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Review

The role of mesolimbic circuitry in aversive signaling and opioid dependence

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SUMMARY

Positive reinforcement via mu-opioid receptor-mediated disinhibition of ventral tegmental area (VTA) dopamine neurons is crucial in opioid use disorder (OUD). However, VTA dopamine neurons are more heterogeneous than initially thought, both at the molecular and computational levels. Besides encoding reward prediction error, subpopulations of dopamine neurons have also been proposed to encode salience and aversion. How opioid use alters these distinct encoding properties remains unclear. Negative reinforcement—learning to avoid adverse outcomes like withdrawal—also drives chronic drug use, implicating the mesolimbic dopamine system in both positive and negative reinforcement in OUD. This review explores how chronic opioid use modifies heterogeneous VTA neuron populations, enhancing sensitivity to aversive stimuli, promoting negative affect, and motivating withdrawal-avoidance behaviors. We also examine how chronic pain may amplify these effects and discuss the importance of charting circuit-level interactions between chronic pain and OUD for clinical translation.

OVERVIEW

Chronic pain is a significant source of disability worldwide and carries major health and societal costs. Opioid therapy remains a common treatment for chronic pain, especially in the United States (US), but with potentially serious side effects, including addiction. New mitigation strategies for both chronic pain and opioid use disorder (OUD) are urgently needed. Efforts to design new strategies require a better understanding of the circuitry subtending chronic pain and OUD, including an understanding of where the circuits for these disorders interact.

Opioid pain medications exert their effects primarily through the activation of mu-opioid receptors (MORs). MORs are highly expressed in brain regions that regulate pain (e.g., periaqueductal gray [PAG], thalamus, anterior cingulate cortex, prefrontal cortex, and insula) and reward (e.g., ventral tegmental area [VTA] and nucleus accumbens [NAc]). This dual action of MOR signaling on pain- and reward-associated circuitry triggers two defining effects of opioid consumption: analgesic/pain-relieving effects and euphoria or intense feelings of well-being. Much research on OUD has focused on the role of the dopaminergic mesolimbic system in producing reinforcing euphoric effects in response to MOR agonists (e.g., morphine, heroin, and fentanyl). However, new observations of heterogeneity in the dopamine system indicate its role may be far more complex.

Importantly, recovery from OUD is difficult in part because of the pronounced and long-lasting affective symptoms of withdrawal that motivate continued opioid use.[1–4] Here, we propose that prolonged opioid use induces maladaptive plasticity in the mesolimbic system, which promotes continued drug use to avoid aversive withdrawal states. We hypothesize that there is maladaptive plasticity not only in aspects of the mesolimbic circuitry involved in reward processing but also in neural populations encoding salience or aversion, which could be particularly relevant to understanding withdrawal. Our hypothesis is inspired by growing evidence for multiple subpopulations of VTA neurons based on function, molecular identity, and input and output patterns. As methodological advances permit more specific targeting of VTA subpopulations, future work can test the causal roles of specific populations in addiction behaviors, including withdrawal. Finally, given the overlap in the neural circuitry implicated in chronic pain and OUD, we discuss how chronic pain may create a persistent negative state that increases the risk of OUD and/or the risk of relapse through similar mechanisms.

THE VTA IS A KEY NODE IN OUD CIRCUITRY

Most drugs of abuse are thought to induce progressive adaptations of the neural systems involved in reinforcement learning. Central among these is the mesolimbic dopamine system, and in particular the projections from the VTA to the NAc, which plays a critical role in reinforcement learning and is widely implicated in substance use disorders. Although dopamine-independent mechanisms of opioid reinforcement have also been described[5]—for example, morphine can induce conditioned place preference even in dopamine-deficient mice[6]—the predominant body of research has centered on dopaminergic pathways as primary drivers for opioid misuse and addiction. The significance of dopamine for positive reinforcement was first demonstrated by classic experiments showing that animals will repeat behaviors to receive electrical stimulation of the medial forebrain bundle, which contains dopaminergic axons,[7,8] and that dopamine antagonists suppress this reinforcement.[9] More recently, the reinforcing effects of dopamine have been confirmed with specific optogenetic manipulation of dopamine neurons in various contexts.[10–16]

Opioid receptors and peptides are heavily expressed throughout the mesolimbic dopamine system,[17] and MOR agonists, like other drugs of abuse, acutely increase dopamine release.[18] Animals will self-administer morphine or MOR agonists into the VTA (e.g., Bozarth and Wise[19] and Devine and Wise[20]), and MOR agonist infusions in the VTA induce conditioned place preference (e.g., Bals-Kubik et al.[21]). Further, optogenetic[22] or chemogenetic[23] inhibition of dopamine neurons reduces heroin self-administration in rodents, suggesting that dopamine is important for reinforcing MOR agonist use.[24]

Canonically, the acute rewarding effects of opioids are thought to result from the disinhibition of dopamine neurons in the VTA. VTA dopaminergic neurons themselves do not express MORs, but many of their inputs do.[25–28] Significant inhibitory control of VTA dopamine neurons comes from neurons in the rostromedial tegmental nucleus (RMTg). These GABAergic neurons express MORs and are inhibited by opioids.[28,29] MOR agonists also decrease the inhibition of dopamine neurons from other GABAergic input sources, including NAc,[28] ventral pallidum,[30] and local GABAergic interneurons in the VTA.[24,31] Inhibition of RMTg results in the disinhibition of dopamine neurons in the VTA,[27,28] increasing the firing rate of dopamine neurons[25,27,28,32] and increasing dopamine release in downstream targets.[23,33]

The primary projection target of VTA dopamine neurons is the NAc, a key region mediating the rewarding effects of opioids. The NAc is divided into two major subdivisions, the core and shell, and most drugs of abuse seem to preferentially target the NAc shell.[34–36] For instance, chronic self-administration of heroin and morphine selectively increases extracellular dopamine in the NAc shell, but not in the core,[35,37] and pharmacological blockade of dopamine signaling in the shell, but not the core, disrupts morphine-induced conditioned place preference[38] (see Di Chiara et al.[39] for a review on the specific roles of NAc core vs. shell). Even within the shell, functional specialization exists: the dorsomedial shell (dmNAc) appears particularly responsive to reward,[40–42] while the lateral shell and ventromedial shell (vmNAc) may subserve distinct behavioral roles,[42–44] an aspect we explore in more detail below.

