The Nucleus Accumbens: An Interface Between Cognition, Emotion, and Action

Stan B. Floresco

Department of Psychology and Brain Research Center, University of British Columbia, Vancouver, British Columbia, V6T 1Z4 Canada; email: floresco@psych.ubc.ca

Annu. Rev. Psychol. 2015. 66:25–52

First published online as a Review in Advance on September 17, 2014

The *Annual Review of Psychology* is online at psych.annualreviews.org

This article's doi: 10.1146/annurev-psych-010213-115159

Keywords

ventral striatum, dopamine, action selection, animal models, fMRI

Abstract

Nearly 40 years of research on the function of the nucleus accumbens (NAc) has provided a wealth of information on its contributions to behavior but has also yielded controversies and misconceptions regarding these functions. A primary tenet of this review is that, rather than serving as a "reward" center, the NAc plays a key role in action selection, integrating cognitive and affective information processed by frontal and temporal lobe regions to augment the efficiency and vigor of appetitively or aversively motivated behaviors. Its involvement in these functions is most prominent when the appropriate course of action is ambiguous, uncertain, laden with distractors, or in a state of flux. To this end, different subregions of the NAc play dissociable roles in refining action selection, promoting approach toward motivationally relevant stimuli, suppressing inappropriate actions so that goals may be obtained more efficiently, and encoding action outcomes that guide the direction of subsequent ones.

Contents

INTRODUCTION

The pioneering work of Lennart Heimer (Heimer & Wilson 1975) and Gordon Mogenson (Mogenson et al. 1980) first identified a nucleus adjacent to the septum [nucleus accumbens (NAc)] as a region of the ventral striatum that was anatomically and potentially functionally distinct from more dorsal striatal compartments. The initial characterization of this nucleus in the rodent brain has since triggered nearly 40 years of intense scientific inquiry into its function, with a major emphasis on its contribution to motivational processes, particularly those related to reward. A prominent, if not overbearing, view is that the NAc serves as a critical node within the brain's reward circuitry, and it is not uncommon to find instances where this nucleus is referred to as a "pleasure center." This impression has, of course, been driven by a multitude of studies in animals and humans implicating the NAc in directing attention and behavior toward appetitive stimuli, including natural rewards such as food and sex as well as drug or secondary reinforcers. Yet, this somewhat superficial emphasis on the NAc and reward has veered from the more general idea initially proposed by Mogenson (Mogenson et al. 1980, 1993) that this region serves as a limbic-motor interface. Owing in part to its neuroanatomical connectivity, the NAc has been proposed to integrate mnemonic and emotional signals from nodes within the limbic system residing in the frontal and temporal lobes that determine the response priorities of an organism. In turn, the NAc is thought to integrate these signals and turn them into action via output to pallidal and other subcortical motor effector sites through which signal outflow from this region may bias the direction and intensity of behavior. Thus, rather than taking a pedantic view that the NAc is a "reward" center, a more accurate way of characterizing its function is that it aids in obtaining motivationally relevant goals by promoting likelihood, efficiency, and vigor of behaviors intended to obtain those goals, whether they be procurement of things worth having (rewards), avoidance of aversive consequences, exploration of novel stimuli, or other objectives. This review provides some historical context in combination with more contemporary findings that support these ideas.

NAc: nucleus accumbens

ANATOMICAL AND NEUROPHYSIOLOGICAL PROPERTIES OF THE NUCLEUS ACCUMBENS: A SERVANT TO MANY MASTERS

Neurocellular Architecture and Subdivisions

DA: dopamine

The anatomical organization of the NAc is heterogeneous, and subregions of this nucleus have been segregated on the basis of histochemical markers and intrinsic afferent and efferent connectivity (Groenewegen et al. 1991; Zahm 2000, 2008). Initial studies in rats segregated the ventral striatum on the basis of the regional distribution of certain neuropeptides (Groenewegen et al. 1987, 1999; Zaborszky et al. 1985; Zahm & Heimer 1990), and similar subdivisions have been observed in primates (Meredith et al. 1996, Voorn et al. 1994). As such, the NAc is now considered as a region consisting of two primary segments: a medial "shell" subregion and a more lateral "core" component (Zahm & Brog 1992), and recent imaging studies have alluded to a similar partitioning of the ventral striatum in humans (Baliki et al. 2013). Inputs from the temporal and frontal lobes display distinct topographical organization throughout these subregions (Brog et al. 1993, Groenewegen et al. 1987, Kelley et al. 1982). The arrangement of these inputs has led to the speculation that the ventral striatum is a collection of "neuronal ensembles," consisting of separate clusters of cells subserving different functional roles determined by their inputs (O'Donnell 1999, Pennartz et al. 1994). The differential connectivity of the shell and core subregions suggests that they may subserve distinct behavioral functions, a supposition supported by numerous lesions and psychopharmacological studies in animals. Although a "grand unified theory" of the dissociable contributions of the NAc shell and core to behavior has yet to be established, the following sections attempt to integrate what is known about their respective functions.

Let us start a discussion of NAc function with the seemingly noncontroversial premise that its contribution to overt behavior is mediated by fine-grained spatiotemporal patterns of increased (or decreased) firing in certain groups of projection neurons. Expanding on this notion requires an understanding of cellular and neuroanatomical properties of NAc neurons that underlie their activity and how these properties differ from those of the frontal and temporal lobe regions that project to it. Cortical pyramidal projection neurons use the fast-acting excitatory transmitter glutamate that resides in long-distance projections to other brain regions (such as the NAc), and they also form networks of intrinsic connections with nearby cells in the same region. As a result, networks of these neurons generate recurrent patterns of activity that is thought to underlie processing of cognitive, mnemonic, or affective information within these systems. In contrast, the NAc medium spiny projection neurons (>90% of all neurons in this nucleus) are considerably less excitable and do not possess intrinsic mechanisms that permit generation of spontaneous firing, unlike other neurons [e.g., dopamine (DA) cells]. Moreover, NAc projection neurons use inhibitory gamma-aminobutyric acid (GABA) as a neurotransmitter, and as such, networks of these cells cannot generate recurrent patterns of activity (Pennartz et al. 1994, Uchimura et al. 1989). Thus, changes in NAc neural activity that may lead to motivationally relevant patterns of behavior are likely the result of increases/decreases in excitatory glutamatergic inputs originating from frontal and temporal lobe regions. In turn, patterns of firing in certain ensembles of NAc neurons may bias the direction (e.g., approach to particular stimuli) or intensity of certain behaviors via projections to regions of the basal ganglia that have more direct influence over motor output. If this premise is accepted, then the function of the NAc may be viewed as that of a servant to many masters, i.e., patterns of neural activity that influence behavior may reflect commands (or at least suggestions) from distinct cortical and limbic regions.

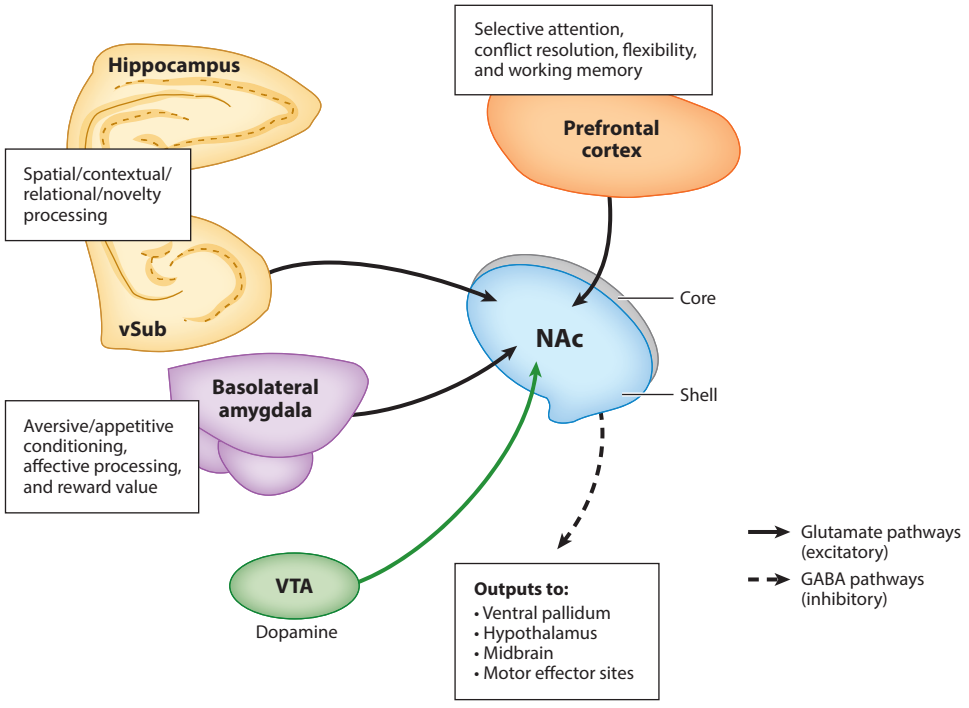

Figure 1

Summary of the key cortical, limbic, and dopaminergic inputs that interface with the nucleus accumbens (NAc), highlighting some of the key cognitive and behavioral functions these afferent regions may regulate via their interactions with the ventral striatum. Abbreviations: GABA, gamma-aminobutyric acid; vSub,ventral subiculum; VTA, ventral tegmental area.

Cortical and Limbic Inputs

Three afferent regions that provide excitatory input to the NAc have been studied in detail: the hippocampus, the basolateral amygdala (BLA), and different subregions of the prefrontal cortex (PFC) (**Figure 1**). Each of these regions processes dissociable types of information that, in turn, may bias distinct patterns of behavior via interactions with the NAc. For example, the hippocampus is essential for spatial navigation, processing the relationships between different stimuli, and recognition of novelty (Floresco et al. 1997, Ito et al. 2008, Mannella et al. 2013). By contrast, the BLA plays a key role in forming associations between neutral stimuli that predict appetitive or aversive consequences as well as in monitoring changes in the affective salience or perceived value of these stimuli (Everitt et al. 1991, Fernando et al. 2013, McLaughlin & Floresco 2008, Shiflett & Balleine 2010). By further comparison, different regions of the rodent medial PFC (anatomically homologous to different regions of the human anterior cingulate cortex) have been implicated in a variety of cognitive, affective, and reward-related functions not easily summarized in a single phrase. As such, interactions between PFC regions and the NAc appear to be important for guiding behavior in a variety of situations, including those that place high demands on attention (Christakou et al. 2004), require linking of behaviors across contexts (Floresco et al. 1999), include evaluation of cost and benefits associated with different actions (Hauber & Sommer 2009), or present some form of discrepancy between expected and actual outcomes associated with certain actions that require an organism to update or reorganize its behavior (Block et al. 2007).

BLA: basolateral amygdala

PFC: prefrontal cortex

Corticolimbic inputs display distinct topographical organization throughout the NAc, and a notable feature of this anatomical connectivity is the degree to which these projections converge within the NAc, often on the same cells (Britt et al. 2012, Floresco et al. 2001b, French & Totterdell 2003, O'Donnell & Grace 1994). The NAc receives information from a variety of systems that promote distinct patterns of behavior, suggesting that it may make a more prominent contribution in situations where there is some sort of ambiguity about either the motivational relevance of environmental stimuli or the best course of action for obtaining certain goals. Furthermore, as individual NAc neurons receive converging (and potentially competing) information from different sources, the intrinsic connectivity of these circuits would necessitate a certain biasing or gating mechanism that could permit information processed by one system to have a preferential influence over behavior via the NAc.

Dopamine Inputs

DA inputs originating from midbrain neurons in the ventral tegmental area have received by far the most attention with regard to their neurophysiological actions within the NAc and their functional contribution to behavior. Indeed, much of our understanding of NAc function and its involvement in reward-related processes has been inferred from studies targeting DA transmission. Mesoaccumbens DA release appears to be compartmentalized into dissociable modes of transmission. "Phasic" signaling induces a rapid (<1 s) and spatially restricted signal driven by DA neuron burst firing. This mode of signaling is triggered by primary or conditioned rewards, whereas presentation of reward-predictive stimuli followed by reward omission induces brief phasic suppressions in DA neural firing (Schultz et al. 1997). These increases/decreases in phasic DA activity are thought to serve as neural teaching signals, encoding prediction errors for anticipated rewards that underlie reward-related associative learning and may facilitate behavioral alterations upon changes in reward contingencies (Schultz 1998). Studies using subsecond measures of DA release in the NAc have further revealed that the magnitude of phasic signals encodes the expected availability or receipt of larger versus smaller rewards (Day et al. 2011, Sugam et al. 2012). By comparison, extrasynaptic or "tonic" DA levels change on relatively slow timescales (minutes), regulated by the overall number of DA neurons that are active and can also be modulated by excitatory presynaptic inputs locally within the NAc (Floresco et al. 2003, Howland et al. 2002). Tonic DA may affect broader populations of NAc neurons and may also serve to modulate incoming signals presynaptically. Recent theory has posited that the absolute value of tonic DA provides an integrated and continuous estimate of the net rate of reward that may influence response vigor or the direction of behavior when choosing between different types of rewards (Niv 2007, St. Onge et al. 2012).

