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Review

Nucleus Accumbens and Its Role in Reward and Emotional Circuitry: A Potential Hot Mess in Substance Use and Emotional Disorders

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Abstract: Nucleus accumbens (NAc) is a key region in the brain that is integral to both the reward and the emotional systems. The aim of the current paper is to synthesize the basic and the clinical neuroscience discoveries relevant to the NAc for the purpose of two-way translation. Selected literature on the structure and the functionality of the NAc is reviewed across animal and human studies. Dopamine, gamma-aminobutyric acid (GABA) and glutamate are the three key neurotransmitters that modulate the reward function and the motor activity. Dissociative roles of the core and the shell of the NAc include getting to the reward and staying on task with discretion, respectively. NAc shows decreased activation to reward in the individuals with major depressive disorder and the bipolar disorder, relative to that healthy controls (HC). The "difficult to please" or insatiability in response to reward in the emotional disorders may possibly be explained by such a neural pattern. Furthermore, it is likely that the increased amygdala activity reported in mood disorders could be accentuating the "wanting" of the reward by the virtue of its connections with the NAc, explaining the potential "hot mess". In contrast, the NAc shows increased reward response in substance use disorders, relative to HC, in response to reward and emotional tasks. Accurate characterization of the NAc and its functionality in the human imaging studies of mood and substance use has important treatment implications.

Keywords: Nucleus accumbens; bipolar; substance abuse; emotion; reward; brain circuitry; fMRI

1. Introduction

The brain regions engaged in reward and emotional circuitry overlap and are interconnected in daily operations [1]. It is, therefore, only natural to hypothesize that any malfunction in the regions of either circuit is likely to impact both circuits and underlie the comorbidity of emotional disorders and drug addiction [2]. Nucleus accumbens (NAc) is one such key region in the brain that is integral to both the reward and the emotional systems involving functions such as motivation, reinforcement learning, pleasure seeking, processing fear or aversive stimuli and initiating motor activity. The aim of the current paper is to provide an in-depth and foundational description of the NAc's structure, connections, and functional role in emotional and substance abuse disorders. This description provides potential explanations for common clinical questions that arise in relation to reward seeking, emotion regulation, and the child development and the impact of associated stimuli. In this regard it is important to understand the structure of the NAc, in the context of the emotional and the reward neural circuitry. This includes the relevant neurochemicals which are dopamine (DA), gamma-aminobutyric acid (GABA), glutamate (Glu), serotonin and noradrenaline, as well as the related neural activity to explain the crucial link between the emotional and substance abuse disorders [3].

2. Basic Neuroscience of NAc

2.1. NAc connectivity

The connectivity between various parts of the prefrontal cortex, dorsal striatum, ventral striatum, pallidum, amygdala, insula, hippocampus and hypothalamus is depicted in Figure 1. As seen, the NAc is shown in cartoon form to depict the hedonic hotspot (orange) in the rostral region that is responsible for "liking" of rewards based on animal studies. The NAc shell also contains a caudal hedonic coldspot (blue) responsible for "not liking". Similarly, the orange region depicted in the pallidum in the caudal area is responsible for the hedonic hot spot with opioid activity, and suppression in the rostral blue spot. The amygdala is responsible for "wanting", and hypothalamic stimulation leads to an increase in both the "liking" and the "wanting". Dopamine (DA) and glutamate (Glu) are motivating neurotransmitters while gamma amino-butyric acid (GABA) has the effect on lowering the activity. DA is transmitted from ventral tegmental area (VTA) to the NAc and the ventral (V) pallidum. DA is also directly transmitted to the dorsal striatum from the VTA. GABA is transmitted from the NAc to the V. pallidum, VTA, and lateral hypothalamus. Orexin is transmitted from the lateral hypothalamus to the V. pallidum. Glu is transmitted to the NAc from the basolateral nucleus of the amygdala, orbitofrontal cortex, and hippocampus in synchrony with "wanting", valuing, and memories, respectively. The NAc's strong connectivity to insula underlies the visceral sensation of arousal and excitability corresponding to increase in DA and decrease

in $GABA_A$.