As opioid use becomes chronic, there is a progressive dysregulation of the acute, positively reinforcing effect of opioids. During chronic morphine exposure, for instance, dopamine firing rates increase,[45] while GABAergic RMTg firing rates decrease.[46] Consistently, disinhibition of dopamine neurons by acute administration of morphine is reduced during chronic morphine exposure.[45] During withdrawal from opioids, dopamine neuron activity is reduced,[47] consistent with the idea that aversive states inhibit dopamine release. Additionally, morphine-mediated disinhibition of dopamine neurons remains reduced during withdrawal[45] even though GABAergic RMTg neurons are effectively inhibited by acute morphine in abstinence,[46] suggesting decreased efficacy of inputs from RMTg to the VTA. Furthermore, repeated activation of MORs decreases receptor efficacy, resulting in tolerance.[48–50] These effects could lead to increased opioid consumption as patients try to achieve the same levels of rewarding sensations. Repeated exposure to opioids also leads to increased activation of aversion- and stress-related neural circuitry, particularly during withdrawal.[1,51]

While this focus on positive reinforcement through disinhibition of dopamine neurons has yielded important insights, it only offers a partial understanding of OUD. Another crucial factor driving repeated drug use—and repeated MOR agonist use in particular—is the intense urge to escape withdrawal. Indeed, prior experience with opioid withdrawal is an important factor that can shape drug-seeking behavior.[52] In patients using opioids for chronic pain management, who will also have heightened pain levels arising during drug abstinence, this effect may be heightened even further.[1,2,51] Thus, both positive and negative reinforcement play a part in OUD and are important to consider in designing effective therapies.[1,24]

The circuitry underlying negative reinforcement in OUD involves several brain regions known to be involved in aversive processing, including the amygdala, hippocampus, cingulate cortex, and other midbrain regions such as the medial raphe, the PAG, and the habenula.[2] During withdrawal, these regions exhibit heightened activity, which is thought to motivate behaviors aimed at seeking relief from negative moods.[2,24] Interestingly, new lines of evidence suggest that the VTA may also play a critical role in negative reinforcement and negative affect in withdrawal states.[28,53,54]

FUNCTIONAL HETEROGENEITY OF THE MESOLIMBIC DOPAMINE SYSTEM: REPRESENTATIONS OF AVERSIVE STATES

Midbrain dopaminergic neurons have been the focus of intense research in the context of OUD for decades. A great deal of research suggests that dopamine neurons in the VTA encode reward prediction error (RPE), which is defined as the difference between expected and experienced reward.[55–57] Given that MOR activation disinhibits VTA dopamine neurons, leading to the release of dopamine in the NAc, MOR agonists have been understood to mimic the responses triggered by unexpected, highly rewarding events, promoting positive reinforcement. With tolerance, the diminished effects of MOR agonists on dopamine release can contribute to the vicious cycle of addiction, with individuals seeking higher doses or more potent agonists to produce effects equivalent to their original experience.[58]

Although historically it was believed that VTA dopamine neurons homogenously encoded RPE, work over the last 10–15 years has challenged this view.[56,57,59] For instance, RPE-encoding dopamine neurons should decrease their activity for aversive

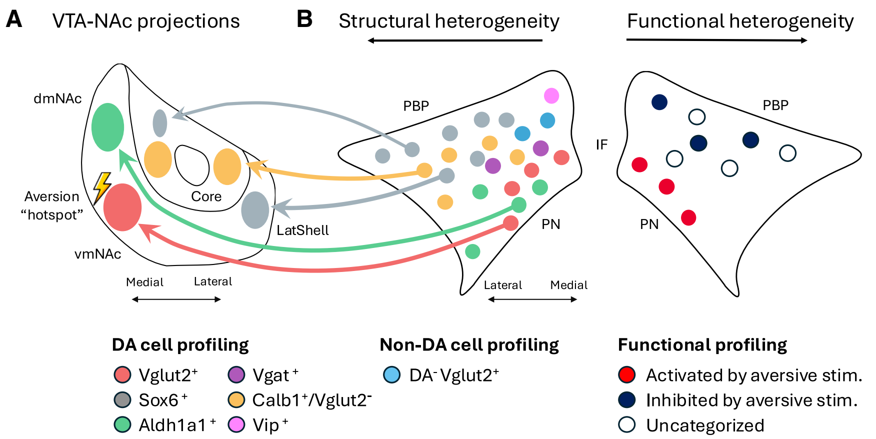

Figure 1. Illustration depicting VTA dopamine projections to NAc and corresponding functional and molecular heterogeneity

(A) The NAc and its subregions, including the NAc dorsomedial shell, the NAc ventromedial shell, the lateral shell, and the NAc core, receive projections from several subtypes of neurons from the VTA.

(B) A unique set of neurons projects to the ventromedial shell NAc, a region that has been labeled the "aversion hotspot" in the NAc since it shows positive-going transients upon noxious stimuli. The NAc lateral shell and core receive projections from more dorsolateral VTA dopamine (DA) neurons, which show more traditional RPE-type responses. This projection specificity likely arises from distinct neural populations, which can be coded molecularly and functionally. The VTA has also been shown to show functional specificity. While some neurons fire for rewards and are inhibited by aversive stimuli (RPE-like, more laterally localized), other neurons, mostly localized in the para-nigral nucleus, also respond to aversive stimuli such as a noxious shock. Indeed, the VTA is known to be molecularly heterogeneous, and VGlut2+ DA neurons (left panel) seem to co-localize well with the neurons that fire for aversive stimuli (right panel). Taken together, DA neurons in the medial VTA are well suited to code for aversive stimuli in a molecularly and projection-specific way.

Note that the illustration above depicts current understanding of molecular and functional heterogeneity and its spatial distribution and does not represent actual data. PN, paranigral nucleus; PBP, parabrachial pigmented area; IF, interfacial nucleus; vmNAc, ventromedial NAc shell; dmNAc, dorsomedial NAc shell; LatShell, lateral NAc shell.

events. However, a subset of VTA dopamine neurons is activated by aversive and noxious stimuli, as well as cues predicting these stimuli.[42,60–62] The presence of dopamine neurons activated by aversive stimuli raises the interesting idea that heterogeneous populations of RPE-encoding and non-RPE-encoding VTA dopamine neurons could play different roles in representing aversive states and in guiding learning from these states. Parsing which aspects of aversion are encoded by separable populations of dopamine neurons, including those responsive to opioid withdrawal states, is an important goal.

Subpopulations of dopamine neurons with different responses to aversive stimuli seem to have different downstream targets (Figure 1). While shocks and shock-predicting cues evoke decreases in dopamine in many NAc subregions—consistent with RPE—a "hotspot" of shock-evoked increases in dopamine release has been identified in the vmNAc.[41,42] Increases in activity for aversive stimuli have also been observed in dopamine neurons that project to the medial prefrontal cortex and basolateral amygdala.[61,63–68] A major point that requires clarification is whether dopamine signals that display increases in response to aversive stimuli are specifically aversion-sensitive or whether these neurons are instead "salience" neurons, which would be expected to increase their activity in response to unexpected salient events of both positive and negative valence.[69] Although there is evidence for salience-encoding in various midbrain dopamine neuron subpopulations,[69–71] some evidence suggests that vmNAc-projecting dopamine neurons could specifically encode aversion. These dopamine neurons show strong positive responses to shocks and to shock-predicting cues but do not show positive responses to reward-predicting cues.[42] Furthermore, stimulation of glutamatergic inputs to these dopamine neurons from the lateral habenula causes real-time place aversion, which would not be expected for a salience-signaling dopamine pathway (where one would expect either no preference for an unvalenced signal or a preference for novelty). Interestingly, increases in vmNAc dopamine for shock-predicting cues are present during Pavlovian training, where cues predict unavoidable shock, but fade after instrumental avoidance training, where cues can be used by the subject to avoid shock.[42,72] This finding suggests that vmNAc dopamine plays a role in learning about aversion, perhaps by imparting aversive motivational salience, but not in sustaining the performance of avoidance actions over time.[73] Identifying an aversion-specific dopamine neuron subpopulation may be difficult using projection targeting alone if dopamine cell types are intermixed or projecting to small neighboring NAc subregions. Going forward, identifying specific aversion-sensitive dopamine populations may be aided by advances in dissecting molecular markers to differentiate dopaminergic subpopulations.[63,67] If distinct gene expression patterns are identified in aversion-sensitive dopamine neurons, these would be useful from both basic and translational perspectives.

