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Prefrontal-Accumbens Opioid Plasticity: implications for relapse and dependence

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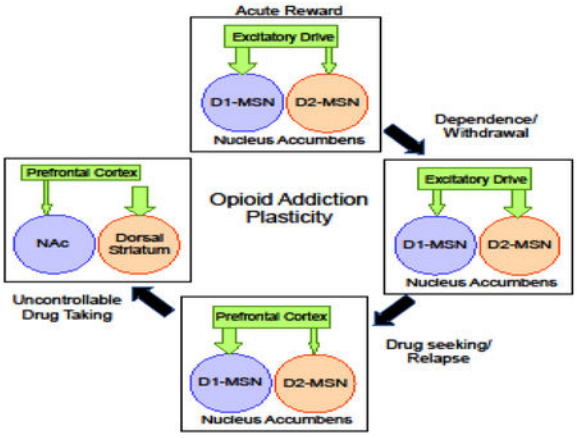
Abstract

In addiction, an individual's ability to inhibit drug seeking and drug taking is thought to reflect a pathological strengthening of drug-seeking behaviors or impairments in the capacity to control maladaptive behavior. These processes are not mutually exclusive and reflect drug-induced modifications within prefrontal cortical and nucleus accumbens circuits, however unlike psychostimulants such as cocaine, far less is known about the temporal, anatomical, and cellular dynamics of these changes. We discuss what is known regarding opioid-induced adaptations in intrinsic membrane physiology and pre-/postsynaptic neurotransmission in principle pyramidal and medium spiny neurons in the medial prefrontal cortex and nucleus accumbens from electrophysiological studies and explore how circuit specific adaptations may contribute to unique facets of opioid addiction.

Graphical abstract



Keywords

addiction; opioids; prefrontal cortex; nucleus accumbens; glutamate plasticity

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INTRODUCTION

Opioid-based drugs are mainstays for clinical pain management, however the misuse of and addiction to opioids—including prescription pain relievers, heroin, and synthetic opioids such as fentanyl—is a serious national crisis that affects public health as well as social and economic welfare [1–3]. Increasing evidence suggest that neural circuit adaptations responsible for withdrawal that accompany dependence are not necessarily synonymous with those responsible for establishing drug seeking behavior, creation of relapse-driving cue/context associations and impaired control over drug intake – highlighting a need to better understand how specific aspects of opioid plasticity uniquely contribute to opioid abuse. The medial prefrontal cortex (mPFC) and nucleus accumbens (NAc) are two brain regions that are critically involved in reward, motivated behavior, and cognitive control where drugs of abuse are believed to promote pathological plasticity that leads to enduring behavioral abnormalities associated with addiction [4–10], however our understanding of this plasticity in relation to opioid abuse remains surprisingly absent. The purpose of this review is to discuss what is known and highlight important knowledge gaps regarding opioid-induced plasticity in the mPFC and NAc using primarily electrophysiology data from preclinical models, and explore potential relevance of this plasticity to unique facets of opioid addiction (e.g., reward, drug-seeking, and dependence).

MEDIAL PREFRONTAL CORTEX

Deep layer glutamatergic pyramidal neurons within the more dorsal prelimbic (PrL) and ventral infralimbic (IL) regions of the mPFC provide widespread glutamatergic input to cortical and subcortical structures [11–14]. Differences in the anatomical connectivity of these regions contribute to their dissociable (often opposing) roles in regulating limbic and cognitive functions, thus regional adaptations may have distinct implications for drug seeking behavior and impaired control of drug intake [5, 10, 15–20]. In addition to anatomical connectivity, recent evidence indicates that these neurons can be further divided into subpopulations based on morphology, molecular and physiological profile – including the expression of D1-versus D2-type dopamine receptors – as well as what type of excitatory or inhibitory input they receive [21–27]. As these sub-populations likely provide an anatomical frame work to regulate complex behavioral control and define how they undergo experience induced plasticity, a critical step towards understanding how addiction alters PFC networks will be to identify cell type and pathway-specific adaptations [26–29].

