153]. Here, diacetylmorphine is considered primarily as a pharmacologic model of intensive agonist stabilization; its clinical accessibility remains highly jurisdiction-dependent.

The treatment-specific evidence remains too limited for a hierarchy based on stress-system outcomes. The more defensible common principle is that sustained agonist treatment changes the biological context in which withdrawal and stress responses occur. Whether one medication produces greater long-term recovery of stress regulation than another requires prospective comparison using standardized endocrine and behavioral measures.

8.2. Stress-System Recovery and Craving: Complementary Treatment Domains

Craving and stress-system measures capture overlapping but non-identical dimensions of treatment response. Craving remains a clinically important predictor and treatment target, yet its intensity varies with cue exposure, affective state, and environmental context. HPA-axis abnormalities may persist during periods in which subjective craving is limited, and cortisol-related measures have been associated with treatment engagement and retention in opioid-dependent populations [147,154]. These observations support assessment of stress regulation alongside conventional symptom and drug-use outcomes.

The distinction is also evident under controlled experimental conditions. In buprenorphine-stabilized participants, the behavioral effect of an acute noradrenergic-glucocorticoid challenge depended on basal cortisol level and shifted responding toward opioid reinforcement [99]. Stress-system state therefore retained behavioral relevance despite pharmacological stabilization. This finding does not establish cortisol as a clinical relapse biomarker, but it supports the broader premise that subjective craving alone does not fully characterize vulnerability during treatment.

For treatment research, the implication is methodological rather than prescriptive. Studies evaluating recovery could combine conventional outcomes such as opioid use and retention with repeated measures of stress reactivity or longer-term endocrine tone. Recent work using wearable physiology in methadone-treated OUD demonstrates the feasibility of capturing stress-related variation in a clinical setting [150]. Such measures remain investigational and require validation against prospective clinical outcomes before they can inform routine decision-making.

8.3. Could OAT Modify the Proposed Neuroprogressive Trajectory?

The possibility that OAT modifies the proposed neuroprogressive trajectory follows directly from the cumulative-stress model, though it has not been demonstrated. If recurrent withdrawal contributes to maladaptive remodeling, sustained agonist treatment would be expected to reduce exposure to that specific stressor. This prediction concerns the prevention of further instability. It does not imply reversal of established structural, cognitive, or molecular abnormalities.

Longitudinal neuroimaging provides indirect support for biological recovery during clinical stabilization. Changes in frontal cortical thickness, white matter microstructure, and drug-cue network function have been observed during sustained abstinence or medication treatment [131,132,140]. Longitudinal immune and white-matter findings similarly suggest that some biological abnormalities vary during treatment [26]. These studies are important because they demonstrate plasticity after chronic heroin exposure, yet they cannot isolate a disease-modifying effect of OAT from abstinence, reduced polysubstance exposure, improved health, or time.

Residual abnormalities provide an equally important boundary condition. Elevated hair cortisol has been reported in methadone-maintained patients, with substantial influence from depression, anxiety, and perceived stress [106]. Experimental stress can increase opioid seeking during buprenorphine stabilization [99], and recent physiological monitoring indicates persistent stress-related differences among people receiving methadone [150]. OAT therefore appears to change the trajectory of exposure without guaranteeing full recovery of stress regulation.

The appropriate conclusion is that OAT is therefore a plausible candidate modifier of the proposed trajectory because it reduces recurrent opioid deprivation and creates conditions in which biological recovery may occur. Evidence that it prevents neuroprogression or an advanced neuroprogressive phenotype is currently absent. Testing that proposition will require longitudinal studies that quantify withdrawal burden before treatment, document subsequent treatment stability, and relate changes in stress-system function to cognitive and brain outcomes over time. This question leads directly to the biomarker and staging strategies considered in the following section.

9. Clinical and Research Implications

The proposed model has its greatest value if it generates measurements and predictions that can be tested prospectively. At present, the evidence does not support a clinical diagnosis based on the proposed neuroprogressive phenotype or the use of any biological marker to assign individual patients to a neuroprogressive stage. The immediate translational goal is therefore narrower: to identify measures that capture persistent stress-system dysregulation, biological recovery, and loss of adaptive function more accurately than drug-use severity alone. Recent proposals for staging substance use disorders similarly emphasize dynamic, multidimensional characterization rather than a fixed sequence of disease states [20,21].