In addition to dopamine neurons that increase activity in response to aversive stimuli, canonical reward-responsive dopamine neurons have been shown to play a role in negative reinforcement and avoidance learning by representing aversive cue outcomes as decreases in firing and the cessation of aversive states (e.g., footshock punishments) as increases in firing.[74,75] In the context of avoidance learning, where subjects can avoid shocks by performing an action, deepening decreases in dopamine in the NAc core during aversive cues are correlated with better performance of actions to avoid aversive outcomes.[73]

Dopamine transients have also been observed by several groups at the offset of shocks,[61,76,77] yet the meaning of this signal and whether it reflects the rewarding nature of pain relief (an affective signal) or instead serves as a prediction error (a teaching signal) is still to be clarified. Dopamine released in response to pain cessation could be a relief prediction error (unexpected relief from a painful experience) or a safety prediction error (unexpected return to a "safe" state). Prediction errors would be expected to fade with learning, as outcomes become predictable, and to reappear during unexpected events. It is possible that representations of relief and safety are present in different dopaminergic subpopulations and that both could play a role in avoidance learning relevant to opioid withdrawal and relapse. There is also some evidence for differential relief and safety prediction error encoding in different NAc subregions. For example, one study found that dopamine projections to the dmNAc are important for relief but not safety learning,[78] while others suggest that dopamine in the NAc core encodes a safety prediction error.[77]

Adding further complexity, mesoaccumbens dopamine pathways may sometimes exert opposing influences on behavior. For instance, a paradoxical increase in opioid-driven locomotion has been observed following dopamine depletion in the NAc,[79] despite the fact that dopamine release is generally considered critical for this behavior.[80] Thus, there may be a competition between mesoaccumbens dopamine pathways that promote and inhibit movement following opioid treatment. This observation, together with the functional heterogeneity within the VTA and the NAc, highlights the need to better characterize these sub-circuits and their modulation by opioids.

When identifying functional heterogeneity within the VTA, a key observation that emerges across studies is that topography matters,[59] although there is still functional heterogeneity within VTA subregions.[81] Figure 1B provides a high-level topographical overview of functional dissociation within VTA subregions. For instance, Brischoux et al.[61] show dopamine neurons that are activated by aversive stimuli are primarily located in the ventral VTA. Similarly, lateral–medial functional dissociations have been reported within the VTA.[59] Since there is a significant historical bias toward the recording of dopamine neurons in the lateral VTA and vmNAc-projecting dopamine neurons are located medially,[59] it is likely that VTA aversive hotspots remain understudied and poorly understood.

Given such functional heterogeneity, what also remains to be clarified is how these putatively aversion- and reward-encoding subregions are modulated by opioids. For example, the different mesoaccumbens dopamine pathways may be differentially modulated by the direct and indirect effects of MOR activation. In addition to the well-defined pathway by which MOR activation in GABAergic neurons disinhibits VTA dopamine neurons,[82] vGlut2-positive neurons in the anterior VTA also express MORs.[83] Notably, MORs in vGlut2-positive neurons are necessary for the aversion and somatic withdrawal symptoms in the naloxone-precipitated withdrawal assay.[84] We also note that approximately 50% of GABAergic neurons in the substantia nigra pars reticulata (SNr) also express Oprm1, and MOR blockade in this region is sufficient to blunt heroin reward[22]—suggesting a distinct pathway with potential relevance to OUD.[82] Nevertheless, given the scope of this review, which centers on VTA circuitry, we will not discuss this pathway further.

Finally, also of note, kappa opioid receptors (KORs) are also expressed in the VTA and contribute significantly to the regulation of stress and aversive states, which in turn influence dopamine-related behaviors and opioid responses.[85–87] Unlike the disinhibitory effects of MOR activation, which enhance dopamine release and mediate reward, activation of KORs suppresses dopamine transmission and induces aversive emotional states such as anxiety and dysphoria.[87–89] These effects are particularly relevant in the context of stress and drug withdrawal, where KOR activation may promote drug-seeking behavior through negative reinforcement—that is, the motivation to alleviate the unpleasant emotional state induced by KOR signaling.[90] Thus, while MORs mediate the positive reinforcing effects of opioids, KORs may drive stress-induced relapse. Additionally, KORs are expressed not only on dopamine neurons but also on afferents to the VTA, adding another layer to the functional complexity.[91]

RELATING ANATOMICAL AND MOLECULAR HETEROGENEITY OF THE VTA TO FUNCTIONAL IDENTITY

In addition to evidence of functional heterogeneity, midbrain dopamine neurons also have heterogeneous anatomical and molecular features. Thus, an important path to targeting and studying functionally distinct dopamine populations will be determining how molecular identity corresponds to functional identity. Identifying molecular markers for function subpopulations could, for example, allow selective pharmacological targeting for therapeutic purposes.

Single-cell profiling has permitted the identification of multiple closely related subpopulations of dopamine neurons within the VTA (Figure 1B). These genetically identified groups display distinct anatomical locations, albeit with significant intermingling, and have distinct projection patterns.[92–94] *Sox6*-expressing dopamine neurons are concentrated in the dorsolateral/parabrachial region of the VTA[95] and project primarily to the NAc lateral shell and parts of the core.[94] Complementary to *Sox6*, albeit with some overlap, there is a *Calbindin*-expressing population concentrated in the ventromedial VTA, although some cells are also observed in the parabrachial/dorsolateral VTA. *Calbindin*-expressing neurons project to the majority of the NAc, except for the most lateral regions. A subset of the *Calbindin*-expressing population is a *Vglut2*-positive VTA subset, which is predominantly located in the medial VTA and projects to the medial shell of the NAc (msNAc), along with the prefrontal cortex, basolateral amygdala, and entorhinal cortex.[95] Different from the molecular logic of the substantia nigra pars compacta (SNc), in the VTA, *Aldh1a1*-expressing neurons are a subset of the *Vglut2*/*Calbindin* population, have their somata located most ventrally, and comprise a subset of the dopamine projection to the msNAc. The *Vgat*-defined subset is a smaller population with an as-yet undefined projection pattern. In addition to those subpopulations, a *Vip*-defined subset is located in the dorsal raphe (DR) and PAG regions and projects specifically to the central amygdala and the oval nucleus of the bed nucleus of the stria terminalis.[94] Thus, despite the closely related nature of dopamine neuron subtypes and the blurriness of transcriptomic boundaries between them, genetic labeling strategies can uncover key anatomical distinctions.