Opioid effects on mPFC pyramidal neuron activity

Preclinical studies have indeed identified a role for mPFC glutamate input to regions such as the NAc and ventral tegmental area (VTA), as well as dopaminergic neurotransmission in the PFC in numerous facets of opioid addiction, including acute reward [30–38], relapse related drug seeking following abstinence and extinction [39–43], precipitated somatic withdrawal [44], and opioid addiction memory formation [45]. Studies examining the acute effects of opioids on pyramidal neuron activity are relatively few in number, however *in vivo* work indicates that morphine attenuates the excitatory response of pyramidal neurons to locally applied and afferent evoked glutamate [31]. Notably, effects of morphine on

transmitter release were more pronounced at mediodorsal thalamus afferents compared to input arising from the baslolateral amygdala (BLA) and hippocampus (HPC) -- highlighting the possibility of pathway- or cell-type specific regulation by mu opioid receptors [31, 46]. Moreover, these findings are in apparent contrast to *in vivo* studies with other drug classes (e.g., cocaine, nicotine, ethanol) where acute exposure produced a transient depolarization and subsequent activation of mPFC layer 5/6 putative pyramidal neurons [47–50].

Following more prolonged opioid exposure, reduced metabolic activity within frontal cortical regions of heroin addicts is thought to reflect impaired functionality that contributes reduced control over limiting drug intake [5, 10, 51] as well as affective withdrawal as it correlated with anhedonia in opioid dependent subjects [52]. Alternatively, drug “craving” in opioid users in response to viewing drug-associated cues is correlated with increased activation of frontal cortex regions [41, 53–58]. This dichotomy is reinforced by clinical imaging studies in cocaine addicts [53, 59] and preclinical findings in cocaine self-administering rats that exhibit a progressive reduction in basal activity of putative pyramidal neurons in the mPFC but increased activity in response to cocaine- and cocaine-related cues [58]. Similarly, exposure to environmental cues linked morphine reward is strongly associated with distinct activity in select neuron populations in the PrLC [60], and reinstatement of heroin-seeking increases neuronal markers of activity such as *c-fos* and *zif268* [61–63].

These observations suggest that PFC neurons may undergo unique forms of plasticity that permit them to exhibit a hypo- and hyperactive state following prolonged drug use (Figure 1). *In vitro* electrophysiology studies in acute slices has shown that repeated, but not acute systemic cocaine exposure increases intrinsic membrane excitability in PrL, but not IL, deep layer pyramidal neurons that persists up to 45 days post drug exposure [64–68]. With more prolonged use, PrL pyramidal neurons show a reduction in intrinsic membrane excitability that is more pronounced in in aversion-resistant rats thought to reflect compulsive behavior, and hat restoring this hypoexcitability using optical stimulation of pyramidal neurons alleviates uncontrolled cocaine intake [69]. Presently, no published findings on the effect of repeated opioid exposure on *mPFC* pyramidal neuron excitability exist, however reductions (cell non-specific) in the activity-regulated gene, *c-fos*, have been reported in the orbitofrontal cortex following a two-week chronic escalating-dose regimen of non-contingent morphine (Piao et al., 2017). Further, unpublished findings from our lab have recently observed that following a 14–21 d abstinence period from two weeks of daily remifentanil self-administration, pyramidal neurons in the PrL show increased excitability and spike firing, and that these changes extend to the IL in a specific population of neurons (Anderson et al., unpublished observations). If the duration of self-administration is extended to 30–45 d, PrL neurons are less excitability (Anderson et al., unpublished observation) but exhibit an increased firing capacity at more depolarized potentials – adaptations that could significantly impact cortical information process and thus function.

Intrinsic and synaptic plasticity

Studies to date have identified alterations in the expression and function of numerous voltage-gated and G protein-coupled ion channel conductance as contributing factors

underlying increased excitability and neuronal firing following cocaine exposure, however almost nothing is known regarding intrinsic factors (non-synaptic factors) underlying opioid-induced changes in pyramidal neuron physiology [6, 64–66, 70–77]. Our preliminary findings suggest that similar to repeated cocaine, reductions in the threshold to fire following remifentanil selfadministration align with reductions in metabotropic inhibitory signaling mediated by GABABR-dependent activation of G protein inwardly-rectifying potassium (Girk) channels in Layer 5/6 pyramidal neurons of the PrL region (Hearing et al., 2013; Anderson et al., unpublished observation). However, unlike cocaine, these effects are no longer present following 45 d abstinence – a temporal distinction that aligns with previous findings that incubating effects of cocaine on "craving" and drug-seeking persisted as long as 90 days, this phenomenon peaks at ~12 d post returned to control levels by 60 d following heroin self-administration [78–81].

