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## Nucleus Accumbens Modulation in Reward and Aversion

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### Abstract

The nucleus accumbens (NAc) is a key node of the brain's circuitry that is responsible for translating motivation into action. It has been implicated in playing critical roles in virtually all forms of adaptive and pathological motivated behaviors. It is subject to modulation by a broad array of inputs that influence NAc activity in complex ways that are still poorly understood. Here, we briefly review current knowledge about the behavioral consequences of NAc modulation, focusing on recent studies that use novel techniques developed and implemented over the last decade.

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The nucleus accumbens (NAc), a key node of mesolimbic dopamine (DA) circuitry (Volkow et al. 2017), has long been conceptualized as a critical functional connection between limbic system structures, such as the amygdala and hippocampus, and motor systems including the basal ganglia (Mogenson et al. 1980). In part because of its anatomical connectivity and the well-accepted hypothesis that NAc DA release accounts for the addictive liability of drugs of abuse (Di Chiara and Imperato 1988; Koob et al. 1998; Nestler 2005), the NAc has received attention as a crucial convergence point for neurocircuitry shaping motivated responses to salient rewarding and aversive stimuli (Volkow et al. 2017). Over the last decade, the advent of new methodologies that facilitate sophisticated identification and manipulation of neural circuits has expanded our understanding of the behavioral consequences of NAc modulation. Here, we briefly review some of the most critical of these studies, focusing on work that highlights the importance and complexity of NAc circuits. Furthermore, we attempt to underline some of the many gaps in how modulation of NAc circuit function influences adaptive and pathological motivated behaviors.

### NUCLEUS ACCUMBENS D1 AND D2 MSNs

The major cell types in both the dorsal and ventral striatum are GABAergic medium spiny neurons (MSNs), which comprise ~95% of the total cell population in these structures. They are commonly subdivided into two neuron populations: those that preferentially express dopamine D1 receptors (D1) and those that express dopamine D2 receptors (D2). It remains well accepted that in the dorsal striatum, D1 MSNs are key components of the so-called direct pathway as they form monosynaptic contacts with basal ganglia output nuclei, the

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substantia nigra pars reticulata, and the internal globus pallidus, whereas D2 MSNs are part of the indirect pathway and send axons to the external globus pallidus (Kreitzer and Malenka 2008). In classic models of basal ganglia function, increases in D1 MSN activity promote movement, whereas increases in D2 MSN activity decrease movement (Nelson and Kreitzer 2014). Although recent work makes it clear that this model is oversimplified (Parker et al. 2018), it has been heuristically useful in guiding research efforts and therapeutic interventions such as deep brain stimulation (DeLong and Benabid 2014).

In large part based on these models describing the role of the dorsal striatum in motor behaviors, NAc D1 and D2 MSNs have been considered to have different anatomical connectivity and therefore subserve different functions. NAc D1 MSNs are commonly thought to project directly to midbrain structures, primarily the ventral tegmental area (VTA), whereas NAc D2 MSNs are thought to project primarily to the ventral pallidum (VP) (Fig. 1; Nicola 2007; Kupchik and Kalivas 2017). This dichotomy applies to both the NAc shell and core, which appear to have different behavioral roles, presumably because of the different inputs that they receive (Di Chiara 2002; Ikemoto 2007; Scofield et al. 2016). Specifically, the shell is thought to be involved in tasks such as reward prediction and affective processing, whereas the core has been proposed to be responsible for acquisition of reward–cue associations and initializing motor actions and therefore may function as an intermediate between the NAc shell and the dorsal striatum. Although some recent studies exploring NAc core and shell circuits suggest some overlap in their behavioral functions (Day et al. 2007; Roitman et al. 2008; Lobo et al. 2010; Bock et al. 2013; Calipari et al. 2016), examining rewarding and aversive behaviors using simple assays such as place preference and self-administration may not detect subtle differences in core and shell functionality. Such differences may be more readily revealed using more sophisticated behavioral assays, real-time measures of neurotransmitter release or neural activity, or input-specific circuit manipulations (Gore and Zweifel 2013; Chuhma et al. 2014; Schmidt et al. 2015; Dreyer et al. 2016; Jedynak et al. 2016; Syed et al. 2016; Sackett et al. 2017; Saddoris et al. 2017).

Several studies using cell type–specific manipulations to investigate the behavioral role of NAc D1 and D2 MSNs support the idea that these two neuronal populations subserve distinct functions (Lobo et al. 2010; Kravitz et al. 2012; Bock et al. 2013; Trifilieff et al. 2013; Danjo et al. 2014; Francis et al. 2015; Calipari et al. 2016; Zhu et al. 2016). For example, optogenetic activation of NAc D1 MSNs reversed the behavioral changes caused by chronic social defeat stress, a model for depression, in susceptible mice, whereas chemogenetic inhibition of NAc D1 MSNs promoted behavioral signs of depression in resilient mice that were not initially affected by the chronic stress. In contrast, repeated activation of NAc D2 MSNs induced social avoidance following subthreshold social defeat stress (Francis et al. 2015). Furthermore, the synaptic adaptations and changes in intrinsic excitability caused by drugs of abuse or stress are different in NAc D1 and D2 MSNs in a manner that appears to contribute to the behavioral adaptations caused by these chronic manipulations (Russo et al. 2010; Lüscher and Malenka 2011; Russo and Nestler 2013; Francis and Lobo 2017).