The function of these dopamine subpopulations remains unknown, but their anatomical differences suggest possibilities. For example, given that *Sox6*-positive dopamine neurons project to the core/lateral NAc, they may provide the putative safety learning signal in the NAc described above.[77] Additionally,

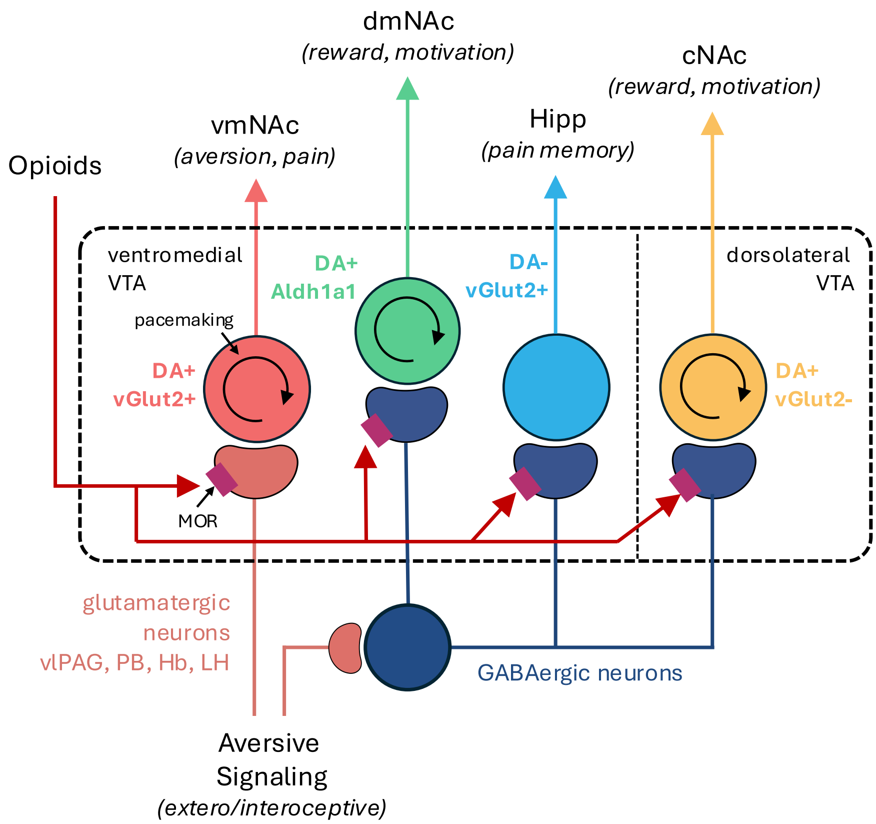

Figure 2. Circuit organization and opioid control of inputs to VTA
VTA circuit adaptations and modulation by mu-opioid receptor (MOR) include aversive signaling, especially following long-access exogenous opioid exposure. Three key concepts are hypothesized. The first centers around the "classical" model of OUD involving MOR disinhibition of VTA dopamine (DA) neurons projecting to the core (cNAc) and dorsomedial shell of the NAc (dmNAc). The second is centered on the novel medial (paranigral [PN]) VTA circuit projecting to vmNAc. The inferred disfacilitation of DA and glutamate co-release in the vmNAc by MOR signaling is hypothesized to modulate pain sensation and behavioral responses to aversive events (e.g., escape behaviors). The third VTA circuit, broadly engaging vGlut2+ non-DA neurons in the dorsal hippocampus, is hypothesized to involve the affectively colored contextual aspects of pain and opiate consumption memories.

dopamine projections implicated in aversive responses, for example, in the basolateral amygdala, prefrontal cortex, and vmNAc, appear to predominantly express *Vglut2*. *Aldh1a1* neurons project to the dmNAc, likely carrying reward signals. In chronic pain and OUD, and their intersection, both the reward-responding and the aversive-responding dopamine subgroups likely play a role, and therefore defining them clearly is imperative.

The molecularly defined populations may have different functions and different connected circuits. For example, the MOR-driven inhibition from the RMTg may be biased toward reward-responsive dopamine neurons. Thus, opioid-mediated increases in dopamine would be restricted to their projection targets. Conversely, aversive signaling dopamine neurons may be under more glutamatergic drive, which, when removed by MOR activation, results in a disfacilitation (Figure 2). Therefore, engaging with the heterogeneity in the dopamine system is critical to examine separable circuits. With a newer, higher-resolution map of VTA dopamine molecular heterogeneity,[92,93] definable genetic subtypes can be individually investigated for their functions. We can then begin to understand whether molecular subtypes map onto functional subtypes. For example, a recent study found that some dopamine subpopulations in the SNc, though they have intermingled somata and projections, have distinct movement-related signaling.[96] This indicates that there can be separable roles for dopamine subpopulations that are only uncoverable by genetic and molecular labeling. Once we have a full picture of the dopamine subtypes, their inputs and outputs, and the adaptations in chronic pain and addiction paradigms, we will have an improved understanding of whether the same or different dopamine cells participate in pain and OUD and whether different dopamine cell types are important for different stages of these disorders (e.g., acute to chronic pain, craving, seeking, withdrawal, etc.). We could then consider subtype-specific targeted therapies to modulate the neurons implicated in specific pathology individually.

VTA INPUTS AND THEIR LINKS TO AVERSIVE PROCESSING

The VTA is innervated by a broad range of ascending and descending projection systems. Over a hundred brain regions have been shown to project to the VTA using modern anatomical methods.[97–99] This innervation has a mediolateral topography, as well as cell-type specificity within the VTA.[43,100,101] In general, more lateral VTA dopaminergic neurons have afferent connectomes that relay information about reward and appetitive events.[63,102] Although much less studied, the more medial regions of the VTA, like the paranigral region, are innervated by regions involved in processing aversive or salient (valence-neutral) events.[44,61] Many of the regions innervating the VTA, particularly the medial VTA, also robustly express MORs, raising the possibility that they confer an opioid dependence to the activity of VTA dopaminergic neurons and are involved in OUD.[23,101,103,104] Currently, there is also emerging evidence supporting a specific topographic organization of GABAergic inputs across medial-lateral subdivisions of the VTA,[105] which could dictate the topography of dopamine disinhibition. Further, recent studies suggest that VTA dopamine neurons projecting to different targets may receive distinct GABAergic inputs.[98,102] For example, dopamine neurons projecting to the msNAc are inhibited by msNAc dopamine striatal projection neurons (dSPNs) through $GABA_A$ receptors, while those projecting to the lateral shell are inhibited via $GABA_B$ receptors.[102] By contrast, dSPNs from the lateral shell preferentially suppress local VTA GABAergic interneurons, resulting in disinhibition of VTA dopamine neurons.[102] Whether MORs are differentially expressed or functionally segregated along these projection-defined circuits remains largely unknown.

Although there are reports of MOR inhibition of VTA GABAergic interneurons, the vast majority of the MOR modulation of VTA neurons is widely viewed as dependent upon MOR modulation of circuits that are extrinsic to the VTA.[22] Key regions involved in this modulation, particularly those linked to aversive processing, are reviewed next.