A number of studies have also provided evidence for enduring changes in glutamate and GABA synaptic transmission following drug exposure. For example, cocaine increases mPFC expression of NMDA and AMPA receptor protein, while chronic alcohol upregulates postsynaptic NMDAR-mediated in layer 5/6 pyramidal cells – the latter of which was associated with elevations in spike-timing dependent plasticity [82–85]. Although opioidinduced glutamate plasticity in the mPFC has been reported, the nature of these adaptations and their functional role in opioid addiction are less clear. Electrophysiology studies indicated that excitatory synaptic strength as measured by changes in the ratio of AMPA-to-NMDA receptor currents in pyramidal neuron is not altered following withdrawal from heroin self-administration (but see [86]), however this may reflect a lack of distinguishing neurons localized to the PrL versus IL and/or plasticity produced by extinction/reinstatement in this study [87]. Alternatively, this same study indicated that short-term glutamate plasticity (in the IL) in the form of AMPAR endocytosis plays a role in reinstatement of drug-seeking [87].

During early withdrawal from an intermediate period of cocaine self-administration, reductions in GABA transmission mediated by the ionotropic, $GABA_A$ receptor, appear to contribute to augmented induction of longterm potentiation at PFC pyramidal neurons, however whether similar adaptations occur following opioid selfadministration is unclear [67, 76]. These modifications, in conjunction with observed increases in excitability of mPFC pyramidal neurons, suggest that a shift in excitation at PFC output neurons may drive initial learning of drug seeking behavior as well as relapse during early opioid use. On the other hand, published work as well as our unpublished findings indicate that hypoexcitability of pyramidal neurons may instead reflect adaptations in synaptic $GABA_AR$ transmission rather than GABAB. In support of this, increased GABAergic inhibition of PrL pyramidal neurons has been shown to facilitate relapse to heroin-seeking [87], while increases in the frequency of IPSCs were found following remifentanil self-administration (Anderson et al., unpublished findings).

Presently, almost nothing is known regarding how opioids alter plasticity in subpopulations of pyramidal neurons based on their anatomical connectivity and physiological phenotype. Effects of opioids on GABAergic interneurons have also not been directly measured, however recent optogenetic manipulation of parvalbumin expressing interneurons indicates

that these neurons play a critical role in cognitive function [88, 89] as well as extinction of reward seeking [90]. As cortical information processing and thus function relies on a balance of excitation:inhibition across multiple neuron types, identifying cell-specific modifications will be an important goal moving forward.

Behavioral and clinical implications of PFC plasticity

The functional implications of the co-occurring increased responsivity to drug-associated cues and reduced basal activation of the mPFC remains a vital question towards understanding how drugs of abuse impair cognitive control. One possibility is that during early drug use, increased excitability serves to lower the threshold for induction of long-lasting plasticity in PFC circuits (i.e., mPFC-to-NAc) important for learning drug seeking and drug taking behaviors or developing drug-cue associations responsible for precipitating craving and subsequent relapse. As drug-cues retain the ability to precipitate craving and activate the PFC, functionality of PrL circuits related to motivation and initiation of drug-seeking may be maintained, with reductions in basal metabolic activity serving to allow only drug-associated cues to ably activate PFC networks and thus maintain control over behavior [58, 91].

Emergence of compulsive and uncontrollable opioid use likely reflects impaired function of the numerous frontal cortical regions as well as increasing activation of neural networks responsible for habit-like behavior [69, 92–97]. Clinical findings indicate that heroin addicts exhibit attention bias in drug-associated contexts and often display increased impulsivity, cognitive inflexibility, and impaired attention [98, 99] that are strong predictors of heroin abuse and relapse [100–102]. Although impulsivity and inflexibility are not synonymous with compulsivity or habit, impulsiveness – either intrinsic or drug-induced – appears to increase vulnerability toward compulsion and habit and may ultimately lead to substance abuse [4, 103, 104]. Moreover, perseverative responding despite its adverse consequences (cognitive inflexibility) is a significant predictor of poorer cocaine addiction treatment outcomes [105].

Preclinical studies in rodents have highlighted the PrL as a critical substrate for cognitive flexibility and attention [106–113]. Recent findings showed reduced excitability of PrL pyramidal neurons in compulsive cocaine-seeking rats, which could be rescued by in vivo optogenetic stimulation of this region [69], thus the observed hypofunction of the PrL pyramidal neurons following remifentanil may contribute to perseverative drug seeking. This is substantiated by impaired performance in mice exhibiting hypo-, but not hyperfrontal states (Anderson et al., unpublished observation). Alternatively, impulsive behavior appears to align more readily with altered functionality of the more ventral IL aspect of the mPFC as well as the OFC [114, 115]. As our unpublished observations indicate that adaptations in IL pyramidal neuron excitability are likely pathway-specific, exploring how opioids alter ILC and OFC-associated circuits will likely provide additional insight into how frontal cortical dysfunction contributes to opioid abuse.