However, as is the case with the simple rate model for the role of basal ganglia direct pathway and indirect path way function in motor behavior, the simple dichotomy between the roles of NAc D1 and D2 MSNs is being questioned. Recent work found that a substantial proportion of NAc core D1 MSNs project to neurons in the dorsal VP, which is the anatomical target of the traditionally defined indirect pathway (Kupchik et al. 2015). Overall, ~50% of the recorded VP neurons received D1 MSN input, whereas ~90% received D2 MSN input. This study further showed that D2 MSNs target a group of VP neurons directly innervating the thalamus. Hence, D1 MSNs projecting to the dorsal VP may function in an “indirect pathway”-like manner, whereas D2 MSNs may function in a “direct pathway”-like manner (Fig. 1; Kupchik and Kalivas 2017). NAc shell D1 and D2 MSNs also both project to VP cells, which in turn innervate the VTA. Surprisingly, however, the behavioral roles of NAc D1 MSN-VP synapses and NAc D2 MSN-VP synapses following chronic cocaine administration appear to differ (Creed et al. 2016; Heinsbroek et al. 2017).

The specific behavioral roles of NAc D1 and D2 MSNs are also beginning to be elucidated based on the additional targets to which they project (e.g., lateral hypothalamus) and the NAc subregions in which they are located (Al-Hasani et al. 2015; O’Connor et al. 2015; Gibson et al. 2018; Yang et al. 2018). An additional, potentially important distinction in the organization of both the dorsal striatum and NAc, which has not been adequately analyzed, is the presence of so-called patch-matrix compartments (also termed striosome-matrix compartments) (Gerfen et al. 1987; Gerfen 1992; Zahm and Brog 1992; Crittenden and Graybiel 2011; Watabe-Uchida et al. 2012; Brimblecombe and Cragg 2017). MSNs in patch compartments preferentially express  $\mu$ -opioid receptors, a molecular distinction that seems likely to have functional importance. As discussed further below, clearly we are in the early stages of understanding the detailed cellular architecture of the NAc, in terms of subregional input–output organization of its major constituent cell types and their myriad behavioral roles.

## EXCITATORY INPUTS TO NUCLEUS ACCUMBENS

NAc MSNs do not generate action potentials spontaneously, and therefore increases in their activity are driven by excitatory synapses from a range of brain regions (O’Donnell et al. 1999; Scofield et al. 2016). Historically, inputs from the prefrontal cortex (PFC), ventral hippocampus (vHip), and basolateral amygdala (BLA) have received the most attention. However, recent work using the cell type–specific monosynaptic rabies virus tracing technique has revealed a large number of additional brain areas that synapse with NAc MSNs (Barrientos et al. 2018). The advent of optogenetics facilitated behavioral tests of the consequences of activating the major inputs to the NAc, with the somewhat surprising result that activation of inputs from either PFC, vHip, or BLA inputs is reinforcing (Stuber et al. 2011; Britt et al. 2012; Prado et al. 2016; Otis et al. 2017). These findings supported the provocative notion that the specific input driving NAc MSN activity may be functionally irrelevant, despite the different behavioral roles of the brain areas providing the inputs. However, recently it has been reported that activation of glutamatergic inputs from the paraventricular nucleus (PVN) of the thalamus causes aversion, and that these inputs, like the PFC, vHip, and BLA inputs, appear to synapse on both NAc D1 and D2 MSNs (Zhu et al. 2016). This finding poses problems for the simple notion that activation of any excitatory

input to the NAc, independent of its source, is reinforcing and points out the critical importance of understanding the connectivity of individual populations of NAc D1 and D2 MSNs based on their anatomical localization, the targets to which they project, and their molecular properties (e.g., patch vs. matrix).

Conceptually, it makes sense that excitatory inputs from different brain regions will subserve different behavioral functions. In support of this idea, the NAc MSN synaptic adaptations caused by drugs of abuse, primarily cocaine, differ depending on the source of the presynaptic inputs (Lüscher and Malenka 2011; Lüscher 2016). For example, recordings from MSNs in the NAc shell suggest that repeated cocaine administration followed by withdrawal leads to synaptic strengthening of some inputs and weakening of others (Pascoli et al. 2011, 2014; Britt et al. 2012; Ma et al. 2014; MacAskill et al. 2014; Creed et al. 2015; Terrier et al. 2016; Barrientos et al. 2018). Furthermore, as mentioned above, the drug- and stress-induced synaptic adaptations in the NAc depend on whether D1 or D2 MSNs are examined. Evidence that these experience-dependent synaptic changes are functionally important is provided by experiments in which optogenetic reversal of drug-induced synaptic changes rescue behavioral adaptations caused by the drug experience (Pascoli et al. 2011, 2014; Bock et al. 2013; Ma et al. 2014; Creed et al. 2015). Based on these findings, it is possible to generate hypotheses concerning the specific NAc synaptic and circuit adaptations that contribute to rodent models of addiction and depression (Lüscher 2016; Francis and Lobo 2017).