DA can either facilitate or suppress NAc neural activity through a complex array of mechanisms. DA alters the excitability of NAc neurons via actions on D_1- and D_2-like receptors residing on these cells; the direction of these effects depends on a variety of factors including the concentration of DA and how active the neurons may be (Hu & Wang 1988, Kiyatkin & Rebec 1996, Pennartz et al. 1994, Uchimura et al. 1986). Certain populations of NAc neurons also express D_3 receptors that can colocalize on cells containing D_1 or D_2 receptors (Le Moine & Bloch 1996), although the neurophysiological and behavioral functions of these receptors are less well characterized and are not a focus of this review. Separate populations of NAc neurons express only D_1 or D_2 receptors (though some populations express both), and studies of the ventral and dorsal striatum suggest that activation of these different cell types mediates distinct types of behavior (e.g., approach versus avoidance) (Kravitz et al. 2012, Lobo et al. 2010).

DA also regulates the influence that different inputs exert over firing of NAc neurons via presynaptic mechanisms (Charara & Grace 2003, Nicola & Malenka 1997, Yang & Mogenson

1984), indicating that it can gate the manner in which these inputs may regulate NAc neuronal activity. Of particular importance, DA exerts its most pronounced effects when neurons are in a more excitable state (driven primarily by afferent input), but it does little when these neurons are relatively inactive (Hernández-López et al. 1997, Hjelmstad 2004, O'Donnell & Grace 1996, Pennartz et al. 1994). As such, the primary function of mesoaccumbens DA transmission is to modulate the impact that excitatory inputs exert over the firing of NAc neurons (augmenting some inputs while suppressing others) that, in turn, may affect specific patterns of behavior that are promoted. Although the majority of these excitatory inputs originate in limbic and cortical regions, recent findings have identified projections from the ventral tegmental area that also contain glutamate (Hnasko et al. 2012, Yamaguchi et al. 2011). Thus, in addition to the modulatory effects of DA, midbrain inputs may also exert rapid and direct impacts on NAc neural firing and behavioral output via glutamate signaling (Yun et al. 2004b).

When integrating these findings, it is important to keep in mind that, despite a tendency to view mesoaccumbens DA and NAc functions as identical, DA is ultimately one of many inputs that converge in the NAc. Accordingly, the behavioral functions of DA may not be the same as those subserved by the NAc, a contention supported by a number of studies revealing that reduced mesoaccumbens DA activity can have differential effects on behavior when compared with lesions or inactivation of intrinsic NAc neurons (Bari & Pierce 2005, Bowman & Brown 1998, Nicola 2007, Yun et al. 2004a). Furthermore, the neurophysiological actions of DA are such that this input cannot drive rapid signaling in the manner that excitatory glutamatergic inputs do. Rather, the differential actions of DA make it ideally suited to gate and integrate different signals to the NAc, amplifying information conveyed by one subset of inputs while concurrently attenuating other inputs (Floresco 2007, Mogenson et al. 1993, Pennartz et al. 1994). As such, when interpreting the behavioral impact of manipulations of NAc DA, it may be more appropriate to view these effects as the result of a dysregulation of how information from limbic, cortical, and midbrain regions is integrated to affect differential patterns of activity in ensembles of NAc neurons.

CONTRIBUTIONS OF THE NUCLEUS ACCUMBENS TO BEHAVIOR: MORE COMPLEX THAN JUST REWARD

The view that the NAc (or mesoaccumbens DA) serves as a "reward" center in the brain remains prominent among some neuroscientists and the lay media, fueled by a plethora of studies showing that disruption of NAc function interferes with certain aspects of reward-related behaviors. However, the idea that this nucleus mediates the hedonic/pleasurable properties of rewards or plays a ubiquitous role in behaviors related to obtaining them has faced increasing scrutiny, and several authors have challenged this idea (Berridge 2007, Nicola 2007, Salamone & Correa 2012). One of the main criticisms of this concept deals with the term "reward": Because it can convey different meanings (e.g., a reinforcer, pleasurable sensations, appetitive motivation, etc.), this term is relatively imprecise to describe the functional contribution of different brain systems (Salamone & Correa 2012).

Perhaps to best serve a discussion of the relationship between the NAc and reward-related behaviors we need first to describe the aspects of reward processing that do not appear to require the NAc, as inferred from the effects of lesions, inactivation, or disruption of DA transmission in this nucleus. For example, lesions and inactivation of the NAc do not reduce the basic consumption of primary rewards such as food. Indeed, the suppression of neural activity in the NAc shell increases feeding (Reynolds & Berridge 2002, Stratford & Kelley 1997). Similarly, hedonic reactions to palatable tastes are also unaffected by depletion of NAc DA (Berridge 2007, Berridge & Robinson 1998). Numerous reports show that intact NAc functioning is neither necessary nor sufficient

to support instrumental learning or performance (e.g., lever pressing for food or conditioned reinforcement), at least when the relative effort required to obtain reinforcement is low (Cardinal & Cheung 2005, Corbit & Balleine 2011, Corbit et al. 2001, Parkinson et al. 1999, Taylor & Robbins 1986, Yin et al. 2008). In fact, under some conditions, NAc lesions enhance instrumental responding for food (Bowman & Brown 1998). In a similar vein, the NAc has been strongly implicated as contributing to the rewarding and addictive properties of drugs that are abused, yet lesions of NAc subregions do not impair learning to self-administer psychostimulant drugs (Ito et al. 2004). Learning to discriminate between two stimuli to obtain food or adjusting behavior when these associations are reversed is unaffected by NAc lesions and inactivation (Castañé et al. 2010, Floresco et al. 2006). Thus, many behaviors related to the procurement of rewards are unaffected by disruption of NAc functioning. As such, the view that the NAc is a reward center both oversimplifies and exaggerates its contributions to these functions.

Despite the abovementioned findings, a prominent view of NAc and mesoaccumbens DA functions is that these substrates play critical roles in associative learning about rewards and related stimuli or actions with which they may be associated. Different variations on these theories draw their influence from how DA neurons encode reward-related stimuli. On the basis of seminal work by Schulz and colleagues, the phasic activity of DA neurons has been well established as encoding reward prediction errors: Increased firing is instigated initially by unexpected rewards, and over the course of learning, this activity is eventually evoked by antecedent cues that predict these rewards (Cohen et al. 2012, Day et al. 2007, Pan et al. 2005, Schultz et al. 1997). Conversely, DA neurons show brief suppression of activity when expected rewards are not delivered. An intriguing aspect about this property of DA neurons is that it meshes with models of reward learning, wherein changes in DA activity serve as teaching signals that may increase or decrease the likelihood of approaching stimuli or selecting actions that may or may not have been associated with reward. Given the dense DA projection to the NAc, it seems reasonable (at least superficially) that the NAc would be a key target of these teaching signals that are integrated to facilitate reward learning.

Nevertheless, others have questioned this idea on both theoretical and empirical grounds (Berridge 2007, Redgrave et al. 1999, Saunders & Robinson 2012, Yin et al. 2008). For example, a key tenet of the DA reward prediction error hypothesis is that, during extinction of previously acquired associations, omission of expected rewards (i.e., a negative reward prediction error) suppresses DA activity. This in turn is presumed to facilitate new learning, manifesting as a gradual reduction in conditioned responses over the course of extinction. Therefore, reduction in NAc DA activity through pharmacological blockade of DA receptors would serve as a functional equivalent to reward omission and induce a similar effect to extinction. However, a recent study by Saunders & Robinson (2012) revealed contradictory findings: Blockade of NAc DA receptors impaired expression of a well-trained Pavlovian approach response toward reward-predictive cues (**Figure 2*a***). However, rather than induce a gradual reduction in approach over trials (as occurs during extinction), NAc DA antagonism blunted responding on the very first trial of a test session, before any "new learning" could have been established (**Figure 2*b***). In addition to other findings described above showing that many forms of Pavlovian or instrumental reward learning are relatively unaffected by NAc lesions and inactivation, these findings suggest that the theory that the NAc plays a general role in associative reward learning is, at the very least, too broad and incomplete.

By contrast, the NAc plays an essential role in enabling stimuli associated with reward to invigorate behavior and/or bias approach toward these stimuli. The idea that the NAc contributes to ambulatory locomotion and approach is rooted in the well-established findings that increasing or reducing DA or glutamatergic activity in this nucleus enhances or suppresses locomotor activity (Maldonado-Irizarry & Kelley 1994, Mogenson et al. 1993, Wu et al. 1993). With this in mind,

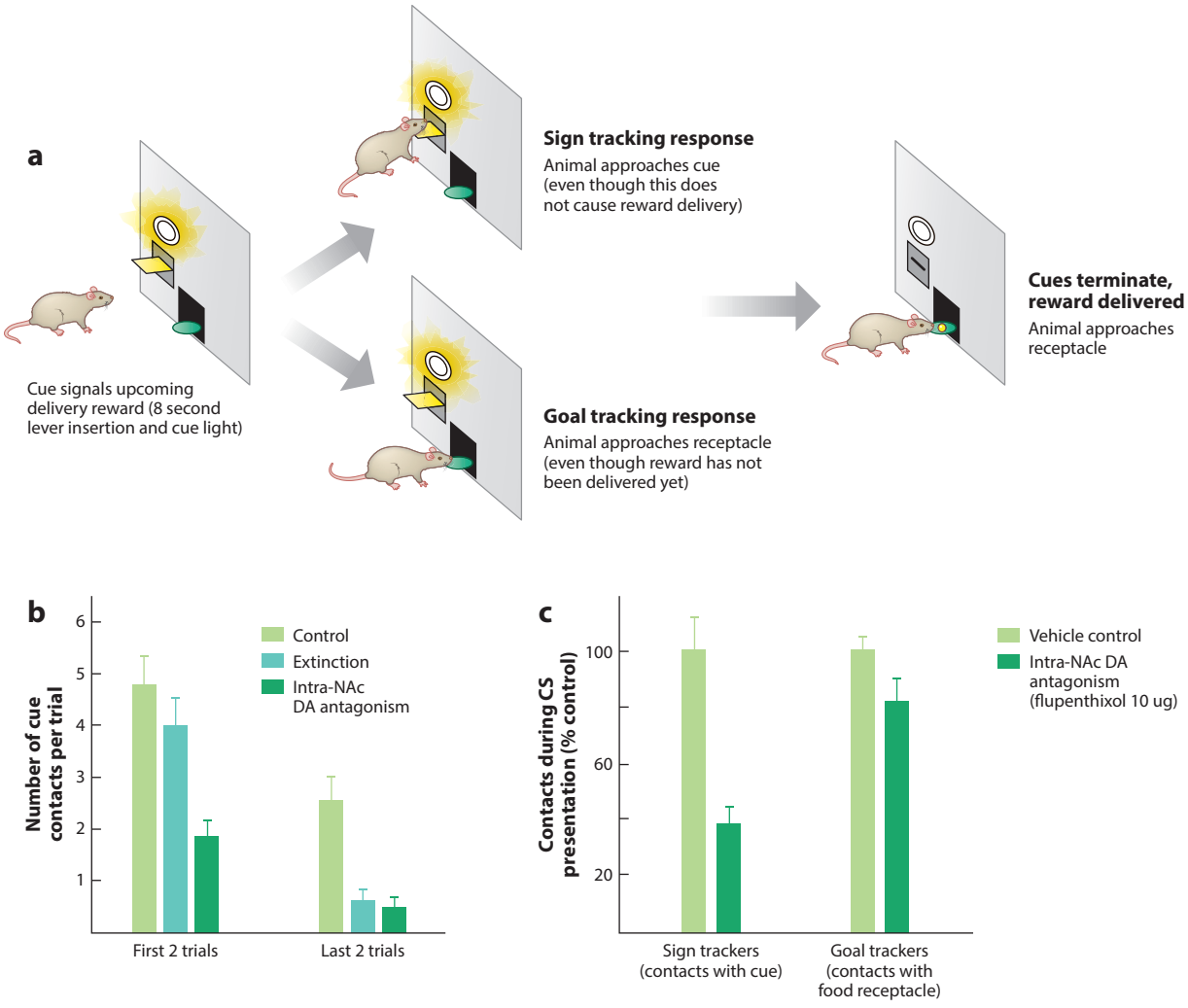

Figure 2

Regulation of the Pavlovian approach toward reward-related cues by nucleus accumbens dopamine (NAc DA). (*a*) In one variant of a Pavlovian autoshaping procedure, presentation of a conditioned stimulus (e.g., insertion of a lever and illumination of a cue light) signals that a reward will be delivered 8 s later (*left*). Over the course of learning, this event can evoke one of two distinct types of responses (*middle*). Animals may approach and interact with the cue (sign tracking), even though the reward delivery is in no way contingent on this response and this behavior displaces the animal some distance from where the reward will be received. Alternatively, animals can approach the food receptacle where the reward will ultimately be delivered (goal tracking), even though food is not yet available. The cue is then terminated and the reward is delivered, irrespective of whether an animal made any type of response (*right*). (*b*) Under control conditions, well-trained rats approach and make contact with the cues at the start of a 25-trial session (the first two trials) and make slightly fewer contacts during the last two trials, likely due to satiety. Notably, during the first session of extinction when the reward is no longer delivered after the cue, rats approach the cue at the start of the session but display a marked reduction in Pavlovian approach by the end. In contrast, blockade of DA transmission in the NAc core with the antagonist flupenthixol disrupts approach toward the cue at the start of a session, in a manner distinct from that observed when the reward is withheld during extinction. (*c*) Blockade of NAc DA selectively disrupts approach toward the conditioned stimulus in rats that predominantly approach the cue (sign trackers) but does not affect approach in animals that primarily enter the food receptacle during cue presentation (goal trackers).

numerous studies have shown that lesions of the NAc or perturbations of mesoaccumbens DA (particularly in the core) impair acquisition and/or expression of approach responses directed toward, or instigated by, reward-predictive cues (Blaiss & Janak 2009, Everitt et al. 1991, Nicola 2010, Parkinson et al. 2000, Saunders & Robinson 2012). Moreover, Pavlovian-conditioned stimuli linked to rewards can also invigorate ongoing instrumental behavior, a phenomenon referred to as Pavlovian-to-instrumental transfer. During ongoing instrumental responding (e.g., lever pressing), presentation of a classically conditioned cue previously associated with passive reward delivery can augment ongoing instrumental behavior. Lesions of the NAc abolish the ability of Pavlovian stimuli to invigorate behavior in this manner (Corbit & Balleine 2011, Corbit et al. 2001), whereas increasing mesoaccumbens DA transmission augments this effect (Wyvell & Berridge 2001). These observations have led to a hypothesis that the NAc, particularly, DA transmission in this nucleus, plays a fundamental role in attributing incentive salience to reward cues, enabling the transformation of certain conditioned stimuli to be perceived as incentive stimuli that motivate approach toward these cues or invigorate ongoing reward seeking (Berridge 2007, Berridge & Robinson 1998).