Increasing evidence indicates that subpopulations of cortical pyramidal neurons exhibit distinctions in anatomical connectivity, molecular and physiological profile (i.e., expression of dopamine D1 vs. D2-receptors), and excitatory/inhibitory innervation that define how

they undergo experience-induced plasticity and provide an anatomical frame work to regulate complex behavior related to cognitive control and reward [21, 22, 27, 28]. Given this framework, it is plausible specific PFC circuits are activated by opioids and associated stimuli, whereas concomitant impairments in other circuits – perhaps those exhibiting hypoactivation – contribute to opioid-related deficits in cognitive control and perpetuate a shift in the balance of behavioral control to more dorsal striatal (i.e., habit) circuits following cue activation

NUCLEUS ACCUMBENS

The NAc is a heterogenous structure that can be divided into a core and shell region based on anatomical connectivity and presumptive role in reward-related behavior [116–122]. GABAergic medium-spiny neurons (MSNs) make up a majority of all neurons in the NAc and receive coordinated input from glutamatergic afferents arising from cortical and limbic brain regions that elicit physiological and behavioral responses [123–126]. Canonically divided into two main subpopulations based on D1- or D2-type dopamine receptor expression and efferent regulation of basal ganglia output structures [127–132], these two subtypes display unique intrinsic physiology, differentially undergo drug-induced plasticity, and play dissociable (often opposing) roles in drug-reward-related behavior [126, 133–138].

Intrinsic MSN physiology

Activity of NAc MSNs is dependent on synaptic input as well as intrinsic membrane properties that directly influence the probability and pattern of neuronal firing (i.e. excitability). These intrinsic properties are dependent on factors extrinsic to the synapse, such as expression and function of voltage-gated and G protein-coupled channels and are known to be altered by drugs of abuse [6, 70–75], but often take a backseat to research focusing on adaptations in transmission mediated by synaptic receptors.

At present, relatively little is known regarding the effect of opioids on intrinsic physiology. Following 10 d of abstinence from repeated non-contingent morphine increase firing capacity of MSNs [74, 75]. While these studies did not identify MSN subpopulations based on dopamine receptor expression, morphine plasticity was examined based on membrane properties, i.e., the intrinsic excitability and spike adaptation. Morphine increased the initial firing frequency and decreased the train duration in “type I” MSNs that show high levels of intrinsic excitability basally, without altering action potential threshold (rheobase). Alternatively, morphine reduced rheobase (increased excitability) of “type II” MSNs, without altering firing frequency or train duration [74]. In contrast to the shell, repeated morphine suppressed excitability in unidentified NAc core MSNs [71]. Although the exact mechanisms underlying morphine adaptations based on neuron sub-type are unclear, increases in NAc shell MSN excitability is due in part to increased activation of extrasynaptic NMDA receptors which in turn inhibits sustained voltage-gated potassium currents, reduced excitability in the core aligns with upregulation of inwardly-rectifying potassium channels [71, 74, 139].

Interpreting the relevance of changes in the NAc core versus shell is challenging given how little is known about how the overall MSN firing is affected by the interplay between

excitatory synaptic inputs projecting to MSNs (which are enhanced following long-term withdrawal of both cocaine or morphine) and MSN intrinsic excitability. Furthermore, it is unclear how alterations in MSN intrinsic activity and their inhibitory regulation of projection sites during long-term withdrawal regulate drug-seeking behaviors. Reduced intrinsic excitability of MSNs likely leaves these neurons less responsive to activation by excitatory drive, whereby only increased glutamate release driven by exposure to drug-related stimuli is sufficient to overcome this dampening of activity – thus increasing signal-to-noise ratio for drug-associated stimuli and reducing it for other stimuli [140].

Notably, intrinsic changes following morphine exposure also appear to directly contrast psychostimulant-induced adaptations. For example, in the shell, repeated non-contingent cocaine or amphetamine exposure increased various K+ currents while decreasing background Na+ and voltage-gated Ca2+ currents mediated by N− and R−type channels in unidentified MSNs that translated into suppression of MSN firing capacity in acute brain slices 1–21 d following the final drug exposure [73, 141–143]. MSNs in the NAc core on the other hand exhibit increased excitability during acute psychostimulant withdrawal, that unlike the shell, returns to control levels by day 10 of withdrawal [73]. The drug-specific discrepancies on MSN intrinsic excitability are intriguing to say the least. Particularly difficult to interpret are the opposing effects in the NAc core given its role in the in the motor activating effects of abused drugs, and that cocaine and morphine doses used in these experiments both produce prominent behavioral sensitization. However, these results appear to align with in vivo studies have previously shown differential responses in single-unit recordings during cocaine and heroin self-administration [144]. Future work using transgenic mice will be of value to address critical questions, including how these properties align based on the expression of D1 or D2Rs and how changes in excitability contribute to regulation of drug-seeking behavior.