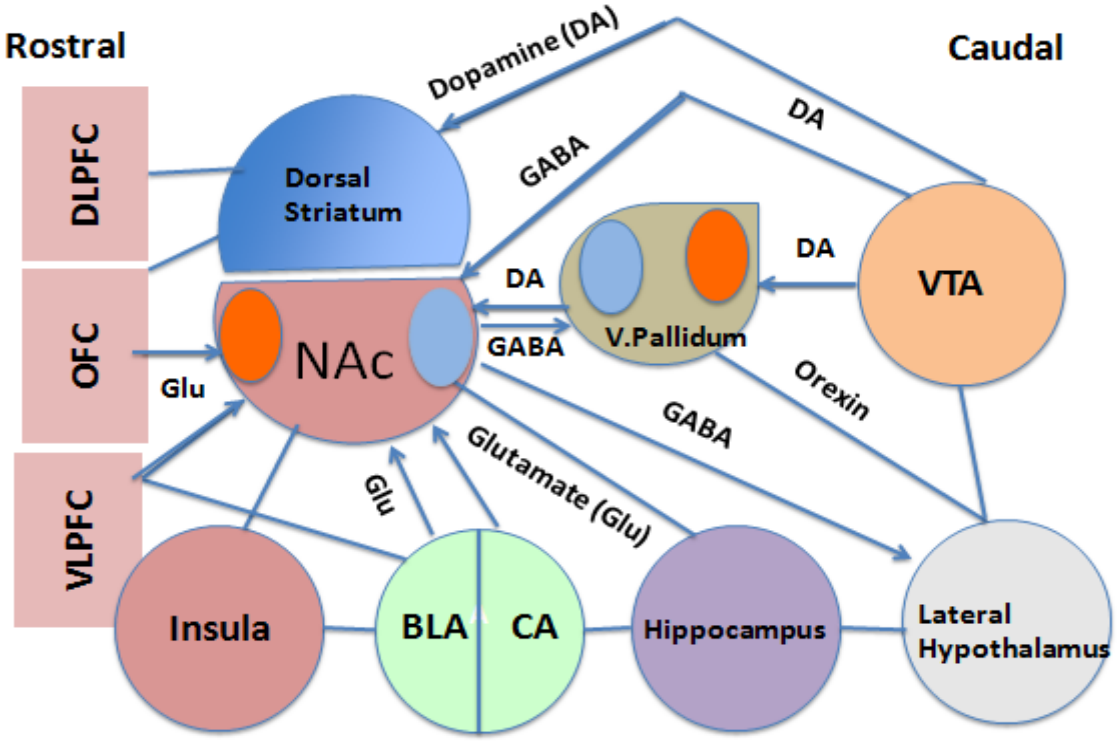

Figure 1. Basic Neuroscience: Nucleus Accumbens Connectivity. The connectivity between various parts of the prefrontal cortex, dorsal striatum, ventral striatum, pallidum, amygdala, insula, hippocampus and hypothalamus is depicted in the sagittal view. The NAc is shown in cartoon form to depict the hedonic hotspot (orange) in the rostral region that is responsible for "liking" of rewards based on animal studies. The NAc shell also contains a caudal hedonic coldspot (blue) responsible for "not liking". Similarly, the orange region depicted in the pallidum in the caudal area is responsible for the hedonic hot spot with opioid activity, and suppression in the rostral blue spot. The amygdala is responsible for "wanting", and hypothalamic stimulation leads to an increase in both the "liking" and the "wanting". Dopamine (DA) and glutamate (Glu) are motivating neurotransmitters while gamma amino-butyric acid (GABA) has the effect on lowering the activity. DA is transmitted from ventral tegmental area (VTA) to the NAc and the ventral (V) pallidum. DA is also directly transmitted to the dorsal striatum from the VTA. GABA is transmitted from the NAc to the V. pallidum, VTA, and lateral hypothalamus. Orexin is transmitted from the lateral hypothalamus to the V. pallidum. Glu is transmitted to the NAc from the basolateral nucleus of the amygdala, orbitofrontal cortex, and hippocampus in synchrony with "wanting", valuing, and memories, respectively. The NAc's strong connectivity to insula underlies the visceral sensation of arousal and excitability corresponding to increase in DA and decrease in $GABA_A$. This figure is adapted in part from Castro et al., 2015, *Frontiers in Systems Neuroscience*. [63]

2.2. The structure within the NAc of the ventral striatum

The accumbens nucleus or the nucleus accumbens septi (Latin for nucleus adjacent to the septum) is part of the basal ganglia, and is located between the caudate and putamen with no specific demarcation from either caudate or putamen [4]. The NAc and the olfactory tubercle together comprise the ventral striatum. It is round in shape with the top portion being flat. The NAc is longer in its rostro-caudal length relative to its dorso-ventral length. It has two components—shell and the core [5,6]. The two parts of the NAc share connections and serve distinct and complementary functions.

2.3. Complementary cellular operations and neurochemical differentiation between the shell and the core

2.3.1. Shell of the NAc

The outer portion (i.e., the shell) of the NAc is like a hammock on the ventral, lateral and medial sides of the core [7,8]. It is part of the extended amygdala, with the amygdala being located rostral to the shell, and sends afferents to the basolateral amygdala. It is a transition zone between the amygdala and the dorsal striatum. The shell also sends afferents to the lateral hypothalamus [8].

Neurons in the shell include medium spiny neurons (MSNs). They contain the D1-type or D2-type dopamine (DA) receptors [9,10]. In the shell, around 40% of the MSNs express both types of neurons. Furthermore, these neurons have lower density of dendritic spines and less branching and terminal segments compared to the core MSNs. Additionally, serotonin receptors are predominantly located in the shell [11,12].

2.3.2. Core of the NAc

Neurons in the core (i.e., inner part of the NAc) consist of densely placed, highly branched outer cells that are either the D1-type or D2-type dopamine receptors [10]. These cells project to the globus pallidus and the substantia nigra.

Enkephalin receptors, which are opioid receptors with enkephalins as ligand responsible for nociception, and $GABA_A$ receptors, which bind the GABA molecules to open chloride channels and increase chloride conductance to inhibit new action potentials, are predominantly present in the core [13,14].

2.4. Neurotransmitters underlying the reward, excitement and habituation dopamine-motivation and reward function

Both in the shell and the core, DA action is greater than that in the dorsal striatum [15]. NAc is

specifically involved in the acquisition of fear response through instrumental conditioning during which animals freeze in the context of aversive stimuli [16–18]. The NAc core is different from the shell in that it is involved in learning to identify the cues of aversive stimuli in order to avoid them, generalizing to the temporally discrete stimuli. NAc shell is known to define or signal safety periods between aversive cues [19,20]. Therefore, when external stimuli are ambiguous or unpredictable, NAc with its dissociable functionality, can aid in avoidance and approach towards intended goal. Therefore, lesions, DA receptor antagonism in the NAc core, or disconnecting inputs from the anterior cingulate cortex to the core, reduce approach toward incentive stimuli [21–23]. This finding supports the concept that the core plays a key role to "get to the reward". Complementary to this finding, NAc shell is the key region responsible for suppressing irrelevant, non-rewarding, and less profitable actions to help "stay on task". Evidence points to the fact that any lesion to the NAc shell leads to uninhibited approach to the reward with less discretion [24]. Also, while high density of transporters renders greater utility of DA in the core, drug induced serotonin and DA antagonism (e.g., clozapine, a treatment for psychosis) leads to greater DA turnover in the shell. Indeed, the shell is the main region of the anti-psychotic action based on corresponding mRNA activity within the shell [25,26]. Appetitive, addictive, excitable, and psychotic behaviors are associated with high levels of DA. High levels of amphetamine will increase DA to equal levels in the extracellular space of the shell and the core [27]. Such an increase in DA due to psychostimulant administration for attention deficit hyperactivity (ADHD) can lead to excitability and mania, psychosis, or more intense drug seeking among vulnerable individuals prone to these illnesses [28,29]. While we understand the clinical phenomena of such occurrences, it remains unclear as to what makes subgroups of individuals prone to such instability with DA administration. Non-drug rewards are also known to increase DA, specifically in the NAc shell, leading to habituation [30,31]. Furthermore, repeated drug induced stimuli and corresponding increase in DA lead to more pernicious habituation in those individuals relative to repeated non-drug related rewards and DA spikes [32]. The possibility that non-drug related rewards could cause DA spikes and habituation may explain the concept of video game addiction, establishing the neural correlates of addiction.

Furthermore, the NAc is a key structure in motivation, emotion regulation and impulse control. With regards to reward seeking and impulsive judgments, both the lesion studies of the NAc in animals and functional imaging studies in gambling have implicated ventral striatum abnormalities as leading to impaired intertemporal choice, risk-taking, or impulsive behaviors in tasks involving options with probability differences. Impulsivity may have many causes, but the NAc is one such channel implicated in reward and emotion regulation [33].

