Nucleus accumbens

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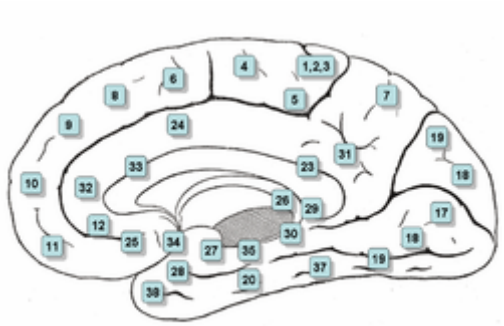


Brodmann area 34

The **nucleus accumbens** (**NAc** or **NAcc**), also known as the **accumbens nucleus** or as the ***nucleus accumbens septi*** (Latin for *nucleus adjacent to the septum*) is a region in the basal forebrain rostral to the preoptic area of the hypothalamus.[1] The nucleus accumbens and the olfactory tubercle collectively form the ventral striatum, which is part of the basal ganglia.[2]

The nucleus accumbens has a significant role in the cognitive processing of motivation, pleasure, and reward and reinforcement learning, and hence has significant role in addiction.[3][4] It plays a lesser role in fear, impulsivity, and the placebo effect.[5][6][7] It is involved in the encoding of new motor programs as well.[3]

Each cerebral hemisphere has its own nucleus accumbens. It is located where the head of the caudate and the anterior portion of the putamen meet just lateral to the septum pellucidum. The nucleus accumbens can be divided into two structures—the nucleus accumbens core and the nucleus accumbens shell. These structures have different morphology and function.

Structure

The nucleus accumbens is an aggregate of neurons which is described as having an outer shell and an inner core.[3]

Input

Major inputs to the nucleus accumbens include prefrontal association cortices, basolateral amygdala, and dopaminergic neurons located in the ventral tegmental area (VTA), which connect via the mesolimbic pathway. Thus the nucleus accumbens is often described as one part of a cortico-striato-thalamo-cortical loop.

Dopaminergic input from the VTA modulate the activity of neurons within the nucleus accumbens. These neurons are activated directly or indirectly by euphoriant drugs (e.g., amphetamine, opiates, nicotine, etc.) and by participating in rewarding experiences (e.g., sex, music, exercise, etc.).[8][9]

Another major source of input comes from the CA1 and ventral subiculum of the hippocampus to the dorsomedial area of the nucleus accumbens. The neurons of the hippocampus have a noteworthy correlation to slight depolarizations of cells in the nucleus accumbens, which makes them more positive and therefore more excitable. The correlated cells of these excited states of the medium spiny neurons in the nucleus accumbens are shared equally between the subiculum and CA1. The subiculum neurons are found to hyperpolarize (increase negativity) while the CA1 neurons "ripple" (fire > 50 Hz) in order to accomplish this priming.[10]

The sole source of histamine neurons in the brain, the tuberomammillary nucleus, projects to the nucleus accumbens as well.[11]

Output

The output neurons of the nucleus accumbens send axon projections to the basal ganglia and the ventral analog of the globus pallidus, known as the ventral pallidum (VP). The VP, in turn, projects to the medial dorsal nucleus of the dorsal thalamus, which projects to the prefrontal cortex as well as the striatum. Other efferents from the nucleus accumbens include connections with the tail of the ventral tegmental area,[12] substantia nigra, and the reticular formation of the pons.[1]

Shell

The **nucleus accumbens shell** is a substructure of the nucleus accumbens. The shell and core together form the entire nucleus accumbens.

Location: The shell is the outer region of the nucleus accumbens, and – unlike the core – is considered to be part of the extended amygdala, located at its rostral pole.

Cell types: Neurons in the nucleus accumbens are mostly medium spiny neurons. The neurons in the shell, as compared to the core, have a lower density of dendritic spines, less terminal segments, and less branch segments than those in the core. The shell neurons project to the subcommissural part of the ventral pallidum as well as the ventral tegmental area and to extensive areas in the hypothalamus and extended amygdala.[13][14][15]

Function: The shell of the nucleus accumbens is involved in the cognitive processing of motivational salience (wanting) as well as reward and reinforcement effects.[3] Particularly important are the effects of drug and naturally rewarding stimuli on the NAc shell because these effects are related to addiction.[3] Addictive drugs have a larger effect on dopamine release in the shell than in the core.[3]

Core

The **nucleus accumbens core** is the inner substructure of the nucleus accumbens.