Opioid reward and relapse-related glutamate plasticity

Ample evidence has shown that glutamate transmission at NAc MSNs contributes to opioid reward, withdrawal, and relapse [8, 9, 39, 40, 43, 108, 139, 145–152]. However neuronal “interpretation” of this glutamate release is complex, as it depends on the afferent, MSN subtype (i.e., D1- vs. D2-MSN), and efferent connectivity (i.e., VP or SN) [130, 153–156]. This complexity combined with the fact that drug-induced modifications in NAc glutamate transmission often involve a postsynaptic receptor number and/or conductance [157], presynaptic release mechanisms, and glutamate clearance mechanisms, represents a major challenge towards identifying the nature and locus of opioid-induced plasticity and how specific neural circuit modifications uniquely contribute to aspects of opioid addiction (dependence versus relapse). Below we will highlight what is known regarding changes in glutamate plasticity within the NAc at both the pre- and postsynaptic level and what circuits these modifications manifest.

AMPA- and NMDA-type ionotropic glutamate receptors are the primary mediators of rapid glutamate transmission and exert a profound influence on synaptic plasticity and cellular physiology [158]. Changes in the conductance, expression, and localization (e.g., synaptic vs. perisynaptic) of these receptors plays a key role in drug-induced and experience-related

plasticity -- making these receptors a key target for studying how opioids promote persistent addicted behavior and development of future pharmacotherapies. Recent electrophysiological findings indicate that repeated non-contingent morphine increases excitatory drive at NAc shell D1-MSNs, while reduced it at D2-MSNs. The increase in synaptic strength reflects upregulation of AMPAtype receptor signaling through insertion of GluA2-lacking calcium permeable AMPARs as well as enhanced glutamate release probability [75, 134, 135]. Alternatively, weakened D2-MSN signaling reflects a reduction in presynaptic release and a time-dependent loss of AMPAR expression and dendritic spines [134, 135]. Similar to cocaine this augmented synaptic strength is not immediately present, as no changes in glutamate receptor signaling were observed 12 h following the final exposure – highlighting a need for time to develop [134–136, 149].

Unlike cocaine, increases in synaptic strength did not extend to MSNs in the NAc core [134], however recent unpublished observations indicate that AMPAR transmission (mEPSC frequency and amplitude) is increased at D1-MSNs in the core and shell following 10–14 d of withdrawal from remifentanil self-administration (Madayag et al., unpublished observations).

Dependence/Withdrawal Glutamate Plasticity

The enduring nature of adaptations within the mPFC-NAc pathway indicate that these changes likely contribute to strengthening of drug-seeking behavior and subsequent relapse in response drug-associated stimuli (Figure 2, top). However, evidence indicates that upregulation of NAc AMPAR signaling also plays a critical role in the development of dependence and expression of withdrawal symptoms. For example, chronic morphine exposure elevated GluA2-lacking AMPAR surface expression in the NAc and intra-shell infusion of a GluA2-lacking selective antagonist blocked naloxone-precipitated affective, but not somatic, withdrawal [152] [152]. Electrophysiology studies following repeated systemic morphine indicate that this upregulation may occur selectively at PVT-to-NAc shell D2-MSN synapses, and contributes to establishing withdrawal-related aversive memories [159]. Given that morphine withdrawal increases extracellular glutamate levels in the NAc (Sepulveda et al., 1998) and appears to increase release probability at D1- and D2-MSNs (pooled afferents) (Madayag et al., unpublished observation), it is possible that upregulation of excitatory signaling at D1-MSNs contribute to conditioned reward and relapse similar to those observed following intermittent non-contingent morphine [134, 135] whereas “priming” of D2-MSNs via increased AMPAR receptor activation is responsible for withdrawalrelated symptoms, with specific pathways contributing to unique aspects of this withdrawal (i.e., negative affect vs. somatic; Figure 2, bottom) that may lead individuals to increase use in attempt to mitigate these negative symptoms.