2.5. Dopamine and glucocorticoid receptors- role in mental excitability and potential psychosis

DA and glucocorticoid receptors are present in the NAc shell [34,35]. Excessive steroids or DA in the NAc, lead to psychosis. Glucocorticoid receptors enhance the DA release and related

activity [35,36], potentially inciting psychosis. Additionally, epigenetic changes, such as DNA methylation of the glucocorticoid receptor gene (NR3C1) due to traumatic events, are particularly present in adolescence [37,38].

Therefore, stress, as well as dopamine increase associated with psychostimulants or drugs of abuse, can precipitate psychosis through interrelated mechanisms in the NAc. Additionally, the NAc receives direct projections from the hippocampus and the basolateral amygdala. When there is a lesion in NAc and/or the stria terminalis pathway that connects to the amygdala, glucocorticoid agonists cannot enhance and modulate memory consolidation [39]. Therefore, dopamine abnormalities leading to psychosis or early adversity may lead to co-occurring cognitive problems, such as those related to memory.

2.6. GABA and glutamate- moderate motoric excitability

2.6.1. GABA

If $GABA_A$ is low in the NAc, it leads to hyperactivity or excitability, and the reverse is true for hypoactivity [12,40,41]. This may have pharmacological value where DA induced hyperactivity can be reduced by $GABA_A$ by way of the NAc connections to V. pallidum (i.e., external segment of the globus pallidus of the basal ganglia in the subcortex) that influences motor activity [42]. Based on the insula's role in processing visceral sensation of arousal [43,44], the NAc's strong connectivity to the insula can explain the physiological arousal associated with DA increase and $GABA_A$ decrease or vice versa [45,46]. The $GABA_B$ receptors also inhibit locomotion, but are mediated by acetylcholine (ACh) [45,47].

2.6.2. Glutamate

This neurotransmitter has parallel, but the opposite effect, of $GABA_A$ via the NAc [48]. It has been shown that locomotor activity or motoric excitability is not contingent on DA activity alone, but is also based on the NAc activity involving GABA and glutamate [49,50]. It was recently demonstrated through animal studies that the motoric decision to reach for reward is not initiated in the NAc, but is facilitated through efficiency in motor action selection while approaching the reward [51].

2.7. Acetylcholine (ACh) and its role in reward system

Striatal muscarinic ACh interneurons include M_1, M_2, and M_4; M_1 is post-synaptic and excitatory, whereas M_2 and M_4 are pre-synaptic and inhibitory. These interneurons synapse with GABA mediated spiny output neurons. The NAc, central to the motivations and reward behaviors that underlie drug addiction, projects ACh output neurons to the V. pallidium. Preclinical studies

showed that ACh from the NAc mediates reinforcement through its effect on reward, satiation, and aversion, and chronic cocaine administration has shown neuroadaptive changes in the NAc. ACh is further involved in the acquisition of conditional associations and drug seeking behavior through its effects on arousal and attention. Long-term drug use was shown to cause neuronal alterations in the brain that affect the ACh system and impair executive functions. As such, it may contribute to impaired decision making that characterize this population and may exacerbate the risk of relapse during recovery [52]. In addition to its interface with the $GABA_B$ receptors in inhibiting locomotion, ACh is also responsible for satiety after feeding, and reduced levels are associated with bulimia like feed-purge cycles [53]. Therefore, ACh has a role in indirectly moderating the reward circuit.

2.8. Connective dynamics of the interfacing reward and emotional circuitry regions involving the NAc: The basis for emotion regulation and habit formation

Disorders involving mood and substance abuse often coexist. Factors that appear to be involved include those related to overt affective processing, motivation, and impaired decision-making. To understand the habit formation, to the first step begins with the reward system's modus operandi. The dorsal and ventral regions of the striatum work in complementary fashion. The dorsal striatum is central to learning the contingencies of the reward stimulus, and entraining the instrumental conditioning [54,55]. In other words, the dorsal striatum optimizes the reward related action-choice. Subsequently, it is the NAc in the ventral striatum that is responsible for the subsequent outcome based predictions [56]. The NAc predicts the error-based outcome and updates the predictions of reward or punishment [57,58]. The mesolimbic neurons of the ventral tegmental area (VTA) synthesize DA and the substantia nigra sends the DA predominantly to the shell and the core of the NAc, to allow it to perform its functions [59,60]. It is the incoming signals from the frontal lobe and the amygdala, modulated by DA, that biases the behavior towards reward [61,62]. Search behavior is facilitated by the connections between the hippocampus and the NAc shell, especially if there is ambiguity and lack of clear direction towards reward [1].

Additionally, the lateral hypothalamus, that is involved in regulatory activities (e.g., the "feeding center") sends signals through mesocorticolimbic projections to NAc and the V. pallidum [63]. It appears the NAc and the V. pallidum serve as hedonic hotspots for "liking" and motivational function of "wanting" rewards [64,65]. The mu opioids and the DA receptors in the shell of NAc and the V. pallidum specifically serve in "liking" and "wanting" functions [66,67]. The DA levels in the NAc and the norepinephrine released at locus coeruleus in the brain stem play a critical role in addiction, specifically in drug seeking when deprived of the habituated drug [68,69].

Additionally, the dopaminergic neurons from the VTA that innervate the olfactory tubercle, part of the striatum next to the NAc [69], and are involved in mediating the rewarding effects of drugs such as amphetamine by generating arousal. Therefore, while the initial learning of pleasure and associated contingencies occur through dorsal fronto-striatal circuitry, it is the ventral reward system

of the orbitofrontal cortex (OFC), striatum, and pallidum that maintains the cycle of habituation [70].

Furthermore, input from the glutamatergic neurons of the amygdala, hippocampus, thalamus and prefrontal cortex (PFC) to the NAc facilitate the synchrony between the "liking" and the "wanting" [71]. More specifically, glutametergic projections from the OFC and ventromedial PFC to the NAc shell are known to strengthen the reward seeking [72,73]. Therefore, the amygdala and the OFC can be viewed as conveying the "want and need" or the opposite state of "not wanting or aversion". It is the NAc that sets the tone for the motivational significance or appreciation in the case of feeding or any other pleasurable activity (i.e., "liking" or "not liking").

The amygdala sends the affective signals that are conducive to the desire for the drug [74,75]. The hippocampus is responsible for storing memories associated with past drug use and associated pleasure [75,76]. The insula provides the aspect of the bodily experiences of pleasure and arousal state related to the drug intake [77]. Relative value of the reward and associated outcome-guided behavior is determined by the OFC, both in relation to the rewarding stimulus or, in the case of devaluation of the stimulus, cessation of the seeking behaviors [61].