Despite considerable empirical support for the idea that the NAc mediates the ability of incentive stimuli to influence and instigate approach behavior, several experimental observations are somewhat difficult to reconcile with this hypothesis. For example, animals can quickly learn to discriminate between stimuli (e.g., maze arms, levers) associated with food and those that are not or among stimuli linked to larger versus smaller rewards. Thus, stimuli associated with some versus no reward, or larger versus smaller rewards, should possess greater incentive salience. Yet, inactivation of the NAc does not impair learning to discriminate between two stimuli (Floresco et al. 2006). Likewise, inactivation of the NAc core or depletion of mesoaccumbens DA does not disrupt preference for larger versus smaller rewards (Ghods-Sharifi & Floresco 2010, Salamone et al. 1994). As such, the lack of involvement of the NAc in these instrumental behaviors may reflect a preferential involvement by the NAc in Pavlovian rather than discriminative instrumental responses, even though both forms of learning likely occur in these situations. However, when reward contingencies are altered in a manner that requires an animal to use a novel discrimination strategy, inactivation of the NAc core or disconnection of prefrontal, thalamic, or DA inputs to this region markedly impairs this type of behavioral flexibility (Block et al. 2007, Floresco et al. 2006, Haluk & Floresco 2009). Likewise, the NAc plays a key role in instrumental action selection during evaluation of relative costs (e.g., uncertainty, delays, effort) and benefits associated with different rewards (Cardinal et al. 2000, Ghods-Sharifi & Floresco 2010, Hauber & Sommer 2009, Salamone et al. 1994, Stopper & Floresco 2011). Perturbations in NAc functioning also disrupt attentional accuracy when an animal must detect and approach one of five visual targets (Christakou et al. 2004, Pezze et al. 2007). Thus, the NAc clearly contributes to discriminative and volitional control of approach, but its involvement appears to be most prominent when there is considerable ambiguity regarding the appropriate course of action for procurement of rewards.

Another important consideration is often overlooked in discussions of the role of the NAc in reward-related processes: This nucleus plays a pivotal role in mediating responses to aversive stimuli. According to a handful of studies, the NAc is involved in the acquisition of Pavlovian fear responses (typically indexed by freezing behavior), although its involvement appears to be restricted to forming associations with contextual, rather than temporally discrete, cues paired with averse stimuli such as shock (Haralambous & Westbrook 1999, Levita et al. 2002, Parkinson et al. 1999). The NAc's seemingly preferential involvement in contextual conditioning may reflect the greater difficulty of disambiguating relationships between contexts and shocks, as they may be less salient compared with discrete conditioned stimuli explicitly paired with aversive events (Pezze & Feldon 2004). By contrast, depletions of NAc DA or lesions of the core reliably impair

acquisition and/or expression of conditioned avoidance (McCullough et al. 1993, Wadenberg et al. 1990, Wendler et al. 2014). A recent study using subsecond monitoring of mesoaccumbens DA transmission suggested that phasic increases in DA evoked by cues signaling impending punishment may instigate behaviors designed to avoid these punishers (Oleson et al. 2012). In this study, rats learned that a light warned of impending foot shock that could be avoided if they pressed a lever. Early in training, the cue light induced a suppression of DA signaling in the NAc core, but once animals learned to make an avoidance response, the warning cue triggered an increase in DA release, the magnitude of which predicted successful avoidance. Whereas these findings suggest that DA transmission in the NAc core can promote instrumental avoidance triggered by cues that predict punishment, another study revealed that the NAc shell promotes avoidance evoked by safety signals that indicate periods when no shocks are delivered (Fernando et al. 2014). Viewed collectively, these data suggest that different portions of the NAc may aid in invigorating instrumental behavior toward stimuli linked with safety and away from those associated with punishment. Although more research is required to fully elucidate how the NAc contributes to aversively motivated behaviors, this nucleus clearly helps an organism get closer to the good things as well as away from the bad things in life.

BIASING THE DIRECTION OF BEHAVIOR

A survey of the data reviewed above gives rise to the impression that disruption of NAc functioning alters behavior most prominently when there is considerable ambiguity or uncertainty regarding what may be the best course of action to achieve a goal. Accordingly, it may be inferred that the NAc is preferentially recruited in the service of guiding behavior in situations where an organism is faced with an array of competing stimuli or actions that may increase the difficulty of ascertaining the most appropriate manner in which to direct approach/avoidance behavior. Ambiguous situations may involve the need to discriminate between multiple stimuli that may or may not be associated with reward (or safety), stimuli that may occur unpredictably; making a choice between rewards that differ in terms of their perceived value and the relative cost necessary to obtain them; or mandating flexibility in determining a set of approach actions to reach a goal.

As an example of how increasing the relative ambiguity of a situation may recruit the NAc into guiding behavior, recall that this nucleus does not appear to be necessary when an animal must discriminate between two response levers or maze arms, one of which is associated with food, or when it is foraging for pellets in a four-arm maze (Castañé et al. 2010, Floresco et al. 2006, Seamans & Phillips 1994). However, if we now make the situation more complex, such that the animal must locate food placed in four arms of an eight-arm maze, inactivation of the NAc or disconnection of its hippocampal input markedly disrupts the accuracy of search behavior (Floresco et al. 1997, Gal et al. 1997, Jongen-Rêlo et al. 2003, Seamans & Phillips 1994). Thus, the NAc does not mediate all types of approach toward rewards, safety, or their associated stimuli, but it does appear to be more crucial when the path to those objectives is laden with obstacles, distracters, or uncertainty that may take a reward or safety seeker off course from an intended goal.

It is important to note that, despite the well-characterized influence the NAc exerts over locomotor activity, this region is not a motor center per se. Suppressing NAc activity does not abolish locomotion, nor does it disrupt basic functions that require movement, such as feeding. Instead, lesions, inactivation, or disrupting DA activity in the NAc diminishes the efficiency of behaviors designed to achieve particular goals, by ultimately leading to a reduced tendency to approach to reward-related stimuli, increasing nonrewarded responses, or impairing the ability to use outcome value to guide instrumental actions. As such, it is reasonable to propose that a main function of the NAc is to bias the direction and/or intensity of behavior, thereby increasing the

likelihood that certain actions are committed. This function is likely mediated through output pathways from the NAc that ultimately feed into motor systems and nudge behavior in certain directions. The representation of these goals is unlikely to be processed by the NAc, but rather is computed by regions in the frontal and temporal lobes that then interface with the NAc to instigate actions to obtain them. In light of these considerations, contemporary theory on NAc function has expanded the original notion that this region serves as a limbic-motor interface to propose that this nucleus is a key component of an action-selection mechanism that facilitates the efficient approach toward reward-related stimuli or other goals (Khamassi & Humphries 2012, Mannella et al. 2013, Nicola 2007). Within this framework, particular response priorities are dictated by frontal/temporal lobe inputs and by DA transmission serving to augment the influence of the most salient inputs and suppress that of weaker ones (Floresco 2007, Nicola 2007, O'Donnell 2003).

The efficient pursuit of rewards or other goals in ambiguous, unpredictable, uncertain, or fluctuating circumstances requires an organism to both identify and approach stimuli that are perceived as attractive while reducing the tendency to emit other irrelevant or nonrewarded behaviors that may displace it from its intended goal. In this regard, recent findings suggest that different subregions of the NAc may contribute to each of these functions in a dissociable manner. Specifically, the core appears to play a greater role in instigating approach toward stimuli associated with rewards or safety, whereas neural activity in the shell aids in inhibiting the emergence of behaviors that may interfere with goal seeking.

The Nucleus Accumbens Core: Go to It

The involvement of the NAc core in instigating approach behavior is exemplified by studies measuring an appetitive Pavlovian approach using autoshaping tasks. In these assays, subjects are presented with a visual stimulus (e.g., insertion of a lever and presentation of a cue light) for a brief period before reward is delivered. In the real world, reward-predictive stimuli are often in close proximity to the rewards. However, in autoshaping procedures, the cues are typically located some distance away from where reward is delivered, which allows for an assessment of the incentive properties of the cues that can be dissociated from the incentive of the locations where rewards are actually received. Importantly, reward delivery is completely noncontingent on the animal making any response toward the reward-predictive stimulus; merely waiting for the cue to end still results in reward delivery (**Figure 2*a***). Despite this, over the course of learning, the cues acquire incentive salience: Most animals approach and interact with the cues, even though doing so displaces the animal from where the reward will ultimately be received.

As discussed above, lesions or DA receptor antagonism in the NAc core or disconnecting inputs from the anterior cingulate cortex to the core reduces approach toward these incentive stimuli (Di Ciano et al. 2001, Parkinson et al. 2000, Saunders & Robinson 2012). Note that these types of situations can require action-selection mechanisms to resolve a conflict between competing responses (i.e., approach the cue or the location where reward will be delivered?). A series of studies by Robinson and colleagues probing individual differences in how animals behave in such situations has shed light on how the NAc contributes to resolving these conflicts. Although many animals (termed sign trackers) approach the cue predicting reward, others (goal trackers) opt to bypass the cue and approach the food receptacle (Robinson & Flagel 2009, Saunders & Robinson 2012). Of interest here is the fact that blocking DA transmission in the NAc core selectively reduces approach to the reward-predictive cues in sign trackers (Saunders & Robinson 2012) (**Figure 2*b*,*c***). Nevertheless, these manipulations did not affect approach toward the food trough in goal trackers, and they actually increased this type of approach in sign trackers, again confirming that mesoaccumbens DA does not play a ubiquitous role in mediating conditioned

approach. These findings have been used to support the view that DA in the NAc is selectively involved in attributing incentive salience to reward cues, transforming predictive conditioned stimuli into incentive stimuli that can elicit approach toward such cues.

Further insight into the specifics of how the NAc facilitates approach to a reward-related object comes from the findings of Nicola and colleagues. In one series of experiments (Nicola 2010), rats were trained to approach and press a lever for food, the availability of which was varied across a number of conditions. In one, food was continuously available so that a single lever press at any time would deliver reward, and under these circumstances, DA blockade in the NAc did not affect responding. In other conditions, reward availability was more restricted as follows: (*a*) 10- to 20-s intervals were imposed between periods when responses delivered reward, (*b*) a discriminative auditory cue presented on a variable interval signaled reward availability, or (*c*) eight lever presses were required to receive reward. A meticulous behavioral analysis revealed these conditions led to periods when animals disengaged from the response lever and moved to different parts of the chamber. As a consequence, when rewards were again available (or responding was reinitiated), there was considerable variability in the specific routes rats took to return to the levers. Blockade of mesoaccumbens DA markedly reduced responding in each of these latter conditions. These data were interpreted to indicate that the NAc and mesoaccumbens DA play a selective role in facilitating flexible approach toward reward-related stimuli when the specific actions required to reach those goals vary across instances of reward availability. In these situations, the variable locations from which animals initiated approach required different actions to reach a goal. The fact that DA transmission within the NAc core is required for those actions to occur in a timely manner is in keeping with the idea that this nucleus aids in action selection to facilitate efficient approach toward motivationally relevant goals. A subsequent neurophysiological study further clarified how neural activity within the NAc core may drive flexible approach behavior (McGinty et al. 2013). In that study, animals learned to discriminate between two auditory cues, one of which signaled reward availability and instructed rats to approach and press a lever. A large proportion of NAc neurons displayed more robust increases in activity to the reward-predictive tone versus the nonpredictive one. Moreover, the relative magnitude of the increase in activity encoded the vigor of the subsequent behavior: The greater the increase in firing, the sooner a rat initiated approach to obtain reward. Additional analyses revealed that this activity did not appear to encode information related to the specifics of movement, suggesting that cue-related firing of NAc neurons does not automatically initiate the specific actions required to approach a goal. Rather, firing of neurons in the NAc core evoked by reward-predictive cues activates these computations in downstream structures or gates their ability to control movement of the organism, by either enhancing the vigor of approach or increasing the likelihood that a reward seeker chooses to approach a particular target.