Surprisingly, however, in contrast to the notion that different inputs to the NAc subserve different functions, a recent imaging study using GCaMP to measure activity in excitatory inputs to the NAc from BLA, vHip, and thalamus found that activity patterns, during a discriminant stimulus operant reward-seeking task with food as the reward, varied along the rostrocaudal axis of the NAc (Reed et al. 2018). Furthermore, similar decreases in activity in all three inputs in the rostral NAc shell occurred during feeding, whereas optogenetic inhibition of each pathway individually promoted food consumption. These results suggest that the anatomical location of inputs within the NAc may be as important as the source of the inputs.

The results obtained over the last decade using modern tools of circuit neuroscience offer abundant evidence in support of the notion that the NAc is a critical node of the circuitry that translates motivation into action. However, these results also reveal how little we know about the detailed circuit connectivity by which NAc neurons contribute to behavior. Just a few of the critical questions that need to be addressed for a more sophisticated understanding of how NAc circuit adaptations contribute to behavioral flexibility include: Do individual NAc MSNs receive inputs from all of the major excitatory projection regions or is there functionally important cell-to-cell variability? Are there functionally important differences in the inputs to NAc D1 versus D2 MSNs? How does the detailed connectivity of D1 and D2 MSNs differ in the various subregions of the NAc (e.g., lateral shell, medial shell) and along the NAc rostrocaudal axis, which has been suggested to have powerful influences on appetitive versus aversive behaviors (Reynolds and Berridge 2008)? Do inputs to NAc MSN show functionally important subcellular topography such that some consistently synapse on more distal dendrites and others on more proximal dendrites? How heterogeneous are the

outputs of individual NAc MSNs, and do these outputs show regional variation? In addition to now standard tools such as optogenetics and monosynaptic rabies virus tracing, incorporating new methods such as dual-eGRASP (Choi et al. 2018) will be critical to the development of a more sophisticated and comprehensive understanding of the complex circuitry in which the NAc is embedded to facilitate the translation of motivation into action.

## DOPAMINE ACTION IN THE NUCLEUS ACCUMBENS

In addition to being influenced by direct glutamatergic inputs from a wide range of brain regions, the NAc is the target of numerous neuromodulatory systems with important roles in cognition and motivated behaviors. Almost 50 years ago, the anatomical demonstration that the NAc is a major target for midbrain VTA DA neurons (Ungerstedt 1971) led to a large body of work demonstrating the behavioral importance of NAc DA release (Wise 2008; Volkow et al. 2017). Because all drugs of abuse lead to DA release in the NAc, as does intracranial electrical stimulation of brain sites that support self-stimulation, initial conceptualizations of the role of NAc DA release suggested that it contributes to instrumental conditioning because it signals “reward” as a direct consequence of the generation of a pleasurable experience (Wise 2008; Volkow et al. 2017). This simple concept was subsequently questioned in part because lesions of DA projections to the NAc impaired the willingness of rats to perform work for larger food rewards while not affecting their hedonic responses (Salamone et al. 1994; Berridge and Robinson 1998). In addition, it became apparent that humans will continue using drugs of abuse even when the acute experience of the drug is no longer pleasurable. These kinds of observations led to the influential idea that DA release in the NAc encodes “incentive salience” (Berridge and Robinson 1998) and that it is important to separate the neural circuit mechanisms that mediate motivation from those that mediate pleasure (Volkow et al. 2017).

Arguably the most influential idea about the functional role of NAc DA release is based on classic *in vivo* electrophysiological recordings in nonhuman primates, suggesting that midbrain DA neurons encode a bidirectional reward prediction error (RPE) signal, which is critical for many forms of instrumental learning (Schultz et al. 1997; Schultz 2016). Specifically, increases in DA neuron firing occur in response to a conditioned stimulus as it is learned to predict a reward, as well as when a better than expected reward occurs after the conditioned stimulus. In contrast, decreases in firing occur when an expected reward does not occur, perhaps signaling “disappointment.” In addition to the studies that directly recorded midbrain DA neuron activity (Schultz 2016), several investigations measuring subsecond DA transients in the NAc using fast scan cyclic voltammetry (FSCV) are consistent with this hypothesis (Day et al. 2007; Roitman et al. 2008; Wassum et al. 2013). Furthermore, optogenetic activation of VTA DA neurons and their inputs in the NAc were found to be reinforcing in that these manipulations are sufficient to drive instrumental conditioning (Tsai et al. 2009; Witten et al. 2011) in a manner that is consistent with the RPE hypothesis (Steinberg et al. 2013).