Pathway-specific plasticity

Increasing evidence indicates that the nature and locus of opioid-induced plasticity in the NAc indicates that this plasticity dictates the relationship to behavior. Initial examination of plasticity within mPFC-to-NAc circuits using optogenetics has shown that IL-to-Shell synapses are strengthened by increased insertion of GluA2-lacking receptors selectively at D1R-MSN synapses following 10–14 withdrawal from repeated non-

contingent morphine exposure [99]. Preliminary findings from our lab have shown that similar adaptations occur at D1-MSN IL-to-Shell synapses following abstinence from remifentanil self-administration (Madayag et al., unpublished observations). While the functional implications of this plasticity following opioid self-administration are unclear, our previous work has shown that reversal of morphine-induced pathophysiology using *in vivo* optogenetic stimulation (10 Hz) of IL-to-Shell inputs disrupts reinstatement of morphine-evoked conditioned place preference [134]. Information regarding adaptations within the PrL-to-Core pathway is essentially non-existent, however recent examination of this pathway following remifentanil self-administration showed an increased presence of synaptic GluA2-lacking AMPAR and release probability at D1-MSNs and reduced excitatory drive at D2-MSNs, the latter of which may reflect adaptations in at the post and presynaptic level (Madayag et al., unpublished observation).

It is tempting to speculate that the emergence of plasticity in the more motor-centric core region of the NAc reflects the use of an operant- and goal-directed based model of opioid self-administration, as non-contingent exposure did not alter AMPAR transmission (or release probability) following non-contingent morphine, however it is also possible that enduring plasticity in the NAc core is primarily expressed at synapses receiving significant innervation from PrL afferents [134]. Regardless, the functional role of this plasticity requires further exploration, as work to date has primarily highlighted a role for the IL-to-Shell pathway in opioid relapse [39, 40, 148, 151, 160]. Based on previous circuit lesion studies [39, 40, 148, 160] it is possible that plasticity within the PrL-Core circuit is responsible for maintaining drug- and drug-cue associations responsible for driving relapse-related behavior, whereas context-based drug-associations are retained by plasticity in the IL-Shell circuit and that these adaptations work in concert to maintain relapse vulnerability.

Examination of circuit plasticity outside of cortico-accumbens circuits indicates that glutamate release probability is elevated at BLA- but not PrL-to-Core MSNs as early as 2 hours following an escalating regimen of morphine over 5 days [161]. Alternatively, while release probability is unchanged at BLA- and PVT-to-Shell MSNs within the first 24 h of repeated non-contingent morphine, there is an upregulation of GluA2-lacking AMPARs at PVT-to-Shell inputs selectively on D2-MSN that when reversed suppressed somatic withdrawal and aversive memories [159]. Taken together, these data highlight an intriguing possibility that enhanced transmission at thalamic transmission at D2-MSNs promote dependence/withdrawal-related negative affective states that drive continued use, whereas developing adaptations within PFC-to-NAc circuits that produce a shift in the ratio between excitatory synaptic drive at D1R- over D2R-MSN synapses represent enduring pathophysiology that drives relapse. Regardless, these data highlight a need to better understand the temporal, state-dependent, and cell-specific dynamics of opioid-induced pre- and postsynaptic plasticity, as it will provide better insight into how each may contribute to unique aspects of behavior (i.e., reward and relapse versus dependence and withdrawal).

Intrinsic and extrinsic factors influencing opioid abuse—A wealth of clinical data indicates that environmental and genetic factors contribute to an individuals susceptibility to addiction. Although outside the scope of this review (see Mistry et al., 2014 for a review), heritability of opioid abuse has been linked into part to polymorphisms in the genes

encoding for dopamine d2 receptors, mu and delta opioid receptors, as well as neurotrophic and growth-related factors such as BDNF and NGF (Mistry et al., 2014). Although the co-occurrence of prolonged environmental and psychological stressors has also been linked to increased risk for opioid abuse, a critical unresolved question is how stress influences opioid use and what specific opioid- and stress-induced adaptations in cellular physiology and synaptic plasticity lead to these maladaptive behaviors. Moreover sex differences in drug use and stress responsivity is evident in humans and animal models, however a vast majority of work continues to focus primarily on males -- leaving major gaps regarding the influence of sex on drug- and stress-induced neural plasticity and behavior [162–164]. In susceptible populations, women escalate cocaine use more rapidly and show a greater tendency to relapse and experience a loss of voluntary control of intake [165, 166].

Despite a 100% increase in the number of women using heroin in recent years [167, 168], data on sex differences in opioid use are relatively lacking. Human studies have shown that women report greater craving and exhibit increased vulnerability to relapse than men [168, 169], however the underlying mechanism for this sex difference are unknown. Our preliminary findings indicate that hypoexcitability states in mPFC pyramidal neurons emerges following only 14 d of self-administration and that these changes may have significant implications for cognitive function and relapse. An important unanswered question is whether this reflects a leftward temporal shift whereby females exhibit hyperexcitability following a shorter period of drug administration (e.g., 5 days), or if this shift occurs due to intrinsic differences in pyramidal excitability (Figure 1A) across sexes [170]. Moreover, it remains unclear whether hypofrontal states reflect a shift in the corticostriatal circuits driving behavior, such as those regulating habit behavior, or if mPFC-NAc circuits are still required for initiation of this behavior.