A study by Ambroggi and colleagues (2008) provides an exquisite example of how inputs to the NAc core can drive firing of these cells and instigate approach. Using a discriminative stimulus task similar to that used by McGinty et al. (2013) (**Figure 3*a***), the authors first demonstrated that functional disconnection of dopaminergic inputs and those originating from the BLA to the NAc core disrupted approach toward a response lever evoked by a reward-predictive cue (**Figure 3*b***). Neurophysiological recordings further revealed that presentation of reward cues evoked time-locked increases in firing of BLA neurons that preceded similar activity in the NAc core. Moreover, inactivation of the BLA not only disrupted approach behavior induced by the reward-predictive cue, but also attenuated cue-evoked firing of NAc neurons (**Figure 3*c***). These findings clearly demonstrate that approach toward reward-related stimuli mediated by the NAc core is the result of periods of increased neural activity within this nucleus driven by upstream regions that detect the presence of these cues and determine appropriate courses of action. As these findings only identified a role for the BLA in driving the firing of NAc neurons that

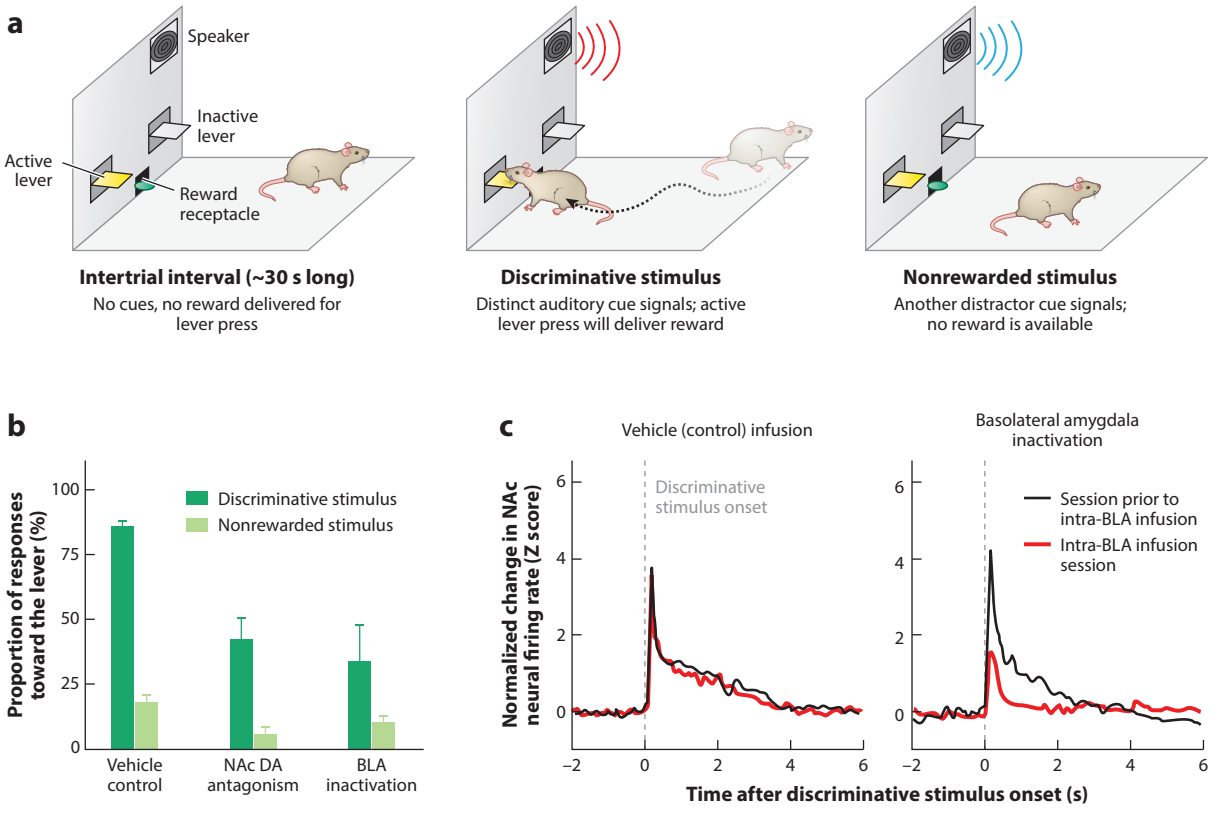

Figure 3

Interactions between the basolateral amygdala (BLA) and the nucleus accumbens (NAc) mediate a goal-directed approach signaled by discriminative cues. (*a*) During a discriminative stimulus task, animals wait during intertrial intervals (~30 s) for an auditory cue signaling that pressing an active lever will deliver a reward (*left*). When the discriminative stimulus is sounded, rats must approach and press the active lever in a timely manner to procure the food reward (*middle*). On other trials, presentation of a separate, nonrewarded auditory stimulus serves as a distractor; responses during this period do not yield reward (*right*). (*b*) Under control conditions, animals respond using the active lever on ~80% of trials when the discriminative stimulus is presented and respond considerably less often during the nonrewarded stimulus. Blockade of dopamine (DA) transmission in the NAc or inactivation of the BLA markedly reduces the proportion of trials when rats press the lever during discriminative stimulus presentation. (*c*) Neurophysiological recordings of NAc neurons from animals performing this task revealed that some cells display a robust increase in firing upon discriminative stimulus presentation. (*Left panel*) Changes in the normalized firing rate of NAc neurons under intact conditions (*black line*) or following control vehicle infusions into the BLA during a session given later the same day (*red line*). (*Right panel*) No differences in the neural response were observed. In contrast, inactivation of the BLA (which reduces goal-directed approach) attenuated firing of NAc neurons evoked by the reward cue. Thus, the pattern of NAc activity and associated reward-seeking behavior are both driven by inputs from the BLA.

facilitates reward-related approach, it would be of considerable interest to use a similar strategy to clarify how disruption of hippocampal or PFC inputs to the NAc may affect other forms of behavior and associated neural activity that encode different events.

The Nucleus Accumbens Shell: Stay on Task

Although considerable evidence suggests the NAc core mediates a type of "go" response toward motivationally relevant stimuli, accumulating evidence suggests that the shell suppresses certain patterns of behavior that may interfere with goal seeking. One of the earliest indications of this

comes from findings that reducing neural activity within the NAc core elicits robust feeding in sated animals (Maldonado-Irizarry et al. 1995, Reynolds & Berridge 2008, Stratford & Kelley 1997). These results were complemented by additional findings showing that initiation of sucrose consumption is associated with pauses in firing of NAc neurons (including those in the shell) and that microstimulation at these recording sites suppresses consumption (Krause et al. 2010, Taha & Fields 2006). Thus, some neurons in the NAc shell appear to gate the expression of appetitive versus consummatory behaviors, likely through (dis)inhibition of target brain regions. Furthermore, whereas inactivation of the more anterior portions of the NAc shell gates the expression of feeding, similar treatments in posterior regions appear to regulate expression of defensive behaviors (Faure et al. 2010, Reynolds & Berridge 2002). Viewed collectively, these findings suggest that neural activity in different regions of the NAc shell appears to actively suppress a variety of unconditioned behaviors related to consumption or defense (eat or stand and fight) that in turn may permit expression of other behaviors related to seeking of rewards or safety.

Inactivation of the NAc shell also increases inappropriate responding instigated by or directed toward stimuli that are not explicitly associated with reward. For example, during tests of cue-induced reinstatement of food or drug-seeking behavior, animals initially make instrumental responses to receive rewards paired with a cue (e.g., tone and/or light). Subsequently, over the course of extinction, they learn that responding no longer delivers reward or the associated cue. During reinstatement tests, responding now delivers only the cue, which normally triggers an increase in responding relative to that observed at the end of extinction training. Inactivation of the NAc shell enhances instrumental responding despite the fact that it no longer delivers the primary reward and can also enhance responding on a nonrewarded lever. By contrast, NAc core inactivation reduces responding for the reward cue (Di Ciano et al. 2008, Floresco et al. 2008, Peters et al. 2008) (**Figure 4**). Along similar lines, other studies have used assays where discrete presentation of two discriminative cues signals different periods where rewards are or are not forthcoming. Suppression of activity within the NAc shell increased Pavlovian or instrumental responding during presentation of cues explicitly unpaired with rewards as well as during intervals when neither the cues nor rewards were available (Ambroggi et al. 2011, Blaiss & Janak 2009, Feja et al. 2014). The shell may also suppress goal-irrelevant behavior in situations requiring choice between rewards of different magnitudes. In one study, we (Stopper & Floresco 2011) observed that rats normally show a strong (>95%) preference for a lever that delivers four reward pellets versus another that gives only one pellet. However, inactivation of the shell slightly reduces preference for the larger reward option (~90%), a result that may be interpreted as a disruption in the ability to suppress actions directed toward inferior rewards. The idea that the shell mitigates nonrewarded or goal-irrelevant behaviors converges with a seasoned literature implicating the shell in facilitating latent inhibition. In these types of studies, initial unreinforced presentation of a to-be-conditioned stimulus can impair the emergence of conditioned behaviors when the stimulus is subsequently paired with a reinforcer. However, lesions of the NAc shell abolish this effect, suggesting that this nucleus is crucial for learning about the irrelevance of stimuli (Gal et al. 2005, Weiner & Feldon 1997).

The NAc shell has also been implicated in mediating search behavior in complex environments, commonly assessed with maze-based tasks where separate locations are either baited with food or not. Once a rat approaches a particular location and either consumes food or ascertains that none is available, it is normally very efficient so as not to visit those locations again. Yet, lesions or inactivation of the NAc shell, DA receptor blockade in this nucleus, or disconnection of hippocampal inputs to the NAc shell markedly disrupts this search behavior, causing rats to revisit locations, irrespective of whether they initially contained food (Floresco & Phillips 1999; Floresco et al. 1996, 1997; Jongen-Rêlo et al. 2003; Seamans & Phillips 1994). Notably, these impairments

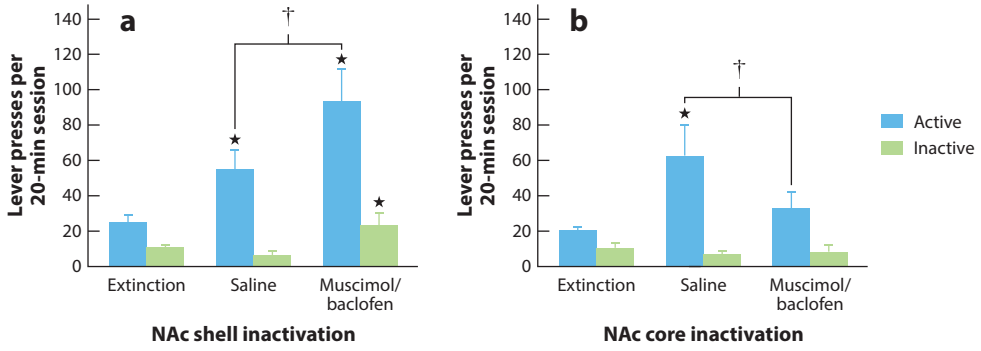

Figure 4

An example of contrasting roles for the nucleus accumbens (NAc) core and shell in reward seeking. In this experiment, rats initially learned to respond on an active lever that delivered food and a reward-associated cue (tone and light). Afterward, they were subjected to extinction, where responding delivered neither reward nor the cue. During tests of cue-induced reinstatement, responding on the active lever delivered the reward-associated cue but not food. Under control conditions (saline), animals increased responding relative to extinction. (*a*) Inactivation of the NAc shell with gamma-aminobutyric acid (GABA) agonists muscimol and baclofen increased instrumental responding during reinstatement, even though the active lever no longer delivered a reward. These treatments also increased responding on the inactive lever, suggesting that the shell normally aids to suppress nonrewarded responding. (*b*) In contrast, inactivation of the NAc core attenuated responding for reward-related cues. Stars and dagger symbols represent $p < 0.05$ versus extinction or saline/inactivation tests, respectively.

emerge when most of the arms have been depleted and the animal must discriminate between many arms that no longer contain food and only a few that are baited (Seamans & Phillips 1994). More recent work has shown that hippocampal-NAc shell circuitry not only mediates foraging behavior, but also facilitates the use of spatial information to guide discriminative approach and express preference for reward-associated cues. Disconnection of this circuit caused rats to enter the maze arms with equal frequency, regardless of whether the arm was paired with food (Ito et al. 2008). When viewing these findings in light of those implicating the NAc shell in suppressing goal-irrelevant behaviors, one potential interpretation is that the shell may refine search behavior guided by the hippocampus by suppressing the tendency to approach locations known not to be associated with reward.