9.1. Biomarkers and Multidimensional Staging

Stress-related biomarkers are plausible candidates because the present framework assigns a central role to recurrent neuroendocrine destabilization. Their interpretation requires attention to timescale. Plasma and salivary cortisol are suited to basal or challenge-related measurements over short intervals, whereas hair cortisol concentration (HCC) provides an integrated estimate of glucocorticoid exposure across longer periods [155]. In OUD, elevated HCC has been reported in chronic heroin users and in some methadone-maintained samples [103,106]. These findings remain too limited and context-dependent to establish HCC as a staging marker. Methodological heterogeneity in hair sampling, processing, and assay procedures further limits comparison across studies and argues for standardized reporting in future work [156].

A useful biomarker would need to provide information that is clinically interpretable across phases of OUD. For the present model, this means distinguishing persistent dysregulation from transient effects of recent opioid exposure or withdrawal. Repeated stress-challenge measures may characterize phasic responsivity, while HCC may provide complementary information about longer-term glucocorticoid exposure. Neither measure is specific to opioid-related remodeling, and both are influenced by psychiatric symptoms and environmental stress. Their value is therefore more likely to emerge from trajectories within individuals than from a single threshold separating OUD from health.

The same principle applies beyond the HPA axis. Longitudinal work has linked peripheral cytokine profiles with changes in white matter microstructure during treatment for heroin-related OUD, suggesting that accessible biological measures may track aspects of neural recovery [26]. Structural and functional imaging studies likewise demonstrate that some abnormalities change during abstinence or treatment [131,132,140,157]. These observations favor a multimodal strategy in which endocrine or immune measures are interpreted alongside neurocognitive and imaging outcomes. No component currently has sufficient specificity to serve as a stand-alone marker of the proposed cerebropathy phenotype.

Staging should therefore remain clinical-functional at its core. A research stage would ideally reflect the persistence and breadth of dysfunction after acute opioid effects have resolved, while biological measures quantify the mechanisms or burden associated with that state. This approach is consistent with recent SUD staging frameworks, which explicitly treat stage as dynamic and sensitive to recovery or deterioration [21]. It also avoids converting group-level biological differences into diagnostic thresholds before their predictive validity has been established.

9.2. Testing the Neuroprogressive Model: Longitudinal and Multimodal Designs

The decisive test of the model requires longitudinal human studies beginning during biologically unstable phases of OUD and extending through treatment stabilization. Repeated intoxication-withdrawal burden should be quantified separately from cumulative opioid exposure, because the framework predicts that these dimensions contribute through partially distinct pathways. Subsequent assessments should determine whether greater withdrawal burden is associated with persistent stress dysregulation and slower recovery of executive or network function after treatment has stabilized opioid exposure.

The temporal sequence of change is especially informative. If recurrent stress-system destabilization contributes to neuroprogression, endocrine volatility should diminish after sustained stabilization before slower structural or cognitive changes become evident. Conversely, persistent neuroendocrine abnormalities despite stable treatment may identify patients in whom stress dysregulation remains biologically embedded. Longitudinal sampling of HCC, standardized basal or challenge-based cortisol measures, and repeated neurocognitive assessment would permit these alternatives to be distinguished. Neuroimaging could then be deployed at longer intervals to test whether biological stabilization accompanies recovery within stress-sensitive and executive networks.

Such studies also need to preserve the heterogeneity of OUD rather than eliminate it statistically. Concurrent substance exposure and major psychiatric or medical conditions may alter both stress physiology and recovery. They should therefore be modeled as potential modifiers of trajectory whenever sample size permits. The same applies to treatment stability: continuous agonist exposure, recurrent missed dosing, sustained abstinence, and ongoing use create biologically different conditions even when participants share the same categorical OUD diagnosis.

The neuroprogressive hypothesis should ultimately be judged by prospective prediction. Candidate biomarkers must show that they anticipate clinically meaningful outcomes or biological change, ideally beyond information already available from routine assessment. This is a demanding standard. Recent individual-level models have predicted return to opioid use using readily available clinical and urine toxicology data, with early treatment information markedly improving discrimination [158]. A stress-related biomarker would therefore be most useful if it adds predictive value beyond such clinical measures or identifies a distinct outcome, such as persistent executive dysfunction or incomplete neural recovery.

Several predictions follow from the framework. Patients with a greater history of recurrent withdrawal should, on average, show more persistent stress-system dysregulation after accounting for overall opioid exposure. Sustained treatment stability should be associated with reduced physiological volatility, although the magnitude and timing of recovery may vary substantially between individuals. Finally, persistent dysregulation should relate more closely to later cognitive or functional impairment than to contemporaneous craving alone. Failure of these predictions in adequately powered longitudinal studies would argue against the proposed causal role of cumulative withdrawal-related stress.