Overall, output from the NAc extends to the regions of the basal ganglia, amygdala, hypothalamus and the PFC regions. Based on neuroimaging studies involving healthy controls (HC), mood disordered subjects, and substance abuse subjects, medial prefrontal cortex (MPFC), anterior cingulate cortex (ACC), ventrolateral prefrontal cortex (VLPFC) and precuneus emerged as hubs in the interlinked reward and emotion circuitries. Impulsive and compulsive drug seeking behaviors are moderated both by nature and nurture. The genetics behind disorders of impulse control and addiction serves to explain the physiological predisposition, while the environmental influencing factors (e.g., parental restrictions or peer pressure in drug usage) may limit or expand the exposure and actively contribute to entraining the habit circuitry.

3. Clinical Neuroscience of NAc

3.1. Nucleus Accumbens' role in the hot mess of emotion dysregulation and addiction

The predominant activation pattern is depicted in Figure 2. This shows patient groups in each of the disorders in comparison to healthy controls with tasks probing either reward or emotion neural circuitry. The arrows represent an increase or a decrease in activation in the key regions of the reward and the emotion circuitry that are intricately connected. In the case of bipolar disorder (BD), the NAc shows increased activation in response to emotional stimuli and decreased activation in response to rewards, the latter pattern being similar to that seen in major depressive disorder (MDD). In MDD, the NAc shows decreased activation to both emotional stimuli and reward, opposite to that observed in substance abuse disorder.

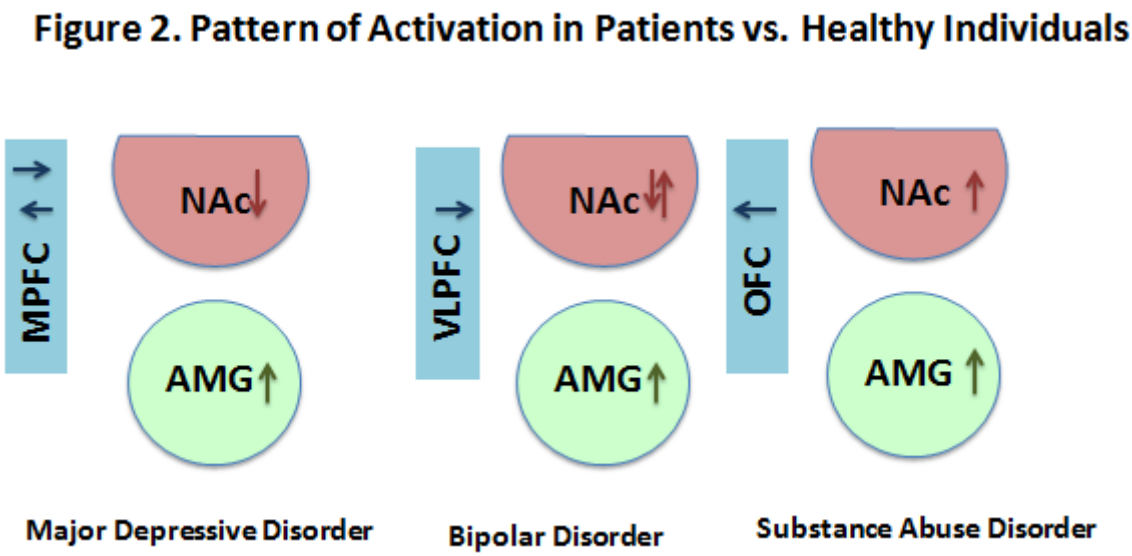

Figure 2. Clinical Neuroscience: Nucleus Accumbens' Role in the Hot Mess of Emotion Dysregulation and Addiction. The predominant activation pattern is depicted in this figure in which patient groups in each of the disorders were directly compared to healthy controls with tasks probing either reward or emotion neural circuitry. The arrows represent an increase or a decrease in activation in the key regions of the reward and the emotion circuitry that are intricately connected. In the case of bipolar disorder, the Nucleus Accumbens (NAc) shows increased activation in response to emotional stimuli and decreased activation in response to rewards, the latter pattern being similar to that seen in major depressive disorder (MDD). In MDD, the NAc shows decreased activation to both emotional stimuli and reward, opposite to that observed in substance abuse disorder. VLPFC: ventrolateral prefrontal cortex; MPFC: medial prefrontal cortex; AMG: amygdala; OFC: orbitofrontal cortex.

3.2. Neural pattern of activation in the NAc in substance abuse and mood disorders: human imaging studies of emotional and reward stimuli

Most of the human studies that extended the knowledge on the role of the NAc are based on fMRI studies probing the reward and/or emotional circuitry. In relation to the NAc, the most accurate view is obtained as T2 images and in the coronal section where it is the longest and shows the most detail [3]. A consistent pattern of brain activation has emerged in identifying the interfacing circuitry dysfunction across the disorders. In the interpretation of these experiments, both increased activity and the absence of activity must be considered. When there is stimulus of moderate intensity, brain region that is partially operating even if impaired, shows increased activation. If the same brain region is probed with stimulus of severe intensity (also mediated by the type of the disorder where perceptions vary, such as patients with bipolar disorder react to angry faces more than fearful faces),

it would show no activation or decreased activation relative to healthy population. This phenomenon has been noted on careful examination of the patterns over multiple studies to make sense of the variability in brain activation in response to varying probes.

3.2.1. Major depressive disorder (MDD)

Relative to that of HC, the individuals with MDD showed decreased activation in the NAc in response to any rewarding stimuli, but increased activation to implicit emotional stimuli (e.g., covert face processing or cognitive generation of positive affect) [78]. In other words, in MDD, the NAc is underactive with reward and this may explain why this population appears to need larger reward to attain the same level of activation as HC (i.e., "not easily pleased") An alternative physiological explanation is that the reward stimuli may serve as explicit emotional triggers in depression, with lower impact on activating the NAc. Hence, it may be that incidental or implicit emotional stimuli trigger the excessive reactivity in the NAc. Corresponding to the NAc activity, the amygdala also shows increased activation in the MDD patients, relative to HC, in response to negative or implicit emotional stimuli [79]. The various prefrontal regions show variable patterns of either increased or decreased activation, unlike the consistent pattern noted in the subcortical areas [80,81]. Within our clinical experience excessive use of substances appears to have the purpose of self-medicating to subdue negative emotional states associated with a lowered threshold for reactivity to negative triggers. This corresponds with the physiological experiments we have summarized.