Suppression of irrelevant, nonrewarded, or less profitable actions would be particularly important for facilitating reward seeking in situations where there is uncertainty about whether certain actions may be rewarded. In this regard, a bourgeoning literature implicates the shell in guiding action selection in situations involving reward uncertainty. A recent study by Dalton et al. (2014) examined the effects of inactivation of either the NAc shell or its core on performance of a probabilistic learning and reversal task. Rats learned that a response on the correct lever delivered reward in 80% of the trials and an incorrect response was reinforced in 20% of the trials; reinforcement contingencies were reversed repeatedly within a session (**Figure 5*a***). In well-trained rats, shell inactivation induced a marked impairment in performance, apparent during the first discrimination of the test session, indicating a more general deficit in the use of probabilistic reward feedback to guide action selection (**Figure 5*b***). In contrast, core inactivation did not affect performance accuracy, but it did slow approach toward the levers when they were available, consistent with the notion that this region facilitates approach to reward-related stimuli. Similar findings have been observed within the context of risk/reward decision making: Stopper & Floresco (2011) used a probabilistic discounting task wherein rats chose between smaller, certain rewards and larger,

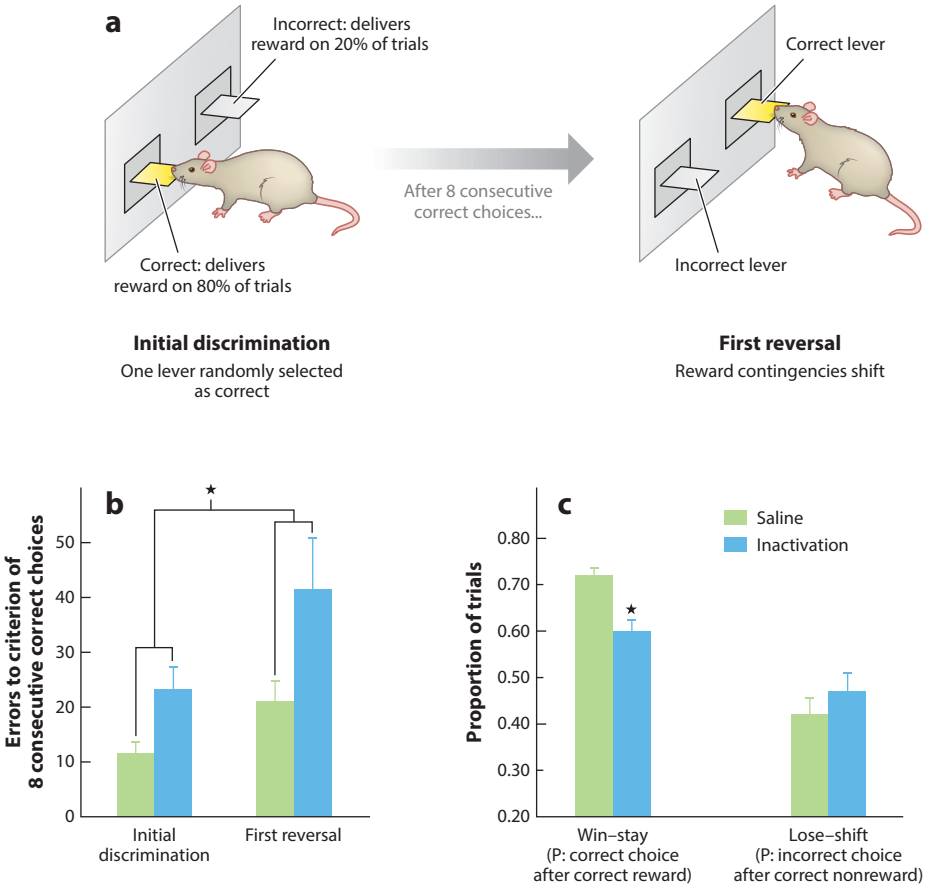

Figure 5

Involvement of the nucleus accumbens (NAc) shell in reward seeking in situations entailing reward uncertainty. (*a*) During a probabilistic learning and reversal task, responding on a correct lever yielded a reward in 80% of the trials, and an incorrect response was rewarded in 20% of the trials. After eight consecutive correct choices, the reward contingencies were switched. The probabilistic nature of this task requires subjects to track the broader context of the reward history to ascertain which response may be more profitable. (*b*) In well-trained animals, inactivation of the NAc shell markedly increased erroneous responding, an effect that was apparent during the initial discrimination of a session. (*c*) These impairments were characterized by reduced probability (P) to follow a rewarded correct choice with another correct choice (win–stay). In comparison, the tendency to make an incorrect choice after a nonrewarded correct one (lose–shift) was unaltered. Stars represent $p < 0.05$ saline versus inactivation treatments.

risky ones delivered with changing probabilities (100–12.5%). Inactivation of the NAc shell (but not the core) reduced choice preference for larger, uncertain rewards. In both studies, alterations in action selection induced by shell inactivation were driven by a selective reduction in the tendency to follow a rewarded choice with another such choice (i.e., reduced win-stay tendencies) (**Figure 5*c***). This may be interpreted as a failure to suppress responses yielding less preferable or frequent rewards. In such cases, behavior is more likely to be directed toward smaller or less likely rewards.

In a similar vein, recent imaging studies in humans reported selective activation of the NAc shell during evaluation of potential gains or losses when uncertain outcomes were evaluated during

a gambling task (Baliki et al. 2013). The supposition that the shell influences response selection in situations involving reward uncertainty corresponds with the recent theoretical framework of Baudonnat et al. (2013, p. 4), who proposed that "NAc shell dopamine is important for signaling the occurrence of novel and potentially salient events, particularly. . .when there is ambiguity over the cause of that event." Taken together, these data suggest that the NAc shell may be preferentially recruited in refining reward seeking in situations when there is considerable uncertainty about whether certain actions will procure rewards.

fMRI: functional magnetic resonance imaging

BOLD: blood-oxygen-level dependent

When integrating the findings from studies probing the respective contributions of the NAc core and shell to goal seeking, it appears that both regions facilitate obtainment of the good things in life but through different mechanisms. By promoting approach to stimuli signaling reward availability, core activity ensures an organism moves to where rewards may be procured, thereby facilitating a flexible approach toward stimuli signaling reward availability so they may be reached in a timely manner. By contrast, when an organism is en route to such a bountiful location or once it has been reached, the shell suppresses behavior that may be directed toward irrelevant, nonrewarded, or less preferable outcomes, thus keeping the reward seeker on task and ensuring rewards may be obtained more efficiently. With this in mind, it bears emphasizing again that the manner in which the NAc biases the direction of behavior is ultimately dependent on incoming signals from the frontal and temporal lobes, which are, in turn, modulated by DA. These signals do not trigger automatic action patterns, but rather increase the likelihood that distinct patterns of approach or avoidance are instigated toward or away from stimuli deemed by upstream regions to have motivational relevance. Thus, to obtain a more comprehensive understanding of the mechanisms through which the NAc contributes to multiple aspects of behavior, research questions must give equal importance to inquiries about what the NAc does as well as what its inputs are telling it to do.

THE NUCLEUS ACCUMBENS IN HUMANS: WHAT IMAGING MAY REVEAL ABOUT ITS FUNCTION

As is apparent from most of the literature reviewed here, our understanding of NAc function comes almost exclusively from studies of rodents. Yet, over the past 20 years, research into the contribution of the NAc to both normal and abnormal behavior in humans has increased markedly, although this interest has arisen in a somewhat unconventional manner. Historically, cases of humans whose brain regions (e.g., the hippocampus, dorsal striatum, frontal lobes) have been damaged by traumatic injury, surgical excision, or degenerative diseases have inspired preclinical studies. Subsequent studies used primates and then rodents to better understand the involvement of these regions in human behavior. By comparison, cases with selective lesions to the ventral striatum are rare. As such, our knowledge of how damage to this region may alter human behavior is limited. However, as a result of functional imaging, research with humans has drawn on the vast literature of NAc function in rodents to instruct studies probing how activity within the NAc encodes information relevant to guiding motivated behavior.

With this in mind, an important caveat in interpreting these studies is that the functional magnetic resonance imaging (fMRI) BOLD (blood-oxygen-level-dependent) signal may not directly reflect firing of intrinsic neurons within a particular brain region. Rather, contemporary theory has posited that the BOLD response correlates with the localized field potential and local processing, which are driven by subthreshold activity and synaptic inputs to the area (Attwell & Iadecola 2002, Logothetis & Wandell 2004, Logothetis et al. 2001). Thus, it may be more appropriate to view imaging results as a reflection of signals an area is processing (i.e., what the NAc is "hearing" from its inputs), rather than as the information that intrinsic NAc neurons may be transmitting

downstream. Nevertheless, these imaging studies have provided insight to the types of information the NAc may integrate to guide behavior in different circumstances.

In keeping with the pervasive idea that the NAc is involved in reward processing, fMRI studies have shown repeatedly that receipt of rewards increases BOLD responses in the NAc (Breiter et al. 2001, Cho et al. 2012, Delgado et al. 2000, Knutson et al. 2001, Zink et al. 2004). In a similar vein, invigoration of instrumental responding by Pavlovian stimuli paired with reward or punishment is associated with increased activation of the NAc (as well as the amygdala) (Lewis et al. 2013, Talmi et al. 2008). However, when compared with the animal literature, imaging studies in humans have provided considerably greater insight into the manner in which the NAc encodes aversive situations. Thus, stimuli signaling aversive events can evoke increased NAc activation, particularly when a certain action can be performed to avoid these events (Delgado et al. 2009, Jensen et al. 2003, Niznikiewicz & Delgado 2011). Moreover, changes in the ventral striatal BOLD response may be particularly sensitive to whether avoidance of aversive stimuli requires emitting versus withholding a behavioral response. In a study by Levita et al. (2012), participants were shown one of two distinct cues that warned of an impending presentation of an aversive (i.e., disgusting) image. Depending on the cue, participants had to press or not press a button to avoid the image (active versus passive avoidance, respectively). Active avoidance increased activation of the left NAc and enhanced amygdala-NAc connectivity. In contrast, passive avoidance significantly deactivated the right NAc. These findings yield two particularly notable features: First, active versus passive avoidance was characterized by opposing changes in NAc activation. Second, activation of the NAc during avoidance may reflect some special case of reward processing, i.e., avoiding an aversive event may be perceived as rewarding (Kim et al. 2006). If so, NAc activation would be similar during both passive and active avoidance, because the participant would have avoided an unpleasant event in both cases. Yet, the opposing changes suggest that NAc activation during avoidance does not simply reflect reward or relief. Instead, this activity seems to encode more complex information related to the need for specific actions to occur (or not) so that aversive outcomes may be avoided.

Providing further support that rewarding versus aversive learning may be associated with different patterns of NAc activation are studies that have directly compared how approach and avoidance learning may activate the NAc within the same subject. In Niznikiewicz & Delgado (2011), participants learned through trial and error to make different discriminative responses to either win or avoid losing monetary rewards. Ventral striatal activity was greater during the early phases of learning than it was when the correct type of response had been well learned later in training. However, their results also revealed an interaction between session type (approach and avoidance) and learning phase (early or late): The NAc displayed greater activation during the acquisition of avoidance versus approach behavior. Thus, despite overlapping neural circuitry mediating approach or avoidance, negative reinforcers can, in some instances, exert a greater influence over NAc activation.

With respect to action selection, imaging studies have revealed increased NAc activation when individuals must choose between different actions to successfully procure rewards or avoid punishments (Botvinick et al. 2009, Kang et al. 2011, Kuhnen & Knutson 2005). When presented with the opportunity to choose their own fate, subjects displayed greater NAc activation compared with when an equivalent reward was received but without an action-selection component (Leotti & Delgado 2011). As mentioned above, it is difficult to disentangle how much of the fMRI BOLD response associated with choice behavior is attributable to the activity either of intrinsic NAc neurons or of inputs arising from frontal and temporal lobe regions. However, a study by Patel et al. (2012) employed electrophysiological recordings from individual NAc neurons in humans. Subjects played a gambling task resembling the card game "War," wherein they drew cards of different numerical values from a deck and had to wager either $20 or $5 that their card would be

higher than the one drawn by a computer opponent. The optimal strategy was for participants to bet high when they drew a high-value card (given their likelihood of winning) and bet low with lower-value cards (to minimize their likely losses). Here, the activity of individual NAc neurons predicted whether a subject would bet high or low: Higher firing rates were associated with increased tendencies to bet high. The manner in which this activity predicted choice was unrelated to whether subjects expected to win, suggesting that NAc neural firing did not merely represent anticipation of upcoming rewards. Notably, this increase in firing occurred ~2 s before subjects physically manifested their bets, in keeping with the idea that increased firing of NAc neurons does not automatically trigger specific actions, but instead may increase the likelihood that certain actions occur by priming downstream regions that exert more direct control over movement (McGinty et al. 2013). This study also revealed that NAc activity encodes reward prediction errors, as indicated by the outcomes of the gambles. Thus, wins or losses were not associated with significant changes in NAc neural firing when these outcomes were expected (i.e., winning or losing after drawing a high- or low-value card). In contrast, NAc neurons increased firing after unlikely wins and decreased in activity after unexpected losses. Taken together, these findings suggest that the firing of individual NAc neurons in humans can reflect two key aspects of action selection: They encode not only the specific direction of choice behavior, but also the outcomes of those choices.