A limitation of the heuristically useful RPE hypothesis of DA neuron function is that it routinely treats all midbrain DA neurons as a homogeneous population. This view does not incorporate the increasing body of evidence that mid-brain DA neurons in general, and VTA

DA neurons specifically, are heterogeneous in that they project to different targets, show distinct electrophysiological and molecular properties, and can respond to aversive as well as reinforcing stimuli (Lammel et al. 2008, 2011, 2012, 2014; Bromberg-Martin et al. 2010; Cohen et al. 2012). Indeed, application of modern monosynaptic viral tracing techniques in mice demonstrates that different subpopulations of both VTA and substantia nigra pars compacta (SNpc) DA neurons are embedded in different circuits with distinct input–output relationships (Beier et al. 2015; Lerner et al. 2015; Menegas et al. 2015). For example, VTA DA neurons projecting to the lateral NAc receive substantially more projections from anterior regions of the cortex including the PFC, whereas VTA DA neurons projecting to the medial NAc receive a greater proportion of their inputs from the dorsal raphe nucleus (Beier et al. 2015).

Further evidence for the complexity of DA action in the NAc derives from work studying the modulation of VTA DA neuron activity in mouse depression models. In mice susceptible to depression-related behaviors following social defeat stress, VTA DA neuron phasic firing has been reported to increase (Krishnan et al. 2007; Cao et al. 2010). In support of this increase being causally related to the depression phenotype, rather than a compensatory response, optogenetic activation of the VTA DA neurons that project to NAc induced susceptibility for social avoidance and anhedonia, whereas inhibition of these neurons made previously susceptible mice resilient to social defeat stress (Chaudhury et al. 2013; Walsh et al. 2014). However, in contrast to these findings, phasic stimulation of VTA DA neurons reversed a depression-related symptom caused by a chronic mild stress protocol and this reversal required DA action in the NAc (Tye et al. 2013). These disparate results, which derive from different rodent models of depression, are not easy to reconcile without evoking great complexity in how VTA DA neuron-mediated modulation of NAc circuitry changes in response to the different forms of stress used to cause “depression.”

It is important to remember that the modulation of NAc activity by DA is bidirectional in that NAc MSNs send direct, monosynaptic projections to the VTA, which form synapses on both GABAergic interneurons and DA neurons (Xia et al. 2011; Bocklisch et al. 2013; Edwards et al. 2017; Yang et al. 2018). An influential hypothesis about the complex relationship between ventral and dorsal striatum and midbrain DA regions proposes that they are hierarchically organized in parallel reciprocal circuits and constitute an ascending spiral moving from the NAc shell toward the dorsal striatum (Nauta et al. 1978; Haber et al. 2000; Haber and Knutson 2010). This pattern of connectivity is often referred to as “striatonigral spiraling” (Haber et al. 2000) and has been suggested to play an important role both in the computation of RPEs (Keiflin and Janak 2015) and in addiction by contributing to the transition from initial encoding of the rewarding drug experience to the habitual behaviors underlying the compulsive seeking of drugs (Volkow et al. 2006; Vollstadt-Klein et al. 2010; Willuhn et al. 2012; Everitt and Robbins 2016).

Recent work on the reciprocal connectivity between VTA and NAc using a combination of state-of-the-art techniques revealed two parallel circuits: one from medial shell NAc D1 MSNs, which synapse on medial VTA DA neurons that project back to the medial NAc, and the other from lateral shell NAc D1 MSNs, which synapse on VTA GABAergic interneurons, leading to disinhibition of DA neurons projecting back to the NAc lateral shell

(Fig. 2; Yang et al. 2018). As a consequence of this connectivity, optogenetic stimulation of lateral shell NAc D1 MSN terminals in VTA increases DA neuron activity and promotes reward-related behaviors, whereas activation of the medial shell NAc inputs inhibits DA neurons and suppresses behavioral output (Yang et al. 2018). These different populations of inhibitory inputs onto VTA DA and GABA cells also appear to activate different subtypes of GABA receptors (i.e., GABA<sub>A</sub> or GABA<sub>B</sub> receptors) (Edwards et al. 2017; Yang et al. 2018), providing additional complexity to the reciprocal interactions between VTA and NAc.

A critical question is how local DA release modifies NAc neural activity to cause its profound behavioral effects. Surprisingly, we have little information on this topic and no satisfying model of exactly how DA release changes NAc neural activity to cause reinforcement in a manner that drives instrumental conditioning and incentive salience. Furthermore, we have limited understanding of how the effects of DA on NAc activity change in models of pathological conditions, such as addiction and depression. Simple ideas include the hypothesis that DA acting on D1 receptors increases MSN excitability, whereas D2 receptor activation leads to a decrease in MSN excitability (Bromberg-Martin et al. 2010; Lobo and Nestler 2011). DA also depresses excitatory and inhibitory synaptic transmission in the NAc (Nicola and Malenka 1997; Nicola et al. 2000), at least in part by reducing lateral inhibition between MSNs (Dobbs et al. 2016). Although application of psychostimulant drugs has been used to evaluate the electro-physiological consequences of enhancing endogenous DA levels in vivo and in vitro, the consequences of more physiological, action-potential evoked endogenous DA release on NAc MSN activity has not been extensively examined (e.g., during optogenetic induced release of DA). The regional complexity of the NAc discussed above highlights an additional challenge in elucidating the detailed neural mechanisms by which DA release influences behavior. We anticipate that the application of recently developed techniques to record activity from identified populations of NAc neurons, as done in dorsal striatum (Parker et al. 2018), will provide important information regarding the actions of DA. However, to generate meaningful hypotheses from such data about how DA action in the NAc elicits robust behavioral changes, it will be necessary to establish the input–output connectivity of each cell ensemble and clarify their molecular and electrophysiological properties.