3.2.2. Bipolar disorder (BD)

In response to reward task and regardless of comorbid substance abuse, relative to HC patients with BD show lower activation of the VLPFC and increased activation of the amygdala for implicit or explicit negative emotions, in addition to compensatory over activation of the ACC [82]. A fascinating observation is that the NAc behaves in the exact manner as the VLPFC; implicit negative affective processing leads to decreased activation, while both implicit and explicit happy or fearful faces lead to increased activation [83]. One notable point is that, in BD, sad or angry emotions tend to be more directly relevant than fear as negative emotional stimuli, which can explain the increased activation associated with fear. Therefore, when emotional tasks are used to activate the emotion circuitry, the intensity of the tasks appears to proportionally trigger a dysfunctional under-activation in the VLPFC of BD subjects relative to the HC. This gives the appearance, that the VLPFC "gives up" in response to severe or intense negative emotions.

In response to reward anticipation, the NAc showed decreased activation in response to monetary reward in BD subjects relative to HC [84]. This is a pattern similar to that seen in MDD, suggesting the need for greater reward to obtain the same emotional impact as in HC. Thus, the pattern in BD differs from MDD in response to emotional stimuli based on pathophysiological

differences, though leading to a similar behavioral response to the reward stimuli.

In explanation as to what could underlie clinical scenarios in BD, the physiological findings of the neuroimaging experiments complement the knowledge derived from animal studies. In this regard, it is possible that increased amygdala activity in BD projects a certain degree of intensity corresponding to the excitability. The decreased activity in the VLPFC and OFC regions may lead to disinhibition, and associated poor impulse control, and result in excessive pleasure seeking related to impairment in PFC-mediated decision-making. Based on animal studies [85] and BD human neuroimaging studies [86], connectivity between the amygdala and the NAc may be relevant in accentuating the "want" and the "like" in seeking rewards. Therefore, the intense reward-seeking behaviors (e.g., excessive shopping, drug use, food consumption, or sex) may be due to the interlinked dysfunction in the emotional and reward systems.

3.2.3. Substance Abuse Disorders

In addiction or substance abuse disorders, relative to HC, passive or implicit perception of craving-related stimuli leads to increased activation in the NAc [87]. This underlies the motivation bias associated with increased activation in the OFC, ACC, and amygdala, the regions that are linked to both reward and emotional circuitry [87]. These regions appear common to all reward seeking, regardless if the stimuli are or are not drugs [88,89]. While motivation toward seeking goals is dependent on the NAc in the ventral striatum, the progressive shift to habit formation appears dependent on the dorsal striatum [90]. This is in correspondence to the "liking" hypothesis in which with the initial observation of the reward is associated with NAc activation. In substance use disorders, relative to HC, decreased NAc activation occurs in this anticipatory observational phase, regardless of any subsequent loss or gain of a reward [91]. Increased DA release in the anterior ventral striatum, but not in the dorsal caudate, was shown to be positively correlated with the hedonic, or "liking", response to dextroamphetamine [92]. In actuality, the positive affective experience of hedonic "liking" is not readily disentangled from "wanting" the drug [93]. Related to depression, seeking a hedonic response is a possible explanation of self-medicating through abuse of drugs. Similarly, stimulant use in a subpopulation of users may be primed due to seeking excessive rewards that is triggered by excessive dopamine.

3.2.4. Treatment implications through deep brain stimulation (DBS)

The DBS of the NAc was attempted for the treatment refractory obsessive-compulsive disorder where compulsion was considered to be similar to that of drug-seeking compulsivity, involuntary motor activity like Tourette syndrome, depression and drug and alcohol abuse [94]. All these attempts yielded no conclusive findings on outcome. Symptoms of depression were reduced by approximately 40% in this cohort [94,95].

3.2.5. Placebo effect in healthy individuals

When healthy adults were given a pain challenge, DA and opioid activity in the NAc were associated with subjectively perceived effectiveness of the placebo based on reductions in pain ratings [96]. Similar to reward expectation, this supports the NAc's involvement with anticipation of a positive response.

4. Summary and Conclusions

The foregoing discussion had the goal of providing an in-depth analysis of the NAc to allow scientists and educators to be aware of multiple aspects of its functionality. In relation to functional imaging, identifying the NAc requires careful analysis due to the multiple, small adjacent regions, such as parts of the caudate and putamen, that could be mistaken for the NAc or vice versa. With this in mind, the shape of the NAc means the best view is accomplished in the coronal section in interpreting the neuroimaging findings. Additionally, an understanding of the role of the NAc in a systems perspective of emotional and reward circuitry offers a broader perspective of its role in brain operations. The current paper has presented findings on the NAc from both human and non-human animal studies, with an examination of those findings as related to a clinical understanding. The existing scientific literature of both the basic and the clinical neuroscience paired with the acumen from clinical insights align a powerful triad toward translation to advance our understanding of the NAc's functional role, as has hopefully been illustrated in this manuscript. In summary, the clinically applicable derivatives of neuroscience, where the NAc plays a key role, are as follows:

1. The NAc plays a significant part in channeling DA, GABA and glutamate in modulating the reward and emotional systems.

2. Dissociable roles of the NAc core and the shell involve selecting the reward and evading distractions, respectively.

3. The NAc shows decreased activation to reward in individuals with MDD and BD, relative to that HC, and this can potentially explain the lack of pleasure with reward (akin to anhedonia) in MDD and the need for intense pursuit of reward in BD.

4. While the NAc shows increased activity in all substance use disorders, relative to HC, animal studies indicate joint increase in activity in the highly connected amygdala and V. pallidum. Anticipating and selecting reward with NAc involvement from human studies and the amygdala's excitability to accentuate the reward seeking in animal studies, can together inform the emotional overlay in addictive behavior.

5. It is also possible that inattention and impulse control associated with low DA or noradrenaline levels may lead to poor frustration tolerance, and potentially, seek reward as gratifying

alternative. In this scenario, optimal treatment with psychostimulants could avoid being habituated to illicit drugs. It appears that adolescence is particularly a vulnerable time for the precipitation of any illness with accentuated glucocorticoid receptor sensitivity in the NAc. While there are no definitive answers, these unanswered questions pose research challenges for the future.

Conflict of Interest

All authors declare no conflicts of interest pertaining to this paper.