Although numerous imaging studies have shown that NAc activation can encode action outcomes, determining what these signals represent has prompted some debate. For example, outcome-related activity may update the relative incentive value of actions or of stimuli that guided them (i.e., an action/stimulus is associated with good or bad outcomes) (Lohrenz et al. 2007, Watkins & Dayan 1992). Conversely, others have proposed that these signals may aid in updating action policies (i.e., an action is correct) (Klein-Flügge et al. 2011, Li & Daw 2011). To address this issue, FitzGerald et al. (2014) used a task wherein participants were presented simultaneously with one of two distinct auditory and visual stimuli that indicated a certain type of offer. Good offers were associated with an 80% probability of monetary gain and 20% probability of loss (vice versa for bad offers). At the start of each trial, subjects were told which type of cue would signify whether a good or bad offer was being presented, after which they had to either accept it (roll the dice) or reject it (no gain, no loss). After making their decision, participants were informed about the outcome of the offer regardless of whether they had accepted or rejected it. If activity during this period encoded whether the action was (or would have been) good or bad, then similar patterns of NAc activation would be expected to occur irrespective of whether the participant accepted or rejected the offer. This is because the decision maker was always informed of the actual or potential outcome of their choice, which could provide a signal that such actions are associated with rewards or punishments (i.e., their choice resulted/would have resulted in something good or bad). However, this was not observed. Instead, NAc activity correlated positively with rewarded outcomes when subjects accepted an offer, but it showed the opposite pattern when they rejected an offer. Thus, accepting a reward or rejecting a loss (i.e., correct choices) was associated with increased activity, and an incorrect choice (rejecting an offer that would have been rewarded or accepting one that resulted in a loss) reduced NAc activity. These findings support the idea that outcome-related activity in the NAc reflects a signal that aids in implementing and updating successful behavioral policies (Klein-Flügge et al. 2011, Li & Daw 2011), which in turn suggests that "at least in certain contexts, the key role of ventral striatum in outcome processing is to signal the success of a particular action, and hence the desirability of repeating it in the future" (FitzGerald et al. 2014, p. 1,278).

The idea that encoding of action outcomes increases the likelihood that recently reinforced actions can bias the direction of subsequent behavior finds additional support in studies of rats.

For example, during performance of a probabilistic reversal-learning task, prechoice changes in the firing of striatal neurons appeared to encode action selection by biasing an animal's choice toward an action that is associated with a higher value (Kim et al. 2009). In addition, some NAc cells encoded information about the outcomes of previous choices, suggesting that these cells may encode the estimated value of a chosen action by integrating information about outcomes of previous and current actions. These findings complement those indicating that inactivation of the NAc reduces the impact that a rewarded action exerts over the direction of subsequent actions in situations where reward delivery is probabilistic (Dalton et al. 2014, Stopper & Floresco 2011) (**Figure 5*c***). In light of findings characterizing the manner in which the NAc may bias the direction of behavior, these findings further suggest that NAc activity occurring after a particular action may also aid in refining goal-directed behavior. Thus, if different subregions of the NAc bias an organism to either "go to it" or "don't do it," NAc activity occurring in certain situations may convey a signal that says, "do it again!"

The question remains as to how outcome-related activity within the NAc may serve to bias the direction of subsequent behavior. One mechanism may involve feedback pathways that project to frontal/temporal regions. Thus, outcome-related signals from the NAc could potentially feedback to the PFC or amygdala, via polysynaptic pathways incorporating the ventral palladium and medial thalamic nuclei (Zahm 2008). Activity within these pathways may inform frontal/temporal regions about whether certain actions have been executed and the outcomes of those actions. Notably, even though feedback loops from the NAc to the PFC and amygdala have been documented for many years, there is a lack of experimental data describing how information transfer through these pathways may aid in guiding and updating behavior. Another mechanism may involve short-term increases in the strength of particular NAc synapses engaged in action selection. Concurrent activation of dopaminergic and excitatory frontal/temporal inputs to the NAc associated with a rewarded choice may modify these circuits so they are more likely to display similar patterns of activity when similar situations present themselves again (Floresco et al. 2001a,b; Humphries & Prescott 2010; Yun et al. 2004b). Thus, in addition to integrating incoming cortical, limbic, and dopaminergic signals to bias action selection, the anatomical connectivity and neurophysiological properties of the NAc permit it to track the outcomes of these actions and influence the direction of future ones. As such, if the NAc is a servant to many masters, it not only executes their commands, but also may serve as a *consigliere* that updates and advises them on whether these actions were beneficial or if different courses of action should be taken.

CONCLUSIONS

Since its initial characterization approximately 40 years ago, research on the function of the NAc has yielded a wealth of information on how it contributes to different aspects of behavior. However, this research has also introduced additional questions, controversies, and misconceptions regarding NAc functions. Although it continues to linger, the idea that this nucleus serves as a reward center is both an insufficient and imprecise description of its role. A primary tenet put forth in this review is that the NAc plays a key role in action selection that facilitates goal-directed behavior and makes such behavior more efficient: These goals are set by frontal and temporal lobe regions with which the NAc interfaces. Recruitment of the NAc by these regions to direct approach/avoidance behaviors appears to be particularly prominent when the most beneficial course of action or the most efficient manner to obtain a goal is ambiguous, uncertain, laden with distractors, or in a state of flux. To this end, an emerging literature suggests that different subregions of the NAc play dissociable roles in refining action selection: The core plays a more prominent role in instigating approach behavior toward motivationally relevant stimuli, and the shell suppresses irrelevant or

nonrewarded actions so that goals may be obtained more efficiently. In addition, studies from humans and animals indicate that the NAc not only serves as a key node that mediates action selection, but also encodes the outcomes of actions that may in turn aid in guiding the direction of subsequent ones. Although the focus of this review is to highlight how normal functioning of the NAc serves to guide behavior, abnormalities within this nucleus have been proposed to underlie numerous psychiatric disorders, including schizophrenia, drug addiction, depression, and obsessive/compulsive disorder. Our understanding of how distinct forms of pathophysiology within the NAc contribute to symptoms of these diseases is in its relative infancy, and as such, a more comprehensive elucidation of how it regulates normal patterns of behavior is essential for resolving these issues. To this end, future integrative and multidisciplinary research on this topic needs to strive not only to unravel the functions of the NAc, but also to build a consensus on what those functions are.

FUTURE ISSUES

1. Although the involvement of the NAc and mesoaccumbens DA in reward-related behaviors is well characterized, our understanding of when and how it contributes to aversively motivated or fear-related behaviors remains underexplored.
2. The neural mechanism underlying suppression of irrelevant or nonrewarded behaviors by the NAc shell requires additional clarification, although research on this topic is complicated owing to the difficulties of unveiling how neural activity may relate to suppression of behaviors.
3. Do prechoice and outcome-related firing of NAc neurons work in concert to guide behavior, or do they serve different functions? Exploitation of optogenetic technologies that can induce temporally discrete suppression of activity may prove fruitful in resolving these issues.
4. Do signals originating in the NAc reach prefrontal and amygdala regions via polysynaptic pathways, and if so, what are the functional consequences of these signals and their underlying mechanisms?

DISCLOSURE STATEMENT

The author is not aware of any affiliations, memberships, funding, or financial holdings that might be perceived as affecting the objectivity of this review.

ACKNOWLEDGMENTS

Some work described in this review was funded by grants from the Natural Sciences and Engineering Research Council and the Canadian Institutes of Health Research to S.B.F. I am indebted and eternally grateful to Gemma Dalton, Mauricio Delgado, Saleem Nicola, and D. Scott Zahm for their insightful suggestions in formulating and refining this review.

LITERATURE CITED

Ambroggi F, Ghazizadeh A, Nicola SM, Fields HL. 2011. Roles of nucleus accumbens core and shell in incentive-cue responding and behavioral inhibition. *J. Neurosci.* 31(18):6820–30

Ambroggi F, Ishikawa A, Fields HL, Nicola SM. 2008. Basolateral amygdala neurons facilitate reward-seeking behavior by exciting nucleus accumbens neurons. *Neuron* 59(4):648–61

Attwell D, Iadecola C. 2002. The neural basis of functional brain imaging signals. *Trends Neurosci.* 25(12):621–25

Baliki MN, Mansour A, Baria AT, Huang L, Berger SE, et al. 2013. Parceling human accumbens into putative core and shell dissociates encoding of values for reward and pain. *J. Neurosci.* 33(41):16383–93

Bari AA, Pierce RC. 2005. D_1-like and D_2 dopamine receptor antagonists administered into the shell subregion of the rat nucleus accumbens decrease cocaine, but not food, reinforcement. *Neuroscience* 135(3):959–68

Baudonnat M, Huber A, David V, Walton ME. 2013. Heads for learning, tails for memory: reward, reinforcement and a role of dopamine in determining behavioral relevance across multiple timescales. *Front. Neurosci.* 7:175

Berridge KC. 2007. The debate over dopamine's role in reward: the case for incentive salience. *Psychopharmacology* 191(3):391–431

Berridge KC, Robinson TE. 1998. What is the role of dopamine in reward: hedonic impact, reward learning, or incentive salience? *Brain Res. Rev.* 28(3):309–69

Blaiss CA, Janak PH. 2009. The nucleus accumbens core and shell are critical for the expression, but not the consolidation, of Pavlovian conditioned approach. *Behav. Brain Res.* 200:22–32

Block AE, Dhanji H, Thompson-Tardif SF, Floresco SB. 2007. Thalamic-prefrontal cortical-ventral striatal circuitry mediates dissociable components of strategy set shifting. *Cereb. Cortex* 17(7):1625–36

Botvinick MM, Huffstetler S, McGuire JT. 2009. Effort discounting in human nucleus accumbens. *Cogn. Affect. Behav. Neurosci.* 9:16–27

Bowman EM, Brown VJ. 1998. Effects of excitotoxic lesions of the rat ventral striatum on the perception of reward cost. *Exp. Brain Res.* 123(4):439–48

Breiter HC, Aharon I, Kahneman D, Dale A, Shizgal P. 2001. Functional imaging of neural responses to expectancy and experience of monetary gains and losses. *Neuron* 30(2):619–39

Britt JP, Benaliouad F, McDevitt RA, Stuber GD, Wise RA, Bonci A. 2012. Synaptic and behavioral profile of multiple glutamatergic inputs to the nucleus accumbens. *Neuron* 76(4):790–803

Brog JS, Salyapongse A, Deutch AY, Zahm DS. 1993. The patterns of afferent innervation of the core and shell in the "accumbens" part of the rat ventral striatum: immunohistochemical detection of retrogradely transported fluoro-gold. *J. Comp. Neurol.* 338(2):255–78

Cardinal RN, Cheung TH. 2005. Nucleus accumbens core lesions retard instrumental learning and performance with delayed reinforcement in the rat. *BMC Neurosci.* 6:9

Cardinal RN, Robbins TW, Everitt BJ. 2000. The effects of *d*-amphetamine, chlordiazepoxide, α-flupenthixol and behavioural manipulations on choice of signalled and unsignalled delayed reinforcement in rats. *Psychopharmacology* 152(4):362–75

Castañé A, Theobald DE, Robbins TW. 2010. Selective lesions of the dorsomedial striatum impair serial spatial reversal learning in rats. *Behav. Brain Res.* 210:74–83

Charara A, Grace AA. 2003. Dopamine receptor subtypes selectively modulate excitatory afferents from the hippocampus and amygdala to rat nucleus accumbens neurons. *Neuropsychopharmacology* 28(8):1412–21

Cho YT, Fromm S, Guyer AE, Detloff A, Pine DS, et al. 2012. Nucleus accumbens, thalamus and insula connectivity during incentive anticipation in typical adults and adolescents. *NeuroImage* 66C:508–21

Christakou A, Robbins TW, Everitt BJ. 2004. Prefrontal cortical-ventral striatal interactions involved in affective modulation of attentional performance: implications for corticostriatal circuit function. *J. Neurosci.* 24(4):773–80

Cohen JY, Haesler S, Vong L, Lowell BB, Uchida N. 2012. Neuron-type-specific signals for reward and punishment in the ventral tegmental area. *Nature* 482(7383):85–88

Corbit LH, Balleine BW. 2011. The general and outcome-specific forms of Pavlovian-instrumental transfer are differentially mediated by the nucleus accumbens core and shell. *J. Neurosci.* 31(33):11786–94

Corbit LH, Muir JL, Balleine BW. 2001. The role of the nucleus accumbens in instrumental conditioning: evidence of a functional dissociation between accumbens core and shell. *J. Neurosci.* 21(9):3251–60

Dalton GL, Phillips AG, Floresco SB. 2014. Preferential involvement by nucleus accumbens shell in mediating probabilistic learning and reversal shifts. *J. Neurosci.* 34(13):4618–26

Day JJ, Jones JL, Carelli RM. 2011. Nucleus accumbens neurons encode predicted and ongoing reward costs in rats. *Eur. J. Neurosci.* 33(2):308–21

Day JJ, Roitman MF, Wightman RM, Carelli RM. 2007. Associative learning mediates dynamic shifts in dopamine signaling in the nucleus accumbens. *Nat. Neurosci.* 10(8):1020–28

Delgado MR, Jou RL, Ledoux JE, Phelps EA. 2009. Avoiding negative outcomes: tracking the mechanisms of avoidance learning in humans during fear conditioning. *Front. Behav. Neurosci.* 3:33