Neurons in the lateral habenula (LHb) are activated by aversive stimuli and inhibited by reward, so the LHb is considered an "anti-reward" hub.[63,106] LHb neurons negatively modulate lateral VTA dopamine neurons either by activating local GABAergic interneurons or by activating VTA-projecting RMTg GABAergic neurons.[25,61] Optogenetic activation of LHb neurons projecting to the RMTg di-synaptically inhibits lateral VTA dopaminergic neurons and blunts cocaine-seeking.[107] However, there is also evidence that some LHb glutamatergic neurons convey aversive information directly to the medial VTA.[63] Moreover, anterograde tracer experiments have shown that LHb neurons preferentially project to the medial VTA with little direct connectivity with the lateral VTA.[63] In agreement with this anatomical data, optogenetic activation of LHb neurons projecting to the medial VTA results in place avoidance. Lastly, MOR agonists inhibit a subset of LHb neurons by presynaptically inhibiting excitatory glutamatergic drive, and injecting morphine into LHb causes analgesia.[108,109] However, the modulation of MORs on LHb terminals in VTA is largely unknown.

The ventrolateral PAG (vlPAG) is another region that projects to the VTA, which is well known to be activated by aversive events.[110,111] Neurons in the vlPAG modulate nociception and behavioral mobilization in response to aversive stimuli.[111–113] Moreover, local infusion of MOR agonists blunts the response to aversive stimuli, presumably through both ascending and descending mechanisms.[114,115] Anatomical and physiological data have revealed that the vlPAG neurons innervating the VTA are a mixture of inhibitory GABAergic and excitatory glutamatergic projection neurons.[116,117] How these two projection systems interact to control the VTA is just beginning to be explored. In a recent study, it was shown that activation of cranium nociceptors increases c-FOS expression in vlPAG. Optogenetic activation of this group of neurons induces avoidance, whereas inhibition promotes conditioned place preference in rodent models of migraine—but not in pain-free controls.[110] What is less clear is how this mixed population of vlPAG projection neurons modulates the VTA circuitry. The glutamatergic vlPAG neurons appear to preferentially innervate lateral VTA non-dopaminergic neurons, creating a possible disynaptic inhibition of neighboring dopaminergic neurons.[118] By contrast, GABAergic vlPAG neurons innervate dopaminergic and non-dopaminergic neurons in the lateral VTA.[117] Interestingly, activation of vlPAG GABAergic neurons projecting to the lateral VTA induced immobility, which may be consistent with a role in aversive signaling.[113] Additionally, activation of MORs attenuated the inhibitory postsynaptic currents (IPSCs) in lateral VTA dopaminergic neurons evoked by optogenetic stimulation of this pathway and blocked the induction of long-term potentiation (LTP) at this synapse.[113] Taken at face value, these studies suggest that vlPAG projections convey information about aversive events to the lateral VTA in parallel pathways. The GABAergic component of this projection system appears to directly innervate lateral VTA dopaminergic neurons. By contrast, the glutamatergic projection may primarily modulate dopaminergic neurons through local GABAergic interneurons.[118] Thus, both pathways would suppress the activity of lateral VTA dopaminergic neurons that signal reward. Opioids may suppress this vlPAG signaling to lateral VTA dopaminergic neurons by presynaptically suppressing GABA release from vlPAG terminals and those of local GABAergic neurons—in agreement with the commonly held view that the reinforcing effects of opioids are a consequence of disinhibition of dopaminergic neurons projecting to the NAc.[23,119] What is unresolved is whether these vlPAG projection systems also reach the medial VTA implicated in coding aversive events and whether MORs modulate this input.

The lateral hypothalamus (LH) is also richly connected with the VTA. The LH is a complex region linked to a wide range of functions, like feeding, reward, drug-seeking, and the response to aversive events.[120–122] LH neurons include glutamatergic, GABAergic, and orexinergic subtype.[89,123] Several lines of evidence suggest that the function of the LH innervation of the VTA may vary along its mediolateral axis. For example, stimulation of LH glutamatergic axons in the medial VTA is aversive and triggers avoidance, whereas their inhibition stops avoidance behavior.[42] By contrast, stimulating LH GABAergic terminals in the lateral VTA is rewarding and promotes place preference by inhibiting local GABAergic interneurons. Consistently, activating LH glutamatergic terminals in the lateral VTA causes place avoidance.[124] LH orexinergic neurons are also implicated in both reward- and aversion-related processes.[125] Most orexinergic neurons express vGlut2, indicating that they co-release glutamate and orexin.[126] Optogenetic stimulation of LH orexinergic terminals in VTA induces place preference and increases the release of dopamine in the NAc.[89] Injection of an orexin receptor 1 (OxR1) antagonist into VTA attenuates morphine-induced place preference.[127] In addition, inhibiting OxR1 in VTA diminishes morphine-induced potentiation of glutamatergic synapses and morphine-induced attenuation of GABAergic synapses on dopaminergic neurons.[127] These results suggest that this orexinergic input is important for learning associations between location and opioid reward and potentially modulating the acute effects of opioids on dopamine release. Moreover, in rodents, genetic knockout of orexin relieves the morphine withdrawal syndrome following naloxone administration.[128] In parallel, human studies indicate that chronic opioid use increases the number of orexin-expressing neurons and enhances orexin signaling.[129,130] Importantly, dual orexin receptor antagonists (DORAs), such as suvorexant, have been shown to attenuate opioid withdrawal symptoms and reduce craving in individuals with OUD.[131] These findings align with the role of LH orexin neurons in arousal, reward processing, and stress—functions that are dysregulated during withdrawal.[132,133] The therapeutic effects of orexin antagonism in humans suggest that targeting the orexin system may modulate motivational and affective components of withdrawal, thereby reducing relapse risk.

The parabrachial nucleus (PBN) also plays a key role in OUD. In addition to being crucially implicated in opioid-induced respiratory depression[134]—one of the main causes of OUD-related deaths—the PBN is also another source of information about aversive events that reaches VTA neurons. Optogenetic activation of PBN glutamatergic neurons or inhibition of neighboring GABAergic neurons triggers pain-like behaviors, suggesting that PBN glutamatergic neurons convey ascending nociceptive signals.[135] Moreover, inhibition of these same PBN neurons reduces the depression-like behavior in mice with neuropathic pain,[136] suggesting they promote negative affect. However, optogenetic stimulation of PBN glutamatergic neurons has been reported to excite lateral VTA dopaminergic neurons and reduce pain-related behaviors.[137] These discrepancies probably reflect PBN heterogeneity,[138] as well as that of the VTA. The PBN is also implicated in the actions of opioids.[139] Although it has been shown that activating MORs in the lateral PBN increases activity in forebrain regions related to reward and cognition,[140] the role of MORs in regulating the PBN projection to the VTA remains to be explored.