Location: The nucleus accumbens core is part of the ventral striatum, located within the basal ganglia.

Cell types: The core of the NAcc is made up mainly of medium spiny neurons. The neurons in the core, as compared to the neurons in the shell, have an increased density of dendritic spines, branch segments, and terminal segments. From the core, the neurons project to other sub-cortical areas such as the globus pallidus and the substantia nigra. GABA is one of the main neurotransmitters in the NAcc, and GABA receptors are also abundant.[16][17]

Function: The nucleus accumbens core is involved in the cognitive processing of motor function related to reward and reinforcement.[3] Specifically, the core encodes new motor programs which facilitate the acquisition of a given reward in the future.[3]

Cell types

The core of the NAcc is made up mainly of medium spiny neurons. Compared to the neurons in the shell, those in the core have an increased density of dendritic spines, branch segments, and terminal segments. From the core, the neurons project to other sub-cortical areas such as the globus pallidus and the substantia nigra. GABA is one of the main neurotransmitters in the NAcc, and GABA receptors are also abundant.[16][18] These neurons are also the main projection or output neurons of the nucleus accumbens.

While 95% of the neurons projecting from the nucleus accumbens are medium spiny GABA-ergic neurons, other projecting neuronal types are also present, such as large cholinergic interneurons.

Neurotransmitters

Dopamine: Dopamine is related to recreational drugs including amphetamines, cocaine, and morphine, which increase extracellular levels of dopamine in both the NAc shell and the NAc core, but the effect of these increases is more pronounced in the shell. Only amphetamine at high levels increased extracellular levels of dopamine to similar levels in both the shell and the core. All of this points to a 'functional heterogeneity' in the nucleus accumbens between the shell region and the core region.[19] Similarly to drug rewards, non-drug rewards also increase levels of extracellular dopamine in the NAc shell, but drug induced DA increase is more resilient to habituation when exposed repeatedly to drug-stimuli, unlike non-drug rewarding stimuli induced dopamine increases, which do succumb to habituation. Recent[*when?*] studies have shown that the repeated influence of drug-inducing DA projection has an abnormal strengthening effect on stimulus-drug associations and increases the drug-reward stimuli's resistance to extinction. This may be

a contributing factor to addiction. This effect was more pronounced in the NAc shell than in the NAc core.[13][13][20]

Phenethylamine and **tyramine**: Phenethylamine and tyramine are trace amine compounds which are synthesized in several types of CNS neurons, including all dopamine neurons.[21] Specifically, these neurotransmitters act within the dopaminergic inputs to the NAcc. These substances regulate the presynaptic release of dopamine through their interactions with VMAT2 and TAAR1, analogous to amphetamine.

Glucocorticoids and dopamine: Glucocorticoid receptors are the only corticosteroid receptors in the nucleus accumbens shell. L-DOPA, steroids, and specifically glucocorticoids are currently known to be the only known endogenous compounds that can induce psychotic problems, so understanding the hormonal control over dopaminergic projections with regards to glucocorticoid receptors could lead to new treatments for psychotic symptoms. A recent study demonstrated that suppression of the glucocorticoid receptors led to a decrease in the release of dopamine, which may lead to future research involving anti-glucocorticoid drugs to potentially relieve psychotic symptoms.[22]

GABA: A recent study on rats that used GABA agonists and antagonists indicated that GABAA receptors in the NAc shell have inhibitory control on turning behavior influenced by dopamine, and GABAB receptors have inhibitory control over turning behavior mediated by acetylcholine.[13][23]

Glutamate: Studies have shown that local blockade of glutamatergic NMDA receptors in the NAcc core impaired spatial learning.[24] Another study demonstrated that both NMDA and AMPA (both glutamate receptors) play important roles in regulating instrumental learning.[25]

Serotonin (5-HT): Overall, 5-HT synapses are more abundant and have a greater number of synaptic contacts in the NAc shell than in the core. They are also larger and thicker, and contain more large dense core vesicles than their counterparts in the core.