References

1. Floresco SB (2015) The nucleus accumbens: an interface between cognition, emotion, and action. *Annu Rev Psychol* 66: 25–52.
2. Diekhof EK, Falkai P, Gruber O (2008) Functional neuroimaging of reward processing and decision-making: a review of aberrant motivational and affective processing in addiction and mood disorders. *Brain Res Rev* 59: 164–184.
3. Salgado S, Kaplitt MG (2015) The Nucleus Accumbens: A Comprehensive Review. *Stereotact Funct Neurosurg* 93: 75–93.
4. Mogenson GJ, Jones DL, Yim CY (1980) From motivation to action: functional interface between the limbic system and the motor system. *Prog Neurobiol* 14: 69–97.
5. Zahm DS, Brog JS (1992) On the significance of subterritories in the "accumbens" part of the rat ventral striatum. *Neuroscience* 50: 751–767.
6. Baliki MN, Mansour A, Baria AT, et al. (2013) Parceling human accumbens into putative core and shell dissociates encoding of values for reward and pain. *J Neurosci Off J Soc Neurosci* 33: 16383–16393.
7. Voorn P, Brady LS, Schotte A, et al. (1994) Evidence for two neurochemical divisions in the human nucleus accumbens. *Eur J Neurosci* 6: 1913–1916.
8. Meredith GE (1999) The synaptic framework for chemical signaling in nucleus accumbens. *Ann N Y Acad Sci* 877: 140–156.
9. Francis TC, Lobo MK (2016) Emerging Role for Nucleus Accumbens Medium Spiny Neuron Subtypes in Depression. *Biol Psychiatry*.
10. Lu XY, Ghasemzadeh MB, Kalivas PW (1998) Expression of D1 receptor, D2 receptor, substance P and enkephalin messenger RNAs in the neurons projecting from the nucleus accumbens. *Neuroscience* 82: 767–780.
11. Shirayama Y, Chaki S (2006) Neurochemistry of the nucleus accumbens and its relevance to depression and antidepressant action in rodents. *Curr Neuropharmacol* 4: 277–291.
12. Ding Z-M, Ingraham CM, Rodd ZA, et al. (2015) The reinforcing effects of ethanol within the nucleus accumbens shell involve activation of local GABA and serotonin receptors. *J*

Psychopharmacol Oxf Engl 29: 725–733.

13. Voorn P, Brady LS, Berendse HW, et al. (1996) Densitometrical analysis of opioid receptor ligand binding in the human striatum—I. Distribution of mu-opioid receptor defines shell and core of the ventral striatum. *Neuroscience* 75: 777–792.
14. Schoffelmeer ANM, Hogenboom F, Wardeh G, et al. (2006) Interactions between CB1 cannabinoid and mu opioid receptors mediating inhibition of neurotransmitter release in rat nucleus accumbens core. *Neuropharmacology* 51: 773–781.
15. O'Neill RD, Fillenz M (1985) Simultaneous monitoring of dopamine release in rat frontal cortex, nucleus accumbens and striatum: effect of drugs, circadian changes and correlations with motor activity. *Neuroscience* 16: 49–55.
16. 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: 925–940.
17. Levita L, Hoskin R, Champi S (2012) Avoidance of harm and anxiety: a role for the nucleus accumbens. *NeuroImage* 62: 189–198.
18. Parkinson JA, Olmstead MC, Burns LH, et al. (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 Off J Soc Neurosci* 19: 2401–2411.
19. Feja M, Hayn L, Koch M (2014) Nucleus accumbens core and shell inactivation differentially affects impulsive behaviours in rats. *Prog Neuropsychopharmacol Biol Psychiatry* 54: 31–42.
20. Fernando ABP, Murray JE, Milton AL (2013) The amygdala: securing pleasure and avoiding pain. *Front Behav Neurosci* 7: 190.
21. Di Ciano P, Cardinal RN, Cowell RA, et al. (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 Off J Soc Neurosci* 21: 9471–9477.
22. Parkinson JA, Willoughby PJ, Robbins TW, et al. (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.
23. Saunders BT, Robinson TE (2012) The role of dopamine in the accumbens core in the expression of Pavlovian-conditioned responses. *Eur J Neurosci* 36: 2521–2532.
24. 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.
25. Deutch AY, Lee MC, Iadarola MJ (1992) Regionally specific effects of atypical antipsychotic drugs on striatal Fos expression: The nucleus accumbens shell as a locus of antipsychotic action. *Mol Cell Neurosci* 3: 332–341.
26. Ma J, Ye N, Cohen BM (2006) Typical and atypical antipsychotic drugs target dopamine and cyclic AMP-regulated phosphoprotein, 32 kDa and neurotensin-containing neurons, but not

GABAergic interneurons in the shell of nucleus accumbens of ventral striatum. *Neuroscience* 141: 1469–1480.

27. Pierce RC, Kalivas PW (1995) Amphetamine produces sensitized increases in locomotion and extracellular dopamine preferentially in the nucleus accumbens shell of rats administered repeated cocaine. *J Pharmacol Exp Ther* 275: 1019–1029.
28. Park SY, Kang UG (2013) Hypothetical dopamine dynamics in mania and psychosis--its pharmacokinetic implications. *Prog Neuropsychopharmacol Biol Psychiatry* 43: 89–95.
29. Mosholder AD, Gelperin K, Hammad TA, et al. (2009) Hallucinations and other psychotic symptoms associated with the use of attention-deficit/hyperactivity disorder drugs in children. *Pediatrics* 123: 611–616.
30. Bassareo V, De Luca MA, Di Chiara G (2002) Differential Expression of Motivational Stimulus Properties by Dopamine in Nucleus Accumbens Shell versus Core and Prefrontal Cortex. *J Neurosci Off J Soc Neurosci* 22: 4709–4719.
31. Di Chiara G, Bassareo V, Fenu S, et al. (2004) Dopamine and drug addiction: the nucleus accumbens shell connection. *Neuropharmacology* 47: 227–241.
32. Di Chiara G, Bassareo V (2007) Reward system and addiction: what dopamine does and doesn't do. *Curr Opin Pharmacol* 7: 69–76.
33. Basar K, Sesia T, Groenewegen H, et al. (2010) Nucleus accumbens and impulsivity. *Prog Neurobiol* 92: 533–557.
34. Ahima RS, Harlan RE (1990) Charting of type II glucocorticoid receptor-like immunoreactivity in the rat central nervous system. *Neuroscience* 39: 579–604.
35. Barrot M, Marinelli M, Abrous DN, et al. (2000) The dopaminergic hyper-responsiveness of the shell of the nucleus accumbens is hormone-dependent. *Eur J Neurosci* 12: 973–979.
36. Piazza PV, Rougé-Pont F, Deroche V, et al. (1996) Glucocorticoids have state-dependent stimulant effects on the mesencephalic dopaminergic transmission. *Proc Natl Acad Sci U S A* 93: 8716–8720.
37. van der Knaap LJ, Oldehinkel AJ, Verhulst FC, et al. (2015) Glucocorticoid receptor gene methylation and HPA-axis regulation in adolescents. The TRAILS study. *Psychoneuroendocrinology* 58: 46–50.
38. Bustamante AC, Aiello AE, Galea S, et al. (2016) Glucocorticoid receptor DNA methylation, childhood maltreatment and major depression. *J Affect Disord* 206: 181–188.
39. Roozendaal B, de Quervain DJ, Ferry B, et al. (2001) Basolateral amygdala-nucleus accumbens interactions in mediating glucocorticoid enhancement of memory consolidation. *J Neurosci Off J Soc Neurosci* 21: 2518–2525.
40. Schwarzer C, Berresheim U, Pirker S, et al. (2001) Distribution of the major gamma-aminobutyric acid(A) receptor subunits in the basal ganglia and associated limbic brain areas of the adult rat. *J Comp Neurol* 433: 526–549.
41. Van Bockstaele EJ, Pickel VM (1995) GABA-containing neurons in the ventral tegmental area