Unlike the LHb, vlPAG, and PBN, the RMTg projection to the VTA is largely GABAergic.[141] RMTg GABAergic neurons are excited by aversive stimuli.[25,142] Importantly, these neurons robustly express MORs that both blunt somatic excitability and inhibit their release of GABA onto lateral VTA dopaminergic neurons.[27,32,113] Optogenetic stimulation of RMTg GABA terminals in VTA induces place avoidance, and damage to this region reduces the ability of aversive stimuli to inhibit lateral VTA dopaminergic neurons.[143] Furthermore, selectively activating inhibitory MORs on RMTg GABAergic neurons induces place preference.[144] In agreement with this picture, chemogenetic inhibition of RMTg GABAergic neurons reduces the response to nociceptive stimuli, mimicking the actions of morphine.[33]

Two other regions of the mesopontine area also innervate the VTA. The laterodorsal tegmental nucleus (LDT) and the pedunculopontine tegmental nucleus (PPT) provide both cholinergic and glutamatergic inputs to the VTA.[145–147] These projection systems have been implicated in reinforcement learning and movement.[148,149] Optogenetics and operant assays suggest that PPT glutamatergic neurons projecting to the VTA drive reward learning.[146] PPT cholinergic neurons also may be involved in this process. However, the VTA circuitry mediating these effects is still unresolved. A recent study found that photoinhibition of PPT cholinergic and glutamatergic axons decreases the activity of non-dopaminergic VTA neurons, dampening cue-elicited anticipatory approach behavior.[150] Optogenetic activation of either LDT cholinergic or glutamatergic projections to the lateral VTA seems to be rewarding,[151,152] and suppression of cholinergic inputs has been linked to depression, stress, and social defeat-induced dysfunction of VTA.[153] In agreement, self-stimulation of LDT projections to the lateral VTA increases dopamine release in the NAc.[154,155] On the other hand, foot shock activates LDT GABAergic projections to the VTA, and chemogenetic inhibition of these neurons reduces the response to shock. As one might predict, optogenetically activating these neurons is aversive.[156] Although both the LDT and PPT have been linked to opioid-induced reward and heroin self-administration,[80] the mechanisms underlying this connection are unclear.

The DR is another region that strongly innervates the VTA.[97] DR neurons have been implicated in a wide range of behaviors, including the response to salience, reward, and drugs of abuse.[157] Like many other regions innervating the VTA, the DR is composed of a heterogeneous mixture of serotonergic, dopaminergic, GABAergic, and glutamatergic neurons,[158–160] complicating the dissection of its function. DR serotonergic neurons projecting to the VTA are activated by salient stimuli independent of valence.[161] Activating this subset of DR neurons induces place preference and mice nose-poke for this stimulation.[162] Consistently, stimulating DR glutamatergic terminals in the lateral VTA is rewarding.[42] Lastly, DR dopaminergic neurons are activated after morphine place preference conditioning but not before, implicating them in the memory of drug exposure but not the initial response to drug exposure.[157] Work by Bruchas and colleagues has demonstrated that endogenous opioids released in the msNAc can act on MORs located on the terminals of DR afferents, promoting consumptive behavior associated with palatable rewards.[163] This state-dependent mechanism for endogenous opioid-driven consumption may also extend to opioid modulation of DR projections in other regions, such as the VTA. Furthermore, understanding how different neurotransmitter populations within the DR—such as serotonergic, GABAergic, and glutamatergic neurons—participate in this circuit, and how they interact with neuromodulator systems like lateral hypothalamic orexin, will be critical for elucidating the functional architecture of opioid reward. Overall, as for other regions projecting to the VTA, the role of the DR projection to the VTA in mediating the actions of mu opioids remains to be sorted out.

MEMORY, HIPPOCAMPUS, AND LINKS WITH NEGATIVE REINFORCEMENT

Although less thoroughly investigated compared with other projections of the VTA, the glutamatergic/GABAergic projection from the VTA to the dorsal hippocampus[164,165] may have an important impact on both chronic pain and OUD. Activation of this input is believed to be important for attributing negative value to specific contexts.[166] A negative affective state is a hallmark of chronic pain,[75,167] and it is possible that VTA-dorsal hippocampus modulates the aversiveness of spatial contexts associated with pain perception. The hippocampus undergoes major functional and cellular changes in rodent models of neuropathic pain, and human brain imaging data show reduced hippocampal volume and connectivity in chronic pain patients.[168,169] Importantly, pharmacological and optogenetic or chemogenetic manipulations of the hippocampus modulate sensory (tactile thresholds) and affective (conditioned place preference) components of pain in rodents.[170,171] Opioid receptors also modulate hippocampal networks. All three types of opioid receptors (δ, k, and μ) are expressed in the hippocampus, although at relatively low densities.[172] Nevertheless, the glutamatergic input from the VTA to the dorsal hippocampus can be dramatically inhibited by the activation of MORs,[166] which reduces neurotransmitter release through inhibition of presynaptic N-type calcium channels.[173]

Given the role of the VTA-to-hippocampus glutamatergic projections in the attribution of negative valence to contextual memories, this pathway is likely engaged in the negative affective state of OUD. In line with this concept, it was recently shown that upregulation of the KOR system in the dorsal hippocampus contributes to the negative affective state associated with morphine withdrawal.[174] In a more general and speculative scenario and in keeping with the role of the hippocampus in declarative memories,[175,176] it may be suggested that the hippocampus provides neurobiological encoding of maladaptive memories (such as drug consumption and neuropathic pain-related episodes), linking these affectively colored experiences to spatiotemporal contexts. Three intriguing case reports suggest a relationship between memory, opioid use, and chronic pain.[177,178] In all cases, the patients had severe, long-standing chronic pain and were being treated with large doses of opioids. Following an episode of retrograde amnesia, they inexplicably recovered from their chronic pain and were able to wean off opioids without experiencing withdrawal symptoms. Although currently no mechanistic interpretations exist for these cases, they provide clinical support for the role of memory in chronic pain and OUD and support the idea that both conditions represent forms of maladaptive memories, perhaps through shared cellular mechanisms. Indeed, in a recent human study, we have shown that increased exchange of information between the hippocampus and the episodic memory network within days of injury predicts the development of chronic pain,[179] tentatively linking the formation of such maladaptive memories with chronic pain—yet their role in the development of OUD remains to be studied in the future.

While the VTA affects the dorsal hippocampus largely through non-dopaminergic inputs, surprisingly, only a small minority of the dopaminergic terminals in this area originate in the VTA. Indeed, the majority of the dopaminergic inputs to the dorsal hippocampus were found to originate in the locus coeruleus,[180] and activation of this dopaminergic input was shown to increase spatial learning by increasing the attention component in the learning phase. This same input, however, was also shown to be activated by salient events, leading to enhanced fear conditioning.[181] Such inputs, therefore, are likely involved in both pain perception and OUD, two conditions where salience plays a critical role.