Function

Reward and reinforcement

The nucleus accumbens, being one part of the reward system, plays an important role in processing rewarding stimuli, reinforcing stimuli (e.g., food and water), and those which are both rewarding and reinforcing (addictive drugs, sex, and exercise).[3][26] The nucleus accumbens is selectively activated during the perception of pleasant, emotionally arousing pictures and during mental imagery of pleasant, emotional scenes.[27][28] A 2005 study found that it is involved in the regulation of emotions induced by music,[29] perhaps consequent to its role in mediating dopamine release. The nucleus accumbens plays a role in rhythmic timing and is considered to be of central importance to the limbic-motor interface (Mogensen).[*citation needed*]

In the 1950s, James Olds and Peter Milner implanted electrodes into the septal area of the rat and found that the rat chose to press a lever which stimulated it. It continued to prefer this even over stopping to eat or drink. This suggests that the area is the "pleasure center" of the brain and is involved in reinforcement learning.[30] In rats, stimulation of the ventral tegmental area causes the release of dopamine in the nucleus accumbens much in the same way as addictive drugs and natural reinforcers, such as water or food, initiate the release of dopamine in the nucleus accumbens.[31] The same results have been seen in human subjects in functional imaging studies. For example, increased dopamine concentration is seen in the extracellular fluid of the nucleus accumbens when subjects believed they were being given money[*citation needed*], and increased activation (i.e., increased fMRI BOLD signal-change) was observed among heterosexual males viewing pictures of attractive women.[32]

Maternal behavior

An fMRI study conducted in 2005 found that when mother rats were in the presence of their pups the regions of the brain involved in reinforcement, including the nucleus accumbens, were highly active.[33] Levels of dopamine increase in the nucleus accumbens during maternal behavior, while lesions in this area upset maternal behavior.[34] When human mothers are presented pictures of their children, fMRIs show an increased brain activity in the nucleus accumbens and other reinforcing brain regions and a decrease in activity in areas of the brain involved with negative emotions.[*citation needed*]

Clinical significance

Addiction

Current models of addiction from chronic drug use involve alterations in gene expression in the mesocorticolimbic projection.[8][35][36] The most important transcription factors that produce these alterations are ΔFosB, cyclic adenosine monophosphate (cAMP) response element binding protein (CREB), and nuclear factor kappa B (NFκB).[8] ΔFosB is the most significant gene transcription factor in addiction since its viral or genetic overexpression in the nucleus accumbens is necessary and sufficient for many of the neural adaptations seen in drug addiction;[8] it has been implicated in addictions to alcohol, cannabinoids, cocaine, nicotine, phenylcyclidine, opiates, and substituted amphetamines.[8][35][37] ΔJunD is the transcription factor which directly opposes ΔFosB.[8] Increases in nucleus accumbens ΔJunD expression can reduce or, with a large increase, even block most of the neural alterations seen in chronic drug abuse (i.e., the alterations mediated by ΔFosB).[8]

ΔFosB also plays an important role in regulating behavioral responses to natural rewards, such as palatable food, sex, and exercise.[8][9] Natural rewards, like drugs of abuse, induce ΔFosB in the nucleus accumbens, and chronic acquisition of these rewards can result in a similar pathological addictive state through ΔFosB overexpression.[8][9][26] Consequently, ΔFosB is the key transcription factor involved in addictions to natural rewards as well;[8][9][26] in particular, ΔFosB in the nucleus accumbens is critical for the reinforcing

effects of sexual reward.[9] Research on the interaction between natural and drug rewards suggests that psychostimulants and sexual behavior act on similar biomolecular mechanisms to induce ΔFosB in the nucleus accumbens and possess cross-sensitization effects that are mediated through ΔFosB.[26][38]