9.3. Clinical Translation and Measurement-Based Care

The current framework does not justify biomarker-guided treatment selection. Clinical care should continue to prioritize evidence-based OUD treatment and established outcomes, including retention, reduction in non-prescribed opioid use, overdose prevention, and functional improvement. Recent work on measurement-based care in OUD has emphasized repeated assessment of clinically actionable domains to guide medication dosing and evaluate treatment response [159]. Stress-system measures could eventually complement this approach, but their clinical utility has yet to be demonstrated.

A neuroprogressive perspective nevertheless changes which outcomes deserve attention in research. Patients may achieve substantial reduction in opioid use while retaining difficulties in executive regulation, stress tolerance, or affective recovery. Repeated assessment of these domains would help determine whether clinical stabilization is accompanied by broader restoration of adaptive function. It would also provide an empirical basis for deciding whether the proposed neuroprogressive phenotype captures information that is not already represented by conventional OUD severity measures.

The model also supports investigation of interventions directed at residual stress dysregulation after opioid exposure has stabilized. Psychological approaches targeting stress regulation and trauma-related symptoms warrant adjunctive investigation, while pharmacologic modulation of stress-related systems remains an experimental avenue. The relevant outcome should be sustained improvement in adaptive regulation; acute suppression of a single endocrine signal would be insufficient. Any claim that such interventions prevent neuroprogression will require prospective evidence linking treatment-induced biological change to later cognitive, functional, or neural outcomes.

Accordingly, the translational agenda is staged in its own right. The first task is to validate reproducible measures of stress-system state and recovery. The second is to determine whether these measures improve prediction of persistent dysfunction or treatment course. Only then would biomarker-informed staging or targeted intervention become clinically defensible. This sequence keeps the neuroprogressive model falsifiable while preserving its potential value for a more individualized understanding of long-term OUD trajectories.

10. Conclusions

This Perspective proposes that the long-term biology of opioid use disorder (OUD) may be understood through a continuum from opioid-induced neuroadaptation to maladaptive brain remodeling and, in susceptible individuals, neuroprogression. Two interacting processes are central to this framework. Repeated opioid exposure drives molecular and circuit adaptations that contribute to tolerance and dependence, while recurrent intoxication-withdrawal cycling repeatedly perturbs neuroendocrine and extrahypothalamic stress systems. Their convergence may help explain why some patients show persistent abnormalities in stress regulation, executive function, affective control, and behavioral flexibility beyond acute intoxication or withdrawal.

The advanced clinical-functional expression proposed in this Perspective is a provisional neuroprogressive phenotype characterized by persistent multidomain dysfunction associated with long-standing OUD and reduced adaptive capacity. It does not imply a uniform course, irreversible neuronal loss, or equivalence with classical neurodegenerative disease. Available human studies document structural, functional, neuroendocrine, and cognitive abnormalities, though their causal attribution remains limited by cross-sectional designs and by the effects of comorbid psychiatric illness, other substance exposure, medical disease, and adverse social conditions. Longitudinal evidence of partial structural and functional recovery further indicates that biological remodeling remains dynamic and that resilience and treatment stability may substantially modify outcome.

OAT provides a clinically relevant context in which this hypothesis can be tested. Sustained agonist treatment reduces recurrent opioid deprivation and may thereby decrease one component of the proposed cumulative stress burden. Evidence for neuroendocrine stabilization during OAT remains incomplete and heterogeneous, and residual stress dysregulation is detectable in some treated patients. Claims that methadone, buprenorphine, or diacetylmorphine prevent neuroprogression therefore remain premature. Stable treatment may reduce further destabilization and permit biological recovery; this remains a prospective prediction.

The next step is prospective validation. Studies should quantify withdrawal burden independently of cumulative opioid exposure and track stress-system function, cognition, and neuroimaging measures across treatment stabilization. Hair cortisol and other endocrine measures may contribute to this strategy if they prove reproducible and add information beyond conventional clinical assessment. The proposed model will gain value only if it predicts persistent dysfunction, recovery, or treatment course at the individual level. Framed in this way, the neuroprogressive model offers a testable account of how chronic opioid exposure and recurrent stress-system

destabilization may become biologically embedded over time, while preserving heterogeneity, reversibility, and the possibility of recovery as central features of OUD.

Author Contributions

F.D.R. & I.M.: conceptualization, methodology; F.D.R.: writing—original draft preparation; A.G.I.M.: conceptualization, methodology and supervision; M.G.C.: writing—reviewing and editing. All authors have read and agreed to the published version of the manuscript.

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The authors declare no conflict of interest.

Use of AI and AI-Assisted Technologies

During the preparation of this work, the authors used ChatGPT and Grammarly to assist with language editing and manuscript formatting. The authors subsequently reviewed and edited the content and take full responsibility for the final manuscript.

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