project to the nucleus accumbens in rat brain. *Brain Res* 682: 215–221.

42. Root DH, Melendez RI, Zaborszky L, et al. (2015) The ventral pallidum: Subregion-specific functional anatomy and roles in motivated behaviors. *Prog Neurobiol* 130: 29–70.
43. Cho YT, Fromm S, Guyer AE, et al. (2013) Nucleus accumbens, thalamus and insula connectivity during incentive anticipation in typical adults and adolescents. *NeuroImage* 66: 508–521.
44. Kelley AE, Baldo BA, Pratt WE, et al. (2005) Corticostriatal-hypothalamic circuitry and food motivation: integration of energy, action and reward. *Physiol Behav* 86: 773–795.
45. Rada PV, Mark GP, Hoebel BG (1993) In vivo modulation of acetylcholine in the nucleus accumbens of freely moving rats: II. Inhibition by gamma-aminobutyric acid. *Brain Res* 619: 105–110.
46. Wong LS, Eshel G, Dreher J, et al. (1991) Role of dopamine and GABA in the control of motor activity elicited from the rat nucleus accumbens. *Pharmacol Biochem Behav* 38: 829–835.
47. Pitman KA, Puil E, Borgland SL (2014) GABA(B) modulation of dopamine release in the nucleus accumbens core. *Eur J Neurosci* 40: 3472–3480.
48. Kim JH, Vezina P (1997) Activation of metabotropic glutamate receptors in the rat nucleus accumbens increases locomotor activity in a dopamine-dependent manner. *J Pharmacol Exp Ther* 283: 962–968.
49. Angulo JA, McEwen BS (1994) Molecular aspects of neuropeptide regulation and function in the corpus striatum and nucleus accumbens. *Brain Res Brain Res Rev* 19: 1–28.
50. Vezina P, Kim JH (1999) Metabotropic glutamate receptors and the generation of locomotor activity: interactions with midbrain dopamine. *Neurosci Biobehav Rev* 23: 577–589.
51. 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.
52. Williams MJ, Adinoff B (2008) The role of acetylcholine in cocaine addiction. *Neuropsychopharmacol Off Publ Am Coll Neuropsychopharmacol* 33: 1779–1797.
53. Avena NM, Bocarsly ME (2012) Dysregulation of brain reward systems in eating disorders: neurochemical information from animal models of binge eating, bulimia nervosa, and anorexia nervosa. *Neuropharmacology* 63: 87–96.
54. Balleine BW, Delgado MR, Hikosaka O (2007) The role of the dorsal striatum in reward and decision-making. *J Neurosci Off J Soc Neurosci* 27: 8161–8165.
55. Liljeholm M, O'Doherty JP (2012) Contributions of the striatum to learning, motivation, and performance: an associative account. *Trends Cogn Sci* 16: 467–475.
56. Asaad WF, Eskandar EN (2011) Encoding of both positive and negative reward prediction errors by neurons of the primate lateral prefrontal cortex and caudate nucleus. *J Neurosci Off J Soc Neurosci* 31: 17772–17787.
57. Burton AC, Nakamura K, Roesch MR (2015) From ventral-medial to dorsal-lateral striatum: neural correlates of reward-guided decision-making. *Neurobiol Learn Mem* 117: 51–59.

58. Mattfeld AT, Gluck MA, Stark CEL (2011) Functional specialization within the striatum along both the dorsal/ventral and anterior/posterior axes during associative learning via reward and punishment. *Learn Mem Cold Spring Harb N* 18: 703–711.
59. Ikemoto S (2007) Dopamine reward circuitry: two projection systems from the ventral midbrain to the nucleus accumbens-olfactory tubercle complex. *Brain Res Rev* 56: 27–78.
60. Matsumoto M, Hikosaka O (2009) Two types of dopamine neuron distinctly convey positive and negative motivational signals. *Nature* 459: 837–841.
61. Gottfried JA, O'Doherty J, Dolan RJ (2003) Encoding predictive reward value in human amygdala and orbitofrontal cortex. *Science* 301: 1104–1107.
62. Stefani MR, Moghaddam B (2016) Rule learning and reward contingency are associated with dissociable patterns of dopamine activation in the rat prefrontal cortex, nucleus accumbens, and dorsal striatum. *J Neurosci Off J Soc Neurosci* 26: 8810–8818.
63. Castro DC, Cole SL, Berridge KC (2015) Lateral hypothalamus, nucleus accumbens, and ventral pallidum roles in eating and hunger: interactions between homeostatic and reward circuitry. *Front Syst Neurosci* 9: 90.
64. Peciña S, Smith KS, Berridge KC (2006) Hedonic hot spots in the brain. *Neurosci Rev J Bringing Neurobiol Neurol Psychiatry* 12: 500–511.
65. Smith KS, Berridge KC, Aldridge JW (2011) Disentangling pleasure from incentive salience and learning signals in brain reward circuitry. *Proc Natl Acad Sci U S A* 108: E255-264.
66. Berridge KC, Robinson TE (1998) What is the role of dopamine in reward: hedonic impact, reward learning, or incentive salience? *Brain Res Brain Res Rev* 28: 309–369.
67. Smith KS, Berridge KC (2007) Opioid limbic circuit for reward: interaction between hedonic hotspots of nucleus accumbens and ventral pallidum. *J Neurosci Off J Soc Neurosci* 27: 1594–1605.
68. Belujon P, Grace AA (2016) Hippocampus, amygdala, and stress: interacting systems that affect susceptibility to addiction. *Ann N Y Acad Sci* 1216: 114–121.
69. Weinshenker D, Schroeder JP (2007) There and back again: a tale of norepinephrine and drug addiction. *Neuropsychopharmacol Off Publ Am Coll Neuropsychopharmacol* 32: 1433–1451.
70. Everitt BJ, Hutcheson DM, Ersche KD, et al. (2007) The orbital prefrontal cortex and drug addiction in laboratory animals and humans. *Ann N Y Acad Sci* 1121: 576–597.
71. Britt JP, Benaliouad F, McDevitt RA, et al. (2012) Synaptic and behavioral profile of multiple glutamatergic inputs to the nucleus accumbens. *Neuron* 76: 790–803.
72. Asher A, Lodge DJ (2012) Distinct prefrontal cortical regions negatively regulate evoked activity in nucleus accumbens subregions. *Int J Neuropsychopharmacol* 15: 1287–1294.
73. Ishikawa A, Ambroggi F, Nicola SM, et al. (2008) Dorsomedial prefrontal cortex contribution to behavioral and nucleus accumbens neuronal responses to incentive cues. *J Neurosci Off J Soc Neurosci* 28: 5088–5098.
74. Connolly L, Coveleskie K, Kilpatrick LA, et al. (2013) Differences in brain responses between