Although difficult to causally disentangle multiple variables, identifying the locus, and temporal dynamics of corticostriatal plasticity produced by opioids and stress as well as relevant sex-specific and genetic-based differences that contribute to this plasticity and impact later opioid use in susceptible populations, will advance our understanding of how these modifications uniquely contribute to behavioral deficits in addiction and neuropsychiatric disease and aide development of more targeted and impactful therapies to treat opioid use disorders.

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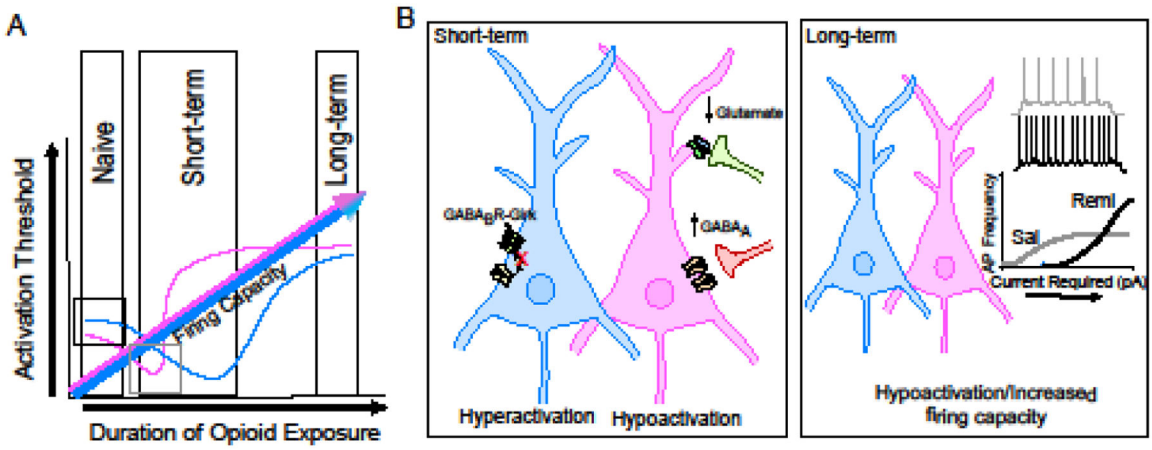

Figure 1. Time- and sex-dependent adaptations in PFC pyramidal neuron physiology and underlying mechanisms.

Data indicate that in males, short-term exposure to opiods increases the intrinsic excitability PrL pyramidal neurons, in part through a downregulation in metabotropic inhibitory signaling mediated by $GABA_BR$-Girk transmission **(A-B)**. Following prolonged exposure, the activation threshold is increased (reduced excitability) in males – a phenomenon that occurs after only two weeks of self-administration in females **(A-B)**. Hypoexcitable states appear to reflect reductions in synaptic AMPAR transmission as well as increased $GABA_A$ transmission and coincides with an increase in action potential frequency at more depolarized potentials **(B)** indicating that while these neurons are more difficult to initiate firing, once activated, mechanisms normally in place to restore firing to basal levels is impaired. Although the function implications are unclear, hypoactivation states may contribute to an impaired ability of the mPFC to exert inhibitory control, that may be further exacerbated by increased (disorganized) firing that disrupts cortical information processing or may contribute to the pathological strengthening of drug-seeking/taking behavior in response to drug-associated cues.