Another property shared by substance use disorders and chronic pain is that both these conditions show sex differences.[182–184] There are also sex differences in opioid modulation of the hippocampus.[166,185,186] Interestingly, oxycodone injections not paired with place conditioning have little effect on opioid expression patterns in the hippocampus,[187] supporting the idea that the hippocampus is not simply responsive to opioids but mediates the association of affective states with a specific context.[166] Accordingly, recent work shows that opioid analgesic tolerance can develop through associative learning mediated by glutamatergic projections from the ventral hippocampus to the prefrontal cortex.[188] In this context, animal work shows that relapse to drug addiction is mediated by activation of hippocampal output.[189] Accordingly, repeated cocaine exposure potentiates the effects of ventral hippocampal stimulation on dopamine release in the NAc,[190] while excitatory projections from the dorsal hippocampus to the core of the NAc are believed to induce dopamine release that may foster motor programs underlying drug-seeking.[191] Accordingly, optogenetic stimulation of the dorsal hippocampal projections to the NAc induces spatial memory-related appetitive behaviors.[192]

Thus, although the neurobiology of the VTA to the hippocampus remains incompletely characterized, modulation of VTA inputs to the hippocampus should be considered important in chronic pain and OUD in chronic pain by supplying aversive coloring to contextual memories, while direct inputs from the dorsal hippocampus to the VTA appear to play a major role in drug-seeking behavior.

PUTTING THE PIECES TOGETHER: A DISFACILITATION HYPOTHESIS AS INTEGRAL TO MOR-MEDIATED AVERSIVE SIGNALING IN THE VTA

In summary, the VTA displays functional, anatomical, and molecular heterogeneity, with certain dopamine subpopulations—particularly in the medial VTA—increasing their activity in response to aversive or noxious stimuli. These aversive-responsive neurons are well suited for aversive processing since they receive inputs from regions known to encode aversion and pain, including the vlPAG, DR, and LH. Further, these input regions to the VTA are expected to be heavily modulated by opioids. Additionally, medial VTA dopamine neurons exhibit distinct molecular profiles and specific projection patterns, with some of these clusters (e.g., VGluT2+ and Aldh1−) projecting prominently to the vmNAc, a region that has also been linked with the processing of aversive stimuli and pain.[193] Taken together, a parsimonious interpretation is that aversive signaling may be enhanced by chronic opioid usage, hence leading to a disfacilitation of medial dopamine VTA neurons. In turn, this heightened sensitivity to aversive stimuli may increase withdrawal severity, heighten pain, and promote seeking behavior through negative reinforcement.

THE ADDED BURDEN OF CHRONIC PAIN: AVERSIVENESS AS A FACILITATOR FOR NEGATIVE REINFORCEMENT IN OUD

The mesolimbic circuitry for OUD intersects with the circuitry for pain. Mesolimbic circuitry is modulated by painful stimuli, pain relief by drugs, and context-dependent pain modulation.[75] For instance, placebo analgesia has been shown to increase NAc activity through dopamine release,[194] and relief from painful stimuli leads to increased NAc activity.[195] Reward-like responses to pain relief can also be observed in the offset of phasic painful stimuli: when a given painful stimulus subsides, there is increased activity in the NAc,[196,197] and particularly in the NAc core,[198] a finding that has since also been observed in rodent imaging studies.[199] Further, during phasic painful stimuli, NAc activity tracks human subjective pain intensity ratings,[197] directly linking it with the affective valuation of the subjective pain

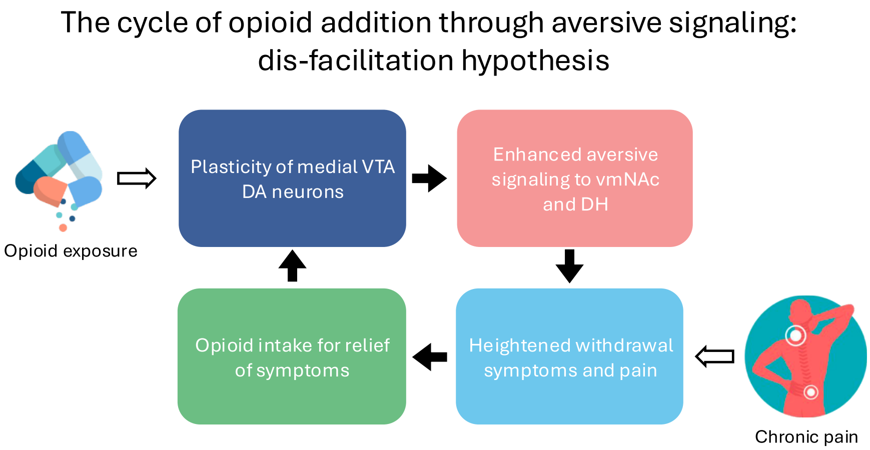

Figure 3. A disfacilitation hypothesis for OUD through negative reinforcement
Repeated opioid exposure is known to induce long-term plastic changes in VTA dopamine (DA) neurons. We posit that changes in VTA DA neurons caused by chronic opioid usage can heighten aversive signaling to upstream targets, including the ventromedial shell of the NAc and the dorsal hippocampus. This, in turn, heightens the severity of aversive withdrawal symptoms and pain. Chronic pain acts here as an additional stressor, further increasing aversive signaling. Since opioids act on this circuit and may inhibit aversive signaling through MOR-mediated inhibition of glutamatergic projections to VTA neurons, they offer relief for symptoms, thus acting as a motivational drive for repeated opioid consumption—ultimately establishing a maladaptive, self-reinforcing cycle.

perception. Further, the NAc shell shows increased activity after the onset of a phasic painful stimulus.[197] Further evidence for the role of dopamine in pain comes from the efficacy of deep-brain stimulation in the VTA for chronic cluster headache.[200,201] Additionally, a case report shows a substantial improvement with VTA deep-brain stimulation in a patient with chronic post-stroke central pain,[202] but see Hollingworth et al.[203] Preclinical evidence also supports the role of the VTA in pain. Chemogenetic stimulation of medial VTA dopamine neurons projecting to the vmNAc of the NAc—the presumed aversion hotspot—can reverse mechanical allodynia in neuropathic mice (spared nerve injury [SNI] model),[204] and stimulation of the vmNAc D2-receptor medium spiny neurons themselves can mimic such findings, while their inhibition further aggravates mechanical allodynia.[193] Similarly, optogenetic stimulation of NAc-projecting VTA dopamine neurons in both neuropathic and cancer models of chronic pain also reduces mechanical allodynia.[205] On the other hand, NAc-core projecting lateral VTA neurons seem important for the motivational and affective effects of chronic pain: chemogenetic stimulation of these neurons further reduces social interaction without affecting mechanical allodynia.[204] Actively manipulating dopamine receptors on medium spiny neurons in the NAc also contributes to pain relief[206]: D2 or D1 receptor agonists in NAc medial and lateral shell attenuate SNI-induced neuropathic pain. Direct optogenetic stimulation of D1 and D2-receptor neurons in the medial shell, the lateral shell, and the NAc core also transiently decreases neuropathic pain-related behaviors. The effect of stimulating D1 NAc-core neurons to induce pain relief seems to be mediated by activation of GABA interneurons in the VTA.[206] Given evidence that dopamine release in the medial shell NAc increases with aversive stimuli, we may expect activation of this projection to enhance rather than diminish the behavioral effects of chronic pain. Perhaps the similarity in effects across NAc subregions in this work is due to the inability to target specific dopaminergic subpopulations. Future research can take advantage of advancements in molecular profiling to test the hypothesis that dopamine neurons activated by aversive stimuli play a distinct role in pain-related behaviors.