lean and obese women to a sweetened drink. *Neurogastroenterol Motil Off J Eur Gastrointest Motil Soc* 25: 579–e460.

75. Robbins TW, Ersche KD, Everitt BJ (2008) Drug addiction and the memory systems of the brain. *Ann N Y Acad Sci* 1141: 1–21.
76. Müller CP (2013) Episodic memories and their relevance for psychoactive drug use and addiction. *Front Behav Neurosci* 7: 34.
77. Naqvi NH, Bechara A (2010) The insula and drug addiction: an interoceptive view of pleasure, urges, and decision-making. *Brain Struct Funct* 214: 435–450.
78. Satterthwaite TD, Kable JW, Vandekar L, et al. (2015) Common and Dissociable Dysfunction of the Reward System in Bipolar and Unipolar Depression. *Neuropsychopharmacol Off Publ Am Coll Neuropsychopharmacol* 40: 2258–2268.
79. Surguladze S, Brammer MJ, Keedwell P, et al. (2005) A differential pattern of neural response toward sad versus happy facial expressions in major depressive disorder. *Biol Psychiatry* 57: 201–209.
80. Elliott R, Rubinsztein JS, Sahakian BJ, et al. (2002) The neural basis of mood- congruent processing biases in depression. *Arch Gen Psychiatry* 59: 597–604.
81. Keedwell PA, Andrew C, Williams SCR, et al. (2005) A double dissociation of ventromedial prefrontal cortical responses to sad and happy stimuli in depressed and healthy individuals. *Biol Psychiatry* 58: 495–503.
82. Yurgelun-Todd DA, Gruber SA, Kanayama G, et al. (2000) fMRI during affect discrimination in bipolar affective disorder. *Bipolar Disord* 2: 237–248.
83. Caseras X, Murphy K, Lawrence NS, et al. (2015) Emotion regulation deficits in euthymic bipolar I versus bipolar II disorder: a functional and diffusion-tensor imaging study. *Bipolar Disord* 17: 461–470.
84. Redlich R, Dohm K, Grotegerd D, et al. (2015) Reward Processing in Unipolar and Bipolar Depression: A Functional MRI Study. *Neuropsychopharmacol Off Publ Am Coll Neuropsychopharmacol* 40: 2623–2631.
85. Namburi P, Beyeler A, Yorozu S, et al. (2015) A circuit mechanism for differentiating positive and negative associations. *Nature* 520: 675–678.
86. Mahon K, Burdick KE, Szeszko PR (2010) A Role for White Matter Abnormalities in the Pathophysiology of Bipolar Disorder. *Neurosci Biobehav Rev* 34: 533–554.
87. Franklin TR, Wang Z, Wang J, et al. (2007) Limbic activation to cigarette smoking cues independent of nicotine withdrawal: a perfusion fMRI study. *Neuropsychopharmacol Off Publ Am Coll Neuropsychopharmacol* 32: 2301–2309.
88. Garavan H, Pankiewicz J, Bloom A, et al. (2000) Cue-induced cocaine craving: neuroanatomical specificity for drug users and drug stimuli. *Am J Psychiatry* 157(11): 1789–1798.
89. Diekhof EK, Falkai P, Gruber O (2008) Functional neuroimaging of reward processing and

decision-making: a review of aberrant motivational and affective processing in addiction and mood disorders. *Brain Res Rev* 59: 164–184.

90. White NM, Packard MG, McDonald RJ (2013) Dissociation of memory systems: The story unfolds. *Behav Neurosci* 127: 813–834.
91. Wrase J, Schlagenhauf F, Kienast T, et al. (2007) Dysfunction of reward processing correlates with alcohol craving in detoxified alcoholics. *NeuroImage* 35: 787–794.
92. Drevets WC, Gautier C, Price JC, et al. (2001) Amphetamine-induced dopamine release in human ventral striatum correlates with euphoria. *Biol Psychiatry* 49: 81–96.
93. Ding YS, Logan J, Bermel R, et al. (2000) Dopamine receptor-mediated regulation of striatal cholinergic activity: positron emission tomography studies with norchloro[18F]fluoroepibatidine. *J Neurochem* 74: 1514–1521.
94. Greenberg BD, Gabriels LA, Malone DA, et al. (2010) Deep brain stimulation of the ventral internal capsule/ventral striatum for obsessive-compulsive disorder: worldwide experience. *Mol Psychiatry* 15: 64–79.
95. Denys D, Mantione M, Figee M, van den Munckhof P, et al. (2010) Deep brain stimulation of the nucleus accumbens for treatment-refractory obsessive-compulsive disorder. *Arch Gen Psychiatry* 67: 1061–1068.
96. Scott DJ, Stohler CS, Egnatuk CM, et al. (2008) Placebo and nocebo effects are defined by opposite opioid and dopaminergic responses. *Arch Gen Psychiatry* 65: 220–231.

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