## SEROTONIN ACTION IN THE NUCLEUS ACCUMBENS

Arguably the neuromodulator that has received the most attention after DA is serotonin (5-HT), which like DA has been implicated in a wide range of adaptive and pathological behaviors (Müller and Jacobs 2010). Innervation of the striatum by 5-HT-containing inputs was first shown in the mid-1960s (Dahlström and Fuxe 1964, 1965), but it was primarily the discovery that antidepressant drugs act by inhibiting 5-HT transporter function (Nestler et al. 2015) that refocused attention on this neuromodulator. Recently, modern circuit elucidation tools have been applied to dissecting the anatomy and functions of the major 5-HT projection neuron populations in the dorsal raphe and median raphe nuclei (Ogawa et al. 2014; Pollak Dorocic et al. 2014; Weissbourd et al. 2014; Ren et al. 2018). These studies suggest that, like midbrain DA neurons, midbrain 5-HT neurons are heterogeneous and can be defined, in part, by their input–output connectivity. Consistent with this heterogeneity, dorsal raphe 5-HT neuron manipulations and recordings suggest complex roles in a range of

behaviors related to cognition and motivation (Liu et al. 2014; Cohen et al. 2015; Brodsky et al. 2016; Li et al. 2016; You et al. 2016; Ren et al. 2018).

Only a small number of studies have attempted to examine the consequences of 5-HT release specifically in the NAc. Chemogenetic activation of 5-HT inputs in the NAc was reported to prevent cocaine elicited conditioned place preference and also decrease immobility time in the tail suspension test (You et al. 2016). On the other hand, over-expression of 5-HT<sub>6</sub> receptors in NAc D2 MSNs appeared to increase the subjects' sensitivity to the reinforcing properties of cocaine (Brodsky et al. 2016). Although intriguing, these results are difficult to incorporate into any coherent hypothesis about the behavioral functions of 5-HT release in the NAc.

Work from our laboratory suggests that 5-HT release in the NAc may have a particularly important role in promoting sociability and nonaggressive social explorations. Using a social conditioned place preference assay to assess the reinforcing component of social interactions, previous work suggested that oxytocin action in the NAc was required for social reward (Dölen et al. 2013). Surprisingly, oxytocin appeared to act by promoting the release of 5-HT in the NAc by activating presynaptic oxytocin receptors on the terminals of dorsal raphe 5-HT inputs in the NAc (Fig.3). Consistent with a critical role of 5-HT in the NAc in social behaviors, bidirectional optogenetic manipulation of 5-HT input activity in the NAc bidirectionally influenced sociability in two different assays (Fig. 4; Walsh et al. 2018). Furthermore, 5-HT release in the NAc rescued sociability deficits in an autism mouse model via the activation of 5-HT<sub>1b</sub> receptors, the activation of which depresses excitatory transmission at unknown inputs onto NAc D1 and D2 MSNs (Fig. 3; Dölen et al. 2013; Walsh et al. 2018).

Importantly, in marked contrast to the consequences of activating DA inputs in the NAc, activation of 5-HT inputs in the NAc does not generate instrumental or Pavlovian conditioning; that is, 5-HT release in the NAc, unlike DA release, is not acutely reinforcing (Walsh et al. 2018). These results indicate that the modulation of NAc neural activity by DA and 5-HT must be significantly different. The sources of these differences are unknown and will require a large amount of work to be elucidated. Some key questions that need to be addressed to achieve further understanding of the differences in the behavioral consequences of DA and 5-HT release in the NAc include: Are similar or distinct NAc neuronal ensembles affected by DA and 5-HT release from the VTA and dorsal raphe nucleus, respectively? Exactly how does NAc D1 and D2 MSN activity change during increases in DA and 5-HT: Can any principles be discerned? Which DA and 5-HT receptor subtypes are activated by endogenous DA and 5-HT and where are these located? How do the effects of DA and 5-HT on NAc activity change in various models of psycho-pathology, such as addiction and depression?