The exact function of the mesolimbic system in pain is only now starting to be studied. It is generally agreed that pain plays a crucial role in learning, which is likely mediated by the midbrain dopamine system. Pain is aversive and salient, while the relief of pain is rewarding.[207] The role of pain in OUD is likely complex: opioids are used to nullify the aversive components of pain and might also enhance the rewarding aspects of pain relief. The clinical study of chronic pain as a risk factor for OUD is sparse, as it is difficult to dissociate causes and consequences. Yet in preclinical models, there is some evidence that chronic neuropathic pain (SNI model) facilitates morphine-seeking behavior.[208] It has also become clear that there is plasticity in the mesolimbic system in chronic pain because of the persistent barrage of nociceptive signaling. There is now compelling evidence that chronic pain leads to changes in VTA firing patterns: in the SNI model, there is a significant decrease in the spontaneous firing rate of VTA neurons,[193,209] and mice with nerve ligation or bone cancer pain show reduced excitability of NAc-projecting dopamine neurons.[205] Decreased dopamine VTA firing rates were also observed in a rat spinal cord injury model, together with an increase of local inhibition by GABAergic interneurons.[210] *In vivo* studies in a rodent model of chronic inflammatory pain (CFA) show decreased activity in VTA dopamine neurons during motivational tasks and increased phasic activity in response to reward.[211] This was accompanied by increased hyperpolarization of VTA dopamine neurons and a decreased resting membrane potential.[211] Inflammatory injuries also lead to increased GABAergic inhibition, both from GABA interneurons and from GABAergic projections from the RMTg. These changes in the dopaminergic circuitry have been further linked to anhedonia-like behavior, a common symptom in chronic pain patients.[211] Human brain imaging studies corroborate the idea that chronic pain leads to changes in dopamine signaling. Human positron emission tomography (PET) studies show that chronic back pain patients have reduced ventral striatal D2/D3 receptor binding, and the levels of receptor binding correlate with both pain threshold and negative affect.[212]

We hypothesize that the balance of engagement of dopamine circuitry for aversion, salience, and reward may be disrupted in chronic pain. Importantly, changes in the balance of engagement of different subpopulations (via changes in inputs, excitability, and/or synaptic adaptations in downstream targets) could contribute to OUD risk in individuals with chronic pain. The overall hypothesis (Figure 3) posits that OUD may initially arise from uncontrolled reward-seeking behavior following opioid exposure for pain treatment but is critically maintained by the drive to avoid withdrawal and the negative emotional states associated with opioid absence. Chronic pain induces neural plasticity within putative aversive dopamine neurons in the medial VTA projecting to the vmNAc, leading to heightened aversive signaling. This enhanced aversion may intensify withdrawal symptoms and the affective dimension of pain, culminating in a hyperkatifeia state that promotes continued drug use and relapse, thereby sustaining the addiction cycle. Importantly, although the dopamine system is on average hypoactive in chronic pain, an important open question is whether there are subpopulations of (e.g., aversion activated) dopamine neurons that are hyperactive in chronic pain. This will be important when considering possible dopamine-based therapies for chronic pain and their likelihood to influence OUD risk. Overall, these changes in aversive subpopulations—alongside the well-established plasticity in motivational and reward-related circuits within the VTA and NAc[75,213]—may increase the vulnerability of chronic pain patients to OUD.

CONCLUSIONS

Chronic pain and OUD are dual epidemics linked by sociological factors as well as underlying neural circuitry. Here, we outline evidence that components of the mesolimbic circuitry itself provide multiple pathways for mutual reinforcement of the aversive states of chronic pain, opioid exposure, and opioid withdrawal. Fragmentary but accumulating evidence is consistent with this idea from the systems-level human brain imaging results and the combination of physiological, behavioral, and genetic profiling of VTA neurons, their inputs, projections, and the control of their inputs with distinct MOR circuits. Although this review provides adequate evidence for the general concepts, much remains unclear and needs further studies.

OUD affects more than 2 million people in the US alone, and this number has been steadily rising.[214–216] The latest numbers attest to the relentless expansion of the opioid epidemic: the Centers for Disease Control and Prevention (CDC) reports 108,000 overdose deaths in 2021 (an additional 15% increase from the previous year, ten times more than a decade ago), of which 80% are linked to opioid use.[217] Chronic pain is a global problem that dramatically diminishes the quality of everyday life.[218] Opioid prescription dispensation in the US has steadily declined in the last 20 years.[219,220] Still, in 2019, 22% of US adults with chronic pain used prescription opioids in the previous 3 months.[221,222] Thus, millions of chronic pain patients continue to be managed with opioids, mainly because there are no widely accepted alternative treatments. Yet, systematic reviews show that long-term opioid use has minimal efficacy in chronic pain,[223–226] and opioids may not be superior to non-steroidal anti-inflammatories in managing chronic pain.[227–230] Pain and analgesic opioid prescriptions[231,232] constitute a recognized entry point toward misuse, OUD, and overdose.[233] To combat the opioid epidemic, the CDC issued guidelines in 2016 to decrease opioid prescriptions nationwide.[234] As a result, opioid dispensation rates dropped (by 2017, 23% of patients prescribed opioids were being tapered or discontinued[219,220,235]). Perhaps surprisingly, this did not diminish overdoses. Instead, it precipitated new risks and harms. It has since been shown that reducing or discontinuing prescribed opioids increases the risk of overdose, overdose deaths, and suicides.[236] In response, the CDC proposed more tempered guidelines.[237] Overall, opioid dose reduction or discontinuation in chronic pain patients has been challenging.[233,238] The central concept that emerges from this review is that the VTA should be considered a hub regarding the competition between rewarding and aversive processing. In these competing processes, chronic pain increases the addictive potential of opioids and diminishes the success of opioid tapering. Adaptations within the VTA-to-NAc circuit and within the VTA-to-hippocampus circuit should be considered critical processes regarding the interaction between chronic pain and opioid exposure. We acknowledge that other circuits also contribute. For example, the amygdala—a mesolimbic nucleus that integrates affective valence and sensation—receives nociceptive afferents and modulates other limbic and spinal cord circuitry.[239] Yet, the latter remains outside the scope of the current review.

Much of the specifics of VTA circuitry adaptations with chronic pain and opioid exposure remain to be uncovered—for example, the dose, duration, and temporal properties of circuit reorganization; the differential roles of the distinct pathways and their respective adaptations, especially regarding opioid withdrawal-related behaviors; and the success and consequences of opioid tapering. Such knowledge, coupled with the genetically identified VTA pathways, should provide the opportunity to develop novel targets to control both chronic pain and OUD better.

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AUTHOR CONTRIBUTIONS

All authors contributed to writing and editing the manuscript and approved its final version.

DECLARATION OF INTERESTS

The authors declare that the research was conducted without any commercial or financial relationships that could be construed as a potential conflict of interest.

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