Delgado MR, Nystrom LE, Fissell C, Noll DC, Fiez JA. 2000. Tracking the hemodynamic responses to reward and punishment in the striatum. *J. Neurophysiol.* 84(6):3072–77

Di Ciano P, Cardinal RN, Cowell RA, Little SJ, Everitt BJ. 2001. Differential involvement of NMDA, AMPA/kainate, and dopamine receptors in the nucleus accumbens core in the acquisition and performance of Pavlovian approach behavior. *J. Neurosci.* 21(23):9471–77

Di Ciano P, Robbins TW, Everitt BJ. 2008. Differential effects of nucleus accumbens core, shell, or dorsal striatal inactivations on the persistence, reacquisition, or reinstatement of responding for a drug-paired conditioned reinforcer. *Neuropsychopharmacology* 33(6):1413–25

Everitt BJ, Morris KA, O'Brien A, Robbins TW. 1991. The basolateral amygdala-ventral striatal system and conditioned place preference: further evidence of limbic-striatal interactions underlying reward-related processes. *Neuroscience* 42:1–18

Faure A, Richard JM, Berridge KC. 2010. Desire and dread from the nucleus accumbens: cortical glutamate and subcortical GABA differentially generate motivation and hedonic impact in the rat. *PLOS ONE* 5(6):e11223

Feja M, Hayn L, Koch M. 2014. Nucleus accumbens core and shell inactivation differentially affects impulsive behaviours in rats. *Prog. Neuropsychopharmacol. Biol. Psychiatry* 54C:31–42

Fernando AB, Murray JE, Milton AL. 2013. The amygdala: securing pleasure and avoiding pain. *Front. Behav. Neurosci.* 7:190

Fernando AB, Urcelay GP, Mar AC, Dickinson TA, Robbins TW. 2014. The role of the nucleus accumbens shell in the mediation of the reinforcing properties of a safety signal in free-operant avoidance: dopamine-dependent inhibitory effects of *d*-amphetamine. *Neuropsychopharmacology* 39(6):1420–30

FitzGerald TH, Schwartenbeck P, Dolan RJ. 2014. Reward-related activity in ventral striatum is action contingent and modulated by behavioral relevance. *J. Neurosci.* 34(4):1271–79

Floresco SB. 2007. Dopaminergic regulation of limbic-striatal interplay. *J. Psychiatry Neurosci.* 32(6):400–11

Floresco SB, Blaha CD, Yang CR, Phillips AG. 2001a. Dopamine D_1 and NMDA receptors mediate potentiation of basolateral amygdala-evoked firing of nucleus accumbens neurons. *J. Neurosci.* 21:6370–76

Floresco SB, Blaha CD, Yang CR, Phillips AG. 2001b. Modulation of hippocampal and amygdalar-evoked activity of nucleus accumbens neurons by dopamine: cellular mechanisms of input selection. *J. Neurosci.* 21(8):2851–60

Floresco SB, Braaksma DN, Phillips AG. 1999. Thalamic-cortical-striatal circuitry subserves working memory during delayed responding on a radial arm maze. *J. Neurosci.* 19(24):11061–71

Floresco SB, Ghods-Sharifi S, Vexelman C, Magyar O. 2006. Dissociable roles for the nucleus accumbens core and shell in regulating set shifting. *J. Neurosci.* 26(9):2449–57

Floresco SB, McLaughlin RJ, Haluk DM. 2008. Opposing roles for the nucleus accumbens core and shell in cue-induced reinstatement of food-seeking behavior. *Neuroscience* 154(3):877–84

Floresco SB, Phillips AG. 1999. Dopamine and hippocampal input to the nucleus accumbens play an essential role in the search for food in an unpredictable environment. *Psychobiology* 27(2):277–86

Floresco SB, Seamans JK, Phillips AG. 1996. A selective role for dopamine in the nucleus accumbens of the rat in random foraging but not delayed spatial win-shift foraging. *Behav. Brain Res.* 80:161–68

Floresco SB, Seamans JK, Phillips AG. 1997. Selective roles for hippocampal, prefrontal cortical, and ventral striatal circuits in radial-arm maze tasks with or without a delay. *J. Neurosci.* 17(5):1880–90

Floresco SB, West AR, Ash B, Moore H, Grace AA. 2003. Afferent modulation of dopamine neuron firing differentially regulates tonic and phasic dopamine transmission. *Nat. Neurosci.* 6(9):968–73

French SJ, Totterdell S. 2003. Individual nucleus accumbens-projection neurons receive both basolateral amygdala and ventral subicular afferents in rats. *Neuroscience* 119(1):19–31

Gal G, Joel D, Gusak O, Feldon J, Weiner I. 1997. The effects of electrolytic lesion to the shell subterritory of the nucleus accumbens on delayed non-matching-to-sample and four-arm baited eight-arm radial-maze tasks. *Behav. Neurosci.* 111(1):92–103

Gal G, Schiller D, Weiner I. 2005. Latent inhibition is disrupted by nucleus accumbens shell lesion but is abnormally persistent following entire nucleus accumbens lesion: The neural site controlling the expression and disruption of the stimulus preexposure effect. *Behav. Brain Res.* 162(2):246–55

Ghods-Sharifi S, Floresco SB. 2010. Differential effects on effort discounting induced by inactivations of the nucleus accumbens core or shell. *Behav. Neurosci.* 124(2):179–91

Groenewegen HJ, Berendse HW, Meredith GE, Haber SN, Voorn P, et al. 1991. Functional anatomy of the ventral, limbic system-innervated striatum. In *The Mesolimbic Dopamine System*, ed. P Willner, J Scheel-Kruger, pp. 19–59. New York: Wiley & Sons

Groenewegen HJ, Mulder AB, Beijer AVJ, Wright CI, Lopes da Silva FH, Pennartz CMA. 1999. Hippocampal and amygdaloid interactions in the nucleus accumbens. *Psychobiology* 27(2):149–64

Groenewegen HJ, Vermeulen-Van der Zee E, te Kortschot A, Witter MP. 1987. Organization of the projections from the subiculum to the ventral striatum in the rat. A study using anterograde transport of *Phaseolus vulgarus* leucoagglutinin. *Neuroscience* 23(1):103–20

Haluk DM, Floresco SB. 2009. Ventral striatal dopamine modulation of different forms of behavioral flexibility. *Neuropsychopharmacology* 34(8):2041–52

Haralambous T, Westbrook RF. 1999. An infusion of bupivacaine into the nucleus accumbens disrupts the acquisition but not the expression of contextual fear conditioning. *Behav. Neurosci.* 113(5):925–40

Hauber W, Sommer S. 2009. Prefrontostriatal circuitry regulates effort-related decision making. *Cereb. Cortex* 19(10):2240–47

Heimer L, Wilson RD. 1975. The subcortical projections of allocortex: similarities in the neuronal associations of the hippocampus, the piriform cortex and the neocortex. In *Golgi Centennial Symposium Proceedings: Perspectives in Neurobiology*, ed. M Santini, pp. 173–93. New York: Raven

Hernández-López S, Bargas J, Surmeier DJ, Reyes A, Galarraga E. 1997. D_1 receptor activation enhances evoked discharge in neostriatal medium spiny neurons by modulating an L-type Ca^{2+} conductance. *J. Neurosci.* 17(9):3334–42

Hjelmstad GO. 2004. Dopamine excites nucleus accumbens neurons through the differential modulation of glutamate and GABA release. *J. Neurosci.* 24(39):8621–28

Hnasko TS, Hjelmstad GO, Fields HL, Edwards RH. 2012. Ventral tegmental area glutamate neurons: electrophysiological properties and projections. *J. Neurosci.* 32(43):15076–85

Howland JG, Taepavarapruk P, Phillips AG. 2002. Glutamate receptor-dependent modulation of dopamine efflux in the nucleus accumbens by basolateral, but not central, nucleus of the amygdala in rats. *J. Neurosci.* 22(3):1137–45

Hu XT, Wang RY. 1988. Disinhibition of nucleus accumbens neurons by the dopamine D_2 receptor agonist LY-141865: prevented by 6-OHDA pretreatment. *Brain Res.* 444(2):389–93

Humphries MD, Prescott TJ. 2010. The ventral basal ganglia, a selection mechanism at the crossroads of space, strategy, and reward. *Prog. Neurobiol.* 90:385–417

Ito R, Robbins TW, Pennartz CM, Everitt BJ. 2008. Functional interaction between the hippocampus and nucleus accumbens shell is necessary for the acquisition of appetitive spatial context conditioning. *J. Neurosci.* 28(27):6950–59

Ito R, Robbins TW, Everitt BJ. 2004. Differential control over cocaine-seeking behavior by nucleus accumbens core and shell. *Nat. Neurosci.* 7(4):389–97

Jensen J, McIntosh AR, Crawley AP, Mikulis DJ, Remington G, Kapur S. 2003. Direct activation of the ventral striatum in anticipation of aversive stimuli. *Neuron* 40(6):1251–57

Jongen-Rêlo AL, Kaufmann S, Feldon J. 2003. A differential involvement of the shell and core subterritories of the nucleus accumbens of rats in memory processes. *Behav. Neurosci.* 117:150–68

Kang MJ, Rangel A, Camus M, Camerer CF. 2011. Hypothetical and real choice differentially activate common valuation areas. *J. Neurosci.* 31(2):461–68

Kelley AE, Domesick VB, Nauta WJ. 1982. The amygdalostriatal projection in the rat: an anatomical study by anterograde and retrograde tracing methods. *Neuroscience* 7:615–30

Khamassi M, Humphries MD. 2012. Integrating cortico-limbic-basal ganglia architectures for learning model-based and model-free navigation strategies. *Front. Behav. Neurosci.* 6:79
Kim H, Shimojo S, O'Doherty JP. 2006. Is avoiding an aversive outcome rewarding? Neural substrates of avoidance learning in the human brain. *PLOS Biol.* 4(8):e233
Kim H, Sul JH, Huh N, Lee D, Jung MW. 2009. Role of striatum in updating values of chosen actions. *J. Neurosci.* 29(47):14701–12
Kiyatkin EA, Rebec GV. 1996. Dopaminergic modulation of glutamate-induced excitations of neurons in the neostriatum and nucleus accumbens of awake, unrestrained rats. *J. Neurophysiol.* 75:142–53
Klein-Flügge MC, Hunt LT, Bach DR, Dolan RJ, Behrens TE. 2011. Dissociable reward and timing signals in human midbrain and ventral striatum. *Neuron* 72:654–64
Knutson B, Adams CM, Fong GW, Hommer D. 2001. Anticipation of increasing monetary reward selectively recruits nucleus accumbens. *J. Neurosci.* 21(16):RC159
Krause M, German PW, Taha SA, Fields HL. 2010. A pause in nucleus accumbens neuron firing is required to initiate and maintain feeding. *J. Neurosci.* 30(13):4746–56
Kravitz AV, Tye LD, Kreitzer AC. 2012. Distinct roles for direct and indirect pathway striatal neurons in reinforcement. *Nat. Neurosci.* 15(6):816–18
Kuhnen CM, Knutson B. 2005. The neural basis of financial risk taking. *Neuron* 47(5):763–70
Le Moine C, Bloch B. 1996. Expression of the D_3 dopamine receptor in peptidergic neurons of the nucleus accumbens: comparison with the D_1 and D_2 dopamine receptors. *Neuroscience* 173:131–43
Leotti LA, Delgado MR. 2011. The inherent reward of choice. *Psychol. Sci.* 22(10):1310–18
Levita L, Dalley JW, Robbins TW. 2002. Disruption of Pavlovian contextual conditioning by excitotoxic lesions of the nucleus accumbens core. *Behav. Neurosci.* 116(4):539–52
Levita L, Hoskin R, Champi S. 2012. Avoidance of harm and anxiety: a role for the nucleus accumbens. *NeuroImage* 62:189–98
Lewis AH, Niznikiewicz MA, Delamater AR, Delgado MR. 2013. Avoidance-based human Pavlovian-to-instrumental transfer. *Eur. J. Neurosci.* 38(12):3740–48
Li J, Daw ND. 2011. Signals in human striatum are appropriate for policy update rather than value prediction. *J. Neurosci.* 31:5504–11
Lobo MK, Covington HE 3rd, Chaudhury D, Friedman AK, Sun H, et al. 2010. Cell type-specific loss of BDNF signaling mimics optogenetic control of cocaine reward. *Science* 330(6002):385–90
Logothetis NK, Pauls J, Augath M, Trinath T, Oeltermann A. 2001. Neurophysiological investigation of the basis of the fMRI signal. *Nature* 412(6843):150–57
Logothetis NK, Wandell BA. 2004. Interpreting the BOLD signal. *Annu. Rev. Physiol.* 66:735–69
Lohrenz T, McCabe K, Camerer CF, Montague PR. 2007. Neural signature of fictive learning signals in a sequential investment task. *Proc. Natl. Acad. Sci. USA* 104:9493–98
Maldonado-Irizarry CS, Kelley AE. 1994. Differential behavioral effects following microinjection of an NMDA antagonist into nucleus accumbens subregions. *Psychopharmacology* 116:65–72
Maldonado-Irizarry CS, Swanson CJ, Kelley AE. 1995. Glutamate receptors in the nucleus accumbens shell control feeding behavior via the lateral hypothalamus. *J. Neurosci.* 15(10):6779–88
Mannella F, Gurney K, Baldassarre G. 2013. The nucleus accumbens as a nexus between values and goals in goal-directed behavior: a review and a new hypothesis. *Front. Behav. Neurosci.* 7:135
McCullough LD, Sokolowski JD, Salamone JD. 1993. A neurochemical and behavioral investigation of the involvement of nucleus accumbens dopamine in instrumental avoidance. *Neuroscience* 52(4):919–25
McGinty VB, Lardeux S, Taha SA, Kim JJ, Nicola SM. 2013. Invigoration of reward seeking by cue and proximity encoding in the nucleus accumbens. *Neuron* 78(5):910–22
McLaughlin RJ, Floresco SB. 2008. The role of different subregions of the basolateral amygdala in cue-induced reinstatement and extinction of food-seeking behavior. *Neuroscience* 146(4):1484–94
Meredith GE, Pattiselanno A, Groenewegen HJ, Haber SN. 1996. Shell and core in monkey and human nucleus accumbens identified with antibodies to calbindin-D28k. *J. Comp. Neurol.* 365(4):628–39
Mogenson GJ, Brudzynski SM, Wu M, Yang CR, Yim CY. 1993. From motivation to action: a review of dopaminergic regulation of limbic→nucleus accumbens→ventral pallidum→pedunculopontine nucleus circuitries involved with limbic-motor integration. In *Limbic-Motor Circuits and Neuropsychiatry*, ed. PW Kalivas, CD Barnes, pp. 193–263. Boca Raton, FL: CRC Press