## PEPTIDE MODULATION OF NUCLEUS ACCUMBENS

In addition to being strongly influenced by classic neuromodulators such as DA and 5-HT, the NAc is also affected by families of neuropeptides, which are too often neglected (Arrigoni and Saper 2014). Among the most prominent of these are the opioid peptides

dynorphin and enkephalin, which preferentially activate  $\kappa$ -opioid and  $\mu$ -opioid receptors, respectively. As mentioned above,  $\mu$ -opioid receptors appear to be preferentially expressed in patch compartments and minimally expressed in matrix (Gerfen 1992; Crittenden and Graybiel 2011; Brimblecombe and Cragg 2017).  $\kappa$ -opioid receptors are found throughout the NAc on MSNs themselves as well as on presynaptic glutamatergic and neuromodulatory inputs (Fallon and Leslie 1986; Mansour et al. 1994; Lalanne et al. 2014; Brooks and O'Donnell 2017; Tejada et al. 2017). The electrophysiological and behavioral actions of  $\mu$ -opioid and  $\kappa$ -opioid receptors in the NAc are complicated, although they clearly have powerful influences in a broad range of motivated behaviors influenced by emotionally salient stimuli.

Of particular interest is the suggestion that there is anatomical segregation of opioid signaling in the NAc beyond the patch-matrix distinction. Meticulous work using microinjections of pharmacological agents showed the presence of a “hedonic hotspot” concentrated in the rostradorsal quadrant of the medial NAc shell, where activation of several types of opioid receptors increased hedonic responses to sucrose. Surprisingly the same types of opioid-receptor stimulation in the caudal NAc suppressed reward reactions and was proposed to constitute a “hedonic coldspot” (Berridge and Kringelbach 2015). Similarly, optogenetic activation of dynorphinergic cells in different subregions of the NAc (i.e., dorsal vs. ventral) caused behaviors with opposite valence (i.e., rewarding vs. aversive) (Al-Hasani et al. 2015). Clearly, much work needs to be done to elucidate the anatomical, molecular, and physiological differences between these NAc regions so a more comprehensive understanding of their behavioral differences can be ascertained.

Oxytocin is another peptide with important actions in the NAc. Oxytocinergic neurons in the PVN of the hypothalamus send direct projections to both the NAc and VTA (Dölen et al. 2013; Hung et al. 2017). As mentioned above, oxytocin release in the NAc promotes social reward by enhancing NAc 5-HT release, which activates 5-HT<sub>1b</sub> receptors that in turn reduce excitatory synaptic responses generated by unknown sets of inputs (Fig. 3; Dölen et al. 2013; Walsh et al. 2018). Stimulation of PVN oxytocin neurons using chemogenetic manipulation was also found to promote social reward, although it was suggested that this was caused by NAc accumulation of the endocannabinoid, anandamide, which like 5-HT, activates presynaptic receptors that depress excitatory synaptic transmission (Wei et al. 2015). In the VTA, oxytocin enhances the excitability of a subset of DA neurons that project to the NAc, thereby enhancing NAc DA release (Hung et al. 2017).

Three other neuropeptides worth mentioning are galanin, melanocortin, and orexin. Galanin receptor-1–triggered depression of excitatory synaptic transmission in NAc D2 MSNs was required for the decreased motivation caused by two different models of chronic pain (Schwartz et al. 2014). In contrast, depression of excitatory transmission in NAc D1 MSNs due to activation of melanocortin 4 receptors was required for the anhedonia caused by severe chronic stress (Lim et al. 2012). A recent study following up on these findings revealed that MC4Rs may be involved in attributing negative valence to aversive states (Klawonn et al. 2018). Finally, orexin also appears to influence NAc function in that orexin-mediated activation of NAc D2 MSNs is critical for innate risk avoidance (Blomeley et al. 2018). Orexin also increases the firing of NAc-projecting VTA DA neurons (Baimel et al.

2017), thereby providing an indirect mechanism by which orexin may influence NAc activity.

## CONCLUSION

Recent advances in techniques that facilitate identification and manipulation of brain circuits have made it possible to functionally investigate neural ensembles based on their genetic profile as well as on their input and output characteristics. Application of these methods over the last decade has made it clear that circuitry involving the NAc is far more heterogeneous and complicated than previously envisioned. Furthermore, it has become clear that NAc activity is influenced in behaviorally important ways by a range of modulators including DA, 5-HT, and a host of neuropeptides. The functioning of NAc circuitry is also not static but dramatically altered by experiences, which are commonly used to model disease states such as addiction and depression. Throughout this review, we mention some of the many gaps in our current knowledge of NAc circuitry and function; addressing these gaps may seem daunting. However, by continuing to apply recently developed and new methods as they become available in creative and rigorous manners, we are confident that important advances in our understanding of NAc circuit function will be made. Such advances will facilitate a more sophisticated understanding of the many adaptive and pathological behavioral and cognitive functions in which the NAc participates.