Summary of addiction-related plasticity

Form of neural or behavioral plasticity	Type of reinforcer						Sources
	Opiates	Psychostimulants	High fat or sugar food	Sexual reward	Exercise	Environmental enrichment	
ΔFosB expression in the nucleus accumbens	↑	↑	↑	↑	↑	↑	[26]
Behavioral Plasticity							
Escalation of intake	Yes	Yes	Yes				[26]
Psychostimulant cross-sensitization	Yes	Not applicable	Yes	Yes	Attenuated	Attenuated	[26]
Psychostimulant self-administration	↑	↑	↓		↓	↓	[26]
Psychostimulant conditioned place preference	↑	↑	↓	↑	↓	↑	[26]
Reinstatement of drug-seeking behavior	↑	↑			↓	↓	[26]
Neurochemical Plasticity							
CREB phosphorylation in the nucleus accumbens	↓	↓	↓		↓	↓	[26]
Sensitized dopamine response in the nucleus accumbens	No	Yes	No	Yes			[26]
Altered striatal dopamine signaling	↓DRD2, ↑DRD3	↑DRD1, ↓DRD2, ↑DRD3	↑DRD1, ↓DRD2, ↑DRD3		↑DRD2	↑DRD2	[26]
Altered striatal opioid signaling	↑μ-opioid receptors	↑μ-opioid receptors ↑κ-opioid receptors	↑μ-opioid receptors	↑μ-opioid receptors	No change	No change	[26]
Changes in striatal opioid peptides	↑dynorphin	↑dynorphin	↓enkephalin		↑dynorphin	↑dynorphin	[26]
Mesocorticolimbic Synaptic Plasticity							

Number of dendrites in the nucleus accumbens	↓	↑		↑	[26]
Dendritic spine density in the nucleus accumbens	↓	↑	No change	↑	[26]