Mogenson GJ, Jones DL, Yim CY. 1980. From motivation to action: functional interface between the limbic system and the motor system. *Prog. Neurobiol.* 14(2–3):69–97
Nicola SM. 2007. The nucleus accumbens as part of a basal ganglia action selection circuit. *Psychopharmacology* 191(3):521–50
Nicola SM. 2010. The flexible approach hypothesis: unification of effort and cue-responding hypotheses for the role of nucleus accumbens dopamine in the activation of reward-seeking behavior. *J. Neurosci.* 30(49):16585–600
Nicola SM, Malenka RC. 1997. Dopamine depresses excitatory and inhibitory synaptic transmission by distinct mechanisms in the nucleus accumbens. *J. Neurosci.* 17(15):5697–710
Niv Y. 2007. Cost, benefit, tonic, phasic: what do response rates tell us about dopamine and motivation? *Ann. N.Y. Acad. Sci.* 1104:357–76
Niznikiewicz MA, Delgado MR. 2011. Two sides of the same coin: learning via positive and negative reinforcers in the human striatum. *Dev. Cogn. Neurosci.* 1(4):494–505
O'Donnell P. 1999. Ensemble coding in the nucleus accumbens. *Psychobiology* 27(2):187–97
O'Donnell P. 2003. Dopamine gating of forebrain neural ensembles. *Eur. J. Neurosci.* 17(3):429–35
O'Donnell P, Grace AA. 1994. Tonic D_2-mediated attenuation of cortical excitation in nucleus accumbens neurons recorded in vitro. *Brain Res.* 634:105–12
O'Donnell P, Grace AA. 1996. Dopaminergic reduction of excitability in nucleus accumbens neurons recorded in vitro. *Neuropsychopharmacology* 15:87–97
Oleson EB, Gentry RN, Chioma VC, Cheer JF. 2012. Subsecond dopamine release in the nucleus accumbens predicts conditioned punishment and its successful avoidance. *J. Neurosci.* 32(42):14804–8
Pan WX, Schmidt R, Wickens JR, Hyland BI. 2005. Dopamine cells respond to predicted events during classical conditioning: evidence for eligibility traces in the reward-learning network. *J. Neurosci.* 25(26):6235–42
Parkinson JA, Olmstead MC, Burns LH, Robbins TW, Everitt BJ. 1999. Dissociation in effects of lesions of the nucleus accumbens core and shell on appetitive Pavlovian approach behavior and the potentiation of conditioned reinforcement and locomotor activity by D-amphetamine. *J. Neurosci.* 19(6):2401–11
Parkinson JA, Willoughby PJ, Robbins TW, Everitt BJ. 2000. Disconnection of the anterior cingulate cortex and nucleus accumbens core impairs Pavlovian approach behavior: further evidence for limbic cortical-ventral striatopallidal systems. *Behav. Neurosci.* 114:42–63
Patel SR, Sheth SA, Mian MK, Gale JT, Greenberg BD, et al. 2012. Single-neuron responses in the human nucleus accumbens during a financial decision-making task. *J. Neurosci.* 32(21):7311–15
Pennartz CMA, Groenewegen HJ, Lopes Da Silva FH. 1994. The nucleus accumbens as a complex of functionally distinct neuronal ensembles: an integration of behavioural, electrophysiological and anatomical data. *Prog. Neurobiol.* 42(6):719–61
Peters J, LaLumiere RT, Kalivas PW. 2008. Infralimbic prefrontal cortex is responsible for inhibiting cocaine seeking in extinguished rats. *J. Neurosci.* 28(23):6046–53
Pezze MA, Dalley JW, Robbins TW. 2007. Differential roles of dopamine D_1 and D_2 receptors in the nucleus accumbens in attentional performance on the five-choice serial reaction time task. *Neuropsychopharmacology* 32(2):273–83
Pezze MA, Feldon J. 2004. Mesolimbic dopaminergic pathways in fear conditioning. *Prog. Neurobiol.* 74(5):301–20
Redgrave P, Prescott TJ, Gurney K. 1999. Is the short-latency dopamine response too short to signal reward error? *Trends Neurosci.* 22(4):146–51
Reynolds SM, Berridge KC. 2002. Positive and negative motivation in nucleus accumbens shell: bivalent rostrocaudal gradients for GABA-elicited eating, taste "liking"/"disliking" reactions, place preference/avoidance, and fear. *J. Neurosci.* 22(16):7308–20
Reynolds SM, Berridge KC. 2008. Emotional environments retune the valence of appetitive versus fearful functions in nucleus accumbens. *Nat. Neurosci.* 11(4):423–25
Robinson TE, Flagel SB. 2009. Dissociating the predictive and incentive motivational properties of reward-related cues through the study of individual differences. *Biol. Psychiatry* 65(10):869–73
Salamone JD, Correa M. 2012. The mysterious motivational functions of mesolimbic dopamine. *Neuron* 76(3):470–85

Salamone JD, Cousins MS, Bucher S. 1994. Anhedonia or anergia? Effects of haloperidol and nucleus accumbens dopamine depletion on instrumental response selection in a T-maze cost/benefit procedure. *Behav. Brain Res.* 65(2):221–29

Saunders BT, Robinson TE. 2012. The role of dopamine in the accumbens core in the expression of Pavlovian-conditioned responses. *Eur. J. Neurosci.* 36(4):2521–32

Schultz W. 1998. Predictive reward signal of dopamine neurons. *J. Neurophysiol.* 80:1–27

Schultz W, Dayan P, Montague PR. 1997. A neural substrate of prediction and reward. *Science* 275(5306):1593–99

Seamans JK, Phillips AG. 1994. Selective memory impairments produced by transient lidocaine-induced lesions of the nucleus accumbens in rats. *Behav. Neurosci.* 108(3):456–68

Shiflett MW, Balleine BW. 2010. At the limbic-motor interface: disconnection of basolateral amygdala from nucleus accumbens core and shell reveals dissociable components of incentive motivation. *Eur. J. Neurosci.* 32(10):1735–43

St. Onge JR, Ahn S, Phillips AG, Floresco SB. 2012. Dynamic fluctuations in dopamine efflux in the prefrontal cortex and nucleus accumbens during risk-based decision making. *J. Neurosci.* 32(47):16880–91

Stopper CM, Floresco SB. 2011. Contributions of the nucleus accumbens and its subregions to different aspects of risk-based decision making. *Cogn. Affect. Behav. Neurosci.* 11:97–112

Stratford TR, Kelley AE. 1997. GABA in the nucleus accumbens shell participates in the central regulation of feeding behavior. *J. Neurosci.* 17(11):4434–40

Sugam JA, Day JJ, Wightman RM, Carelli RM. 2012. Phasic nucleus accumbens dopamine encodes risk-based decision-making behavior. *Biol. Psychiatry* 71(3):199–205

Taha SA, Fields HL. 2006. Inhibitions of nucleus accumbens neurons encode a gating signal for reward-directed behavior. *J. Neurosci.* 26:217–22

Talmi D, Seymour B, Dayan P, Dolan RJ. 2008. Human Pavlovian-instrumental transfer. *J. Neurosci.* 28(2):360–68

Taylor JR, Robbins TW. 1986. 6-Hydroxydopamine lesions of the nucleus accumbens, but not of the caudate nucleus, attenuate enhanced responding with reward-related stimuli produced by intra-accumbens *d*-amphetamine. *Psychopharmacology* 90(3):390–97

Uchimura N, Cherubini E, North RA. 1989. Inward rectification in rat nucleus accumbens neurons. *J. Neurophysiol.* 62(6):1280–86

Uchimura N, Higashi H, Nishi S. 1986. Hyperpolarizing and depolarizing actions of dopamine via D_1 and D_2 receptors on nucleus accumbens neurons. *Brain Res.* 375(2):368–72

Voorn P, Brady LS, Schotte A, Berendse HW, Richfield EK. 1994. Evidence for two neurochemical divisions in the human nucleus accumbens. *Eur. J. Neurosci.* 6(12):1913–16

Wadenberg ML, Ericson E, Magnusson O, Ahlenius S. 1990. Suppression of conditioned avoidance behavior by the local application of (−)sulpiride into the ventral, but not the dorsal, striatum of the rat. *Biol. Psychiatry* 28(4):297–307

Watkins CJCH, Dayan P. 1992. Q-learning. *Mach. Learn.* 8:279–92

Weiner I, Feldon J. 1997. The switching model of latent inhibition: an update of neural substrates. *Behav. Brain Res.* 88:11–25

Wendler E, Gaspar JC, Ferreira TL, Barbiero JK, Andreatini R, et al. 2014. The roles of the nucleus accumbens core, dorsomedial striatum, and dorsolateral striatum in learning: performance and extinction of Pavlovian fear-conditioned responses and instrumental avoidance responses. *Neurobiol. Learn. Mem.* 109:27–36

Wu M, Brudzynski SM, Mogenson GJ. 1993. Functional interaction of dopamine and glutamate in the nucleus accumbens in the regulation of locomotion. *Can. J. Physiol. Pharmacol.* 71(5–6):407–13

Wyvell CL, Berridge KC. 2001. Incentive sensitization by previous amphetamine exposure: increased cue-triggered "wanting" for sucrose reward. *J. Neurosci.* 21(19):7831–40

Yamaguchi T, Wang HL, Li X, Ng TH, Morales M. 2011. Mesocorticolimbic glutamatergic pathway. *J. Neurosci.* 31(23):8476–90

Yang CR, Mogenson GJ. 1984. Electrophysiological responses of neurones in the nucleus accumbens to hippocampal stimulation and the attenuation of the excitatory responses by the mesolimbic dopaminergic system. *Brain Res.* 324:69–84

Yin HH, Ostlund SB, Balleine BW. 2008. Reward-guided learning beyond dopamine in the nucleus accumbens: the integrative functions of cortico-basal ganglia networks. *Eur. J. Neurosci.* 28(8):1437–48

Yun IA, Nicola SM, Fields HL. 2004a. Contrasting effects of dopamine and glutamate receptor antagonist injection in the nucleus accumbens suggest a neural mechanism underlying cue-evoked goal-directed behavior. *Eur. J. Neurosci.* 20:249–63

Yun IA, Wakabayashi KT, Fields HL, Nicola SM. 2004b. The ventral tegmental area is required for the behavioral and nucleus accumbens neuronal firing responses to incentive cues. *J. Neurosci.* 24(12):2923–33

Zaborszky L, Alheid GF, Beinfeld MC, Eiden LE, Heimer L, Palkovits M. 1985. Cholecystokinin innervation of the ventral striatum: a morphological and radioimmunological study. *Neuroscience* 14:427–53

Zahm DS. 2000. An integrative neuroanatomical perspective on some subcortical substrates of adaptive responding with emphasis on the nucleus accumbens. *Neurosci. Biobehav. Rev.* 24:85–105

Zahm DS. 2008. Accumbens in a functional-anatomical systems context. In *The Nucleus Accumbens: Neurotransmitters and Related Behaviors*, ed. HN David, pp. 1–36. Kerala, India: Res. Signpost

Zahm DS, Brog JS. 1990. On the significance of subterritories in the "accumbens" part of the rat ventral striatum. *Neuroscience* 50(4):751–67

Zahm DS, Heimer L. 1990. Two transpallidal pathways originating in the nucleus accumbens. *J. Comp. Neurol.* 302(3):437–46

Zink CF, Pagnoni G, Martin-Skurski ME, Chappelow JC, Berns GS. 2004. Human striatal responses to monetary reward depend on saliency. *Neuron* 42(3):509–17

Annual Review of Psychology

Volume 66, 2015

Contents

Indexes

Errata

An online log of corrections to *Annual Review of Psychology* articles may be found at http://www.annualreviews.org/errata/psych