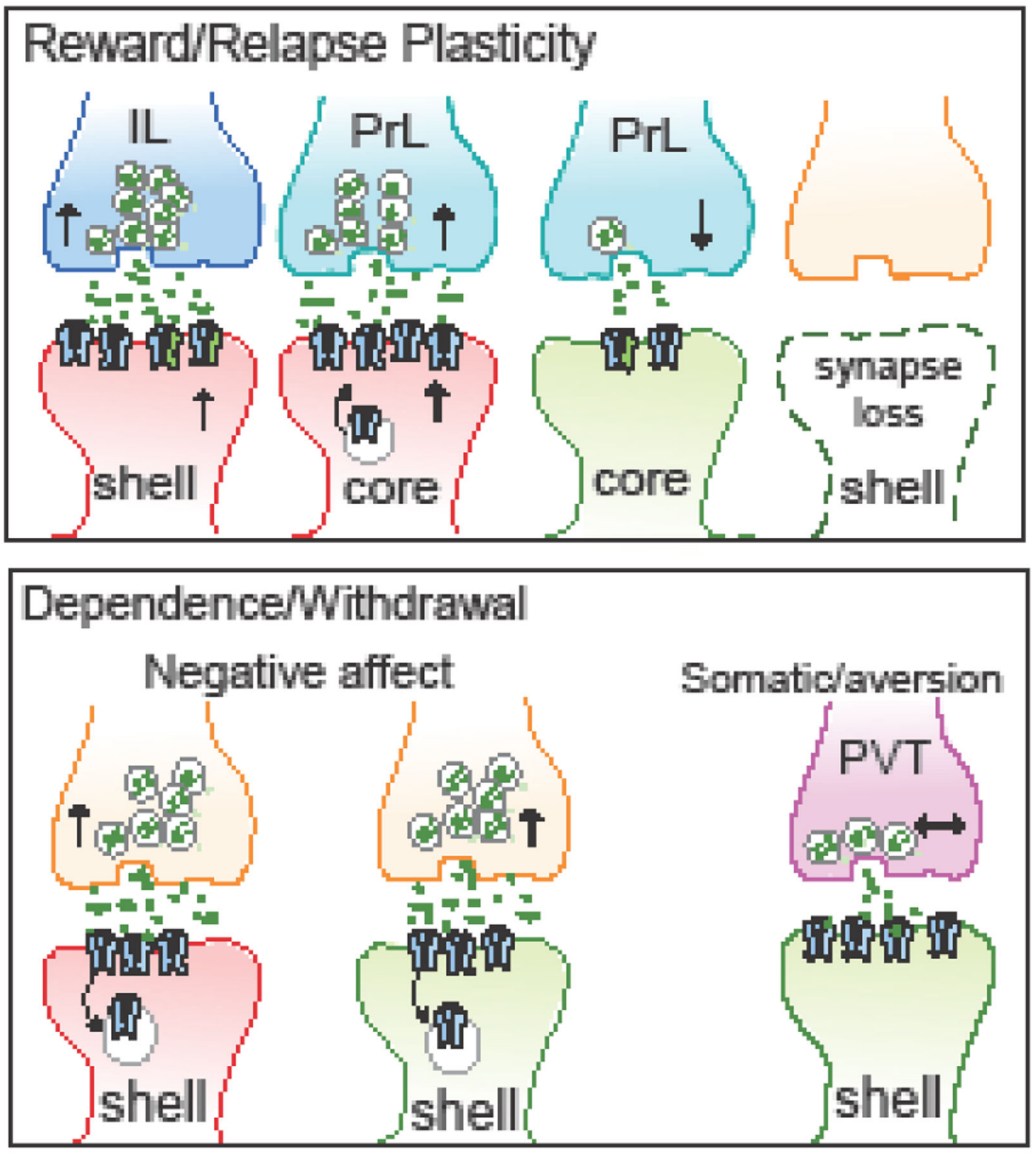

Figure 2. Proposed role of known opioid adaptations in nucleus accumbens glutamate transmission in opioid addiction.

Repeated exposure to opioids promotes a number of pre- and postsynaptic modifications in excitatory currents, most of which appears to be mediated by the ionotropic AMPA-type receptors. **(Top)** Enduring adaptations at mPFC-to-NAc synapses aligning with plasticity associated with establishing learned drug associations, drug-seeking/taking behavior, and relapse. Modifications include increased glutamate release probability and insertion of AMPARs that are permeable (GluA1/GluA1; blue-blue) or impermeable (GluA1/GluA2; blue-green) at PrL-to-Core (light blue) and IL-to-Shell (dark blue) synapses on D1-MSNs (red) as well as reduced excitatory drive and increased synapse numbers in D2-MSNs (green). These cell-specific adaptations promote an overall shift in excitatory drive within D1- and D2-MSN circuits that favors strengthening of D1-MSN pathways. **(Bottom)** The cellular, temporal, and mechanistic nuances of NAc glutamate plasticity contributing to dependence and withdrawal are less clear. Morphine withdrawal is associated with increased

extracellular glutamate, which may reflect increased release probability or impaired clearance, or both. It is possible that upregulation of excitatory signaling plays distinct roles depending on the MSN sub-type, with increased signaling at D1-MSNs reflecting changes related to reward/relapse whereas signaling at D2-MSNs is responsible for withdrawal-related symptoms, with specific pathways contributing to unique aspects of this withdrawal (i.e., negative affect vs. somatic).