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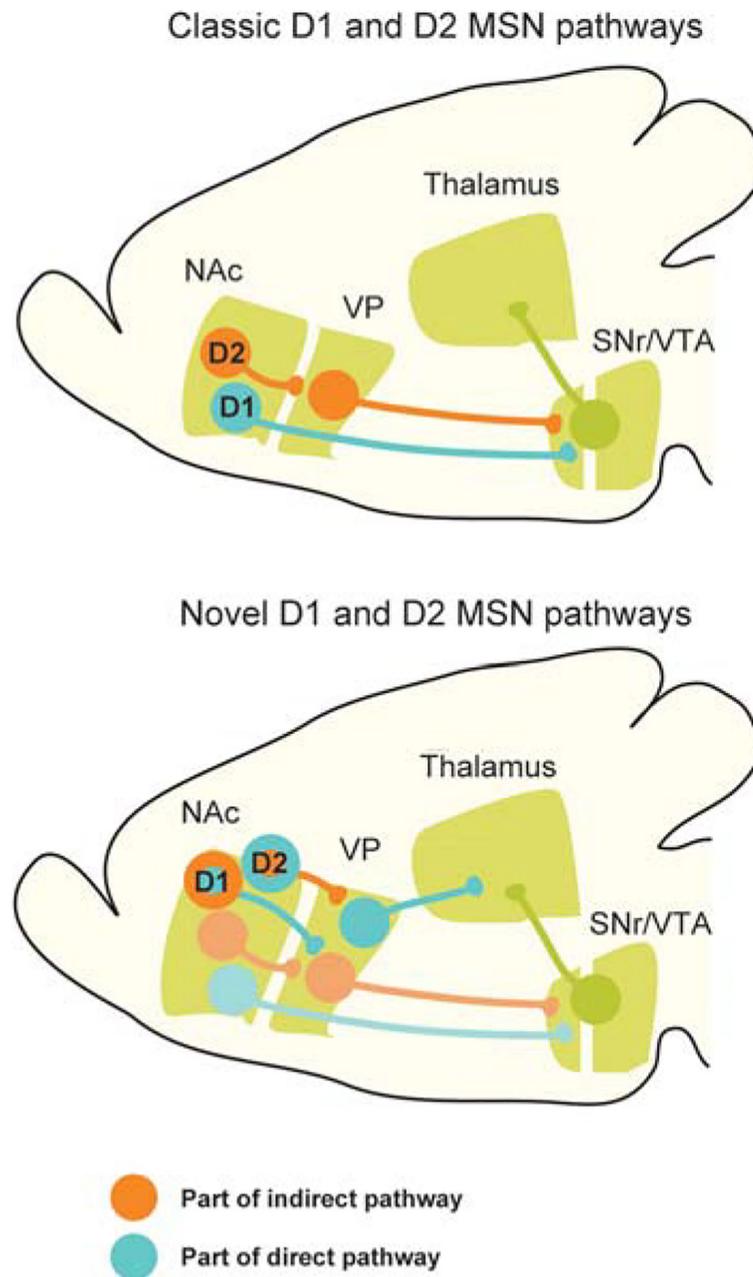
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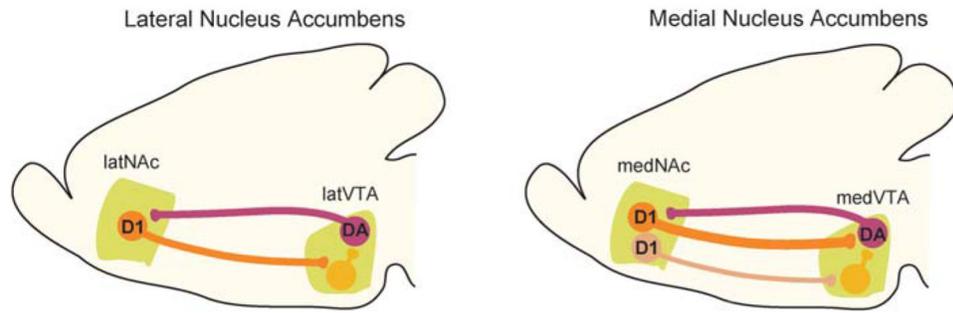
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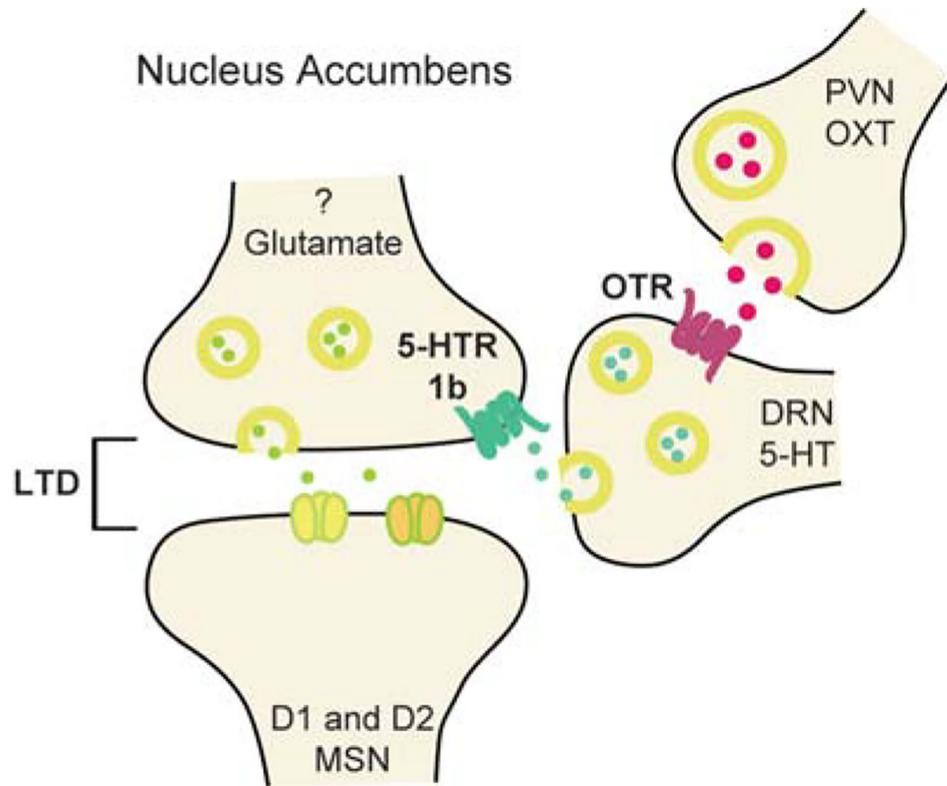
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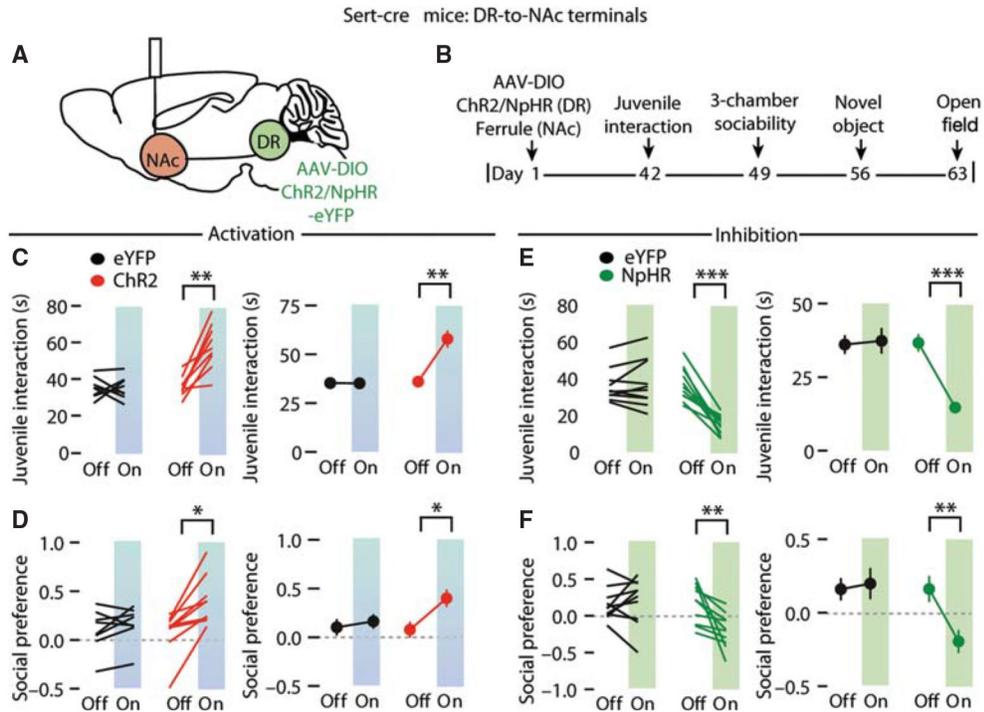
**Figure 1.** Schematic overview of NAc D1 and D2 MSN anatomical connectivity emphasizing the differences between the classic conceptualization of indirect and direct pathways and a novel view (based on Kupchik et al. 2015). All illustrated cells are thought to be GABAergic. (NAc) Nucleus accumbens, (VP) ventral pallidum, (SNr) substantia nigra pars reticulata, (VTA) ventral tegmental area. (Modified from Kupchik and Kalivas 2017.)



**Figure 2.** Diagram of proposed differences between circuitry of medial and lateral nucleus accumbens emphasizing differences in connectivity onto ventral tegmental area (VTA) GABAergic interneurons and dopamine (DA) neurons. (Modified from Yang et al. 2018.)



**Figure 3.** Model of the interactions of oxytocin (OXT) and serotonin (5-HT) in the nucleus accumbens in a manner that promotes sociability and social reward by generating long-term depression at excitatory synapses on D1 and D2 MSNs. (Modified from Dölen et al. 2013.)



**Figure 4.** Bidirectional optogenetic modulation of dorsal raphe 5-HT neuron inputs in the nucleus accumbens bidirectionally influences sociability in two different assays. (A) Schematic of optogenetic manipulation. (B) Time line of experiments. (C,D) Quantification of juvenile interaction (C) and three-chamber sociability (D) assays in optogenetic activation experiments using ChR2 along with eYFP controls. *Left* panels show results from individual subjects; right panels show mean  $\pm$  SEM. (E,F) Optogenetic inhibition experiments using NpHR along with eYFP controls. (Reprinted, with permission, from Walsh et al. 2018.)