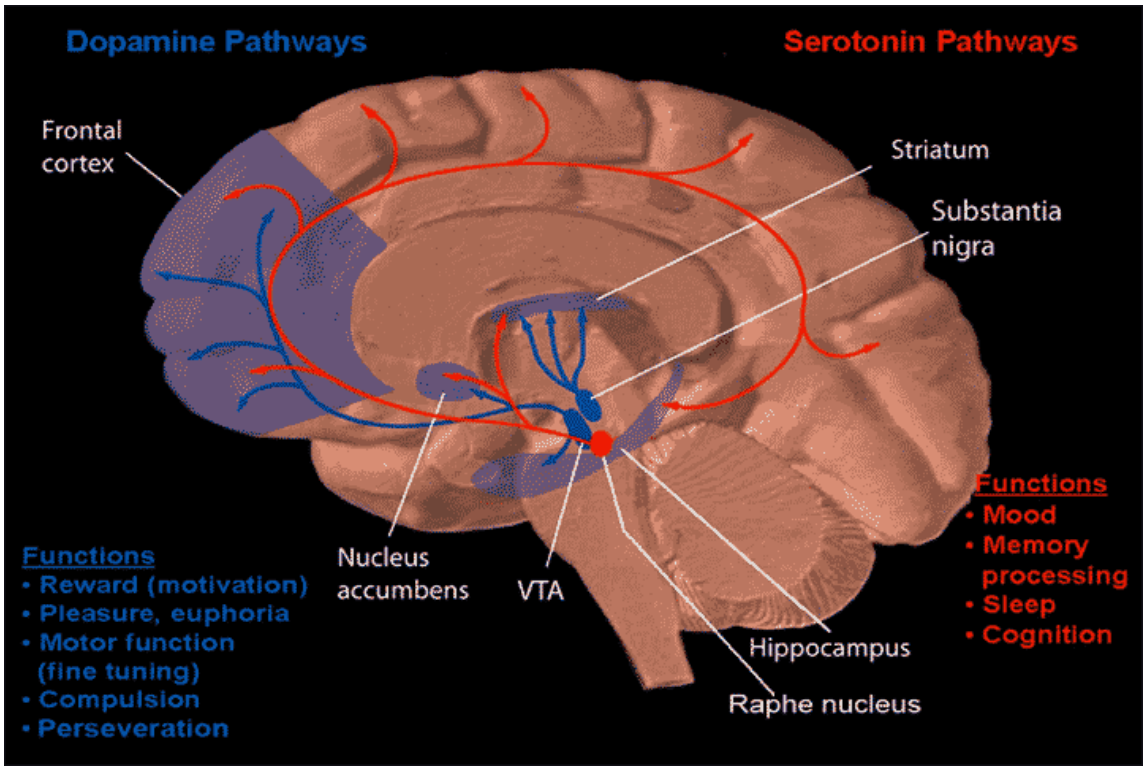
Depression

In April 2007, two research teams reported on having inserted electrodes into the nucleus accumbens in order to use deep brain stimulation to treat severe depression.[39] In 2010 experiments reported that deep brain stimulation of the nucleus accumbens was successful in decreasing depression symptoms in 50% of patients who did not respond to other treatments such as electroconvulsive therapy.[40] Nucleus accumbens has also been used as a target to treat small groups of patients with therapy-refractory obsessive-compulsive disorder.[41]

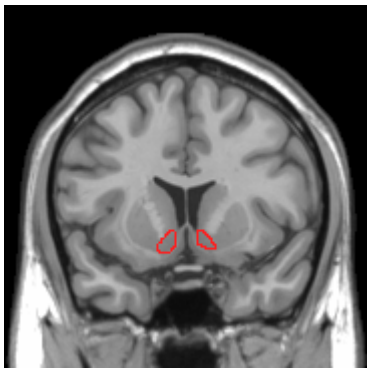
Placebo effect

Activation of the NAcc has been shown to occur in the anticipation of effectiveness of a drug when a user is given a placebo, indicating a contributing role of the nucleus accumbens in the placebo effect.[6][42]

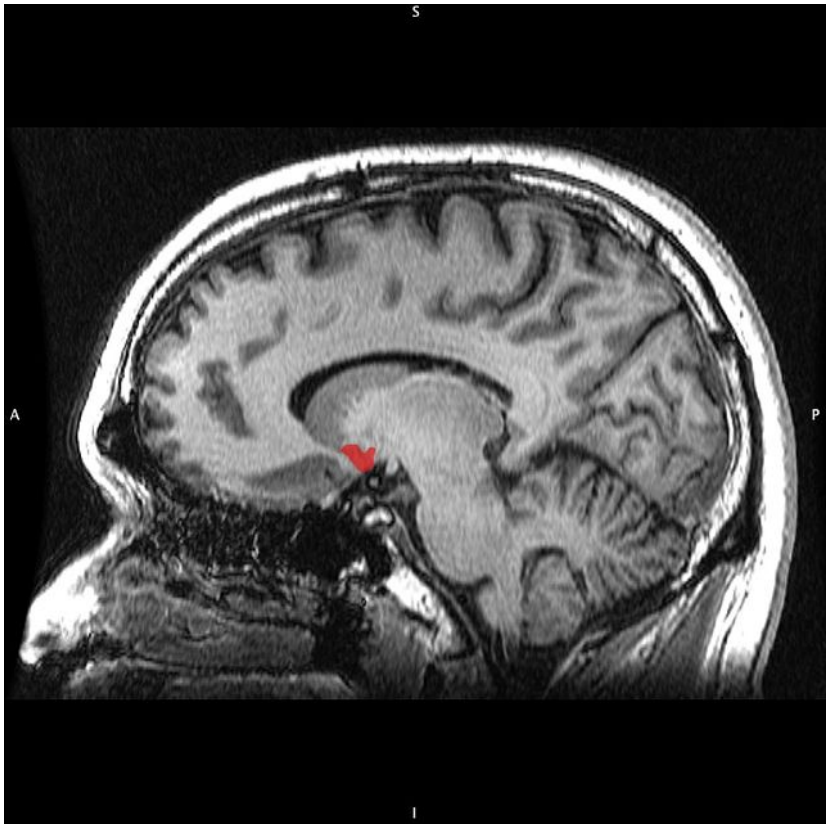
Additional images

- 

  Dopamine and serotonin

- 

  MRI coronal slice showing nucleus accumbens outlined in red

- 

  Sagittal MRI slice with highlighting (red) indicating the nucleus accumbens.

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2. Nucleus Accumbens
3. Malenka RC, Nestler EJ, Hyman SE (2009). Sydor A, Brown RY, ed. *Molecular Neuropharmacology: A Foundation for Clinical Neuroscience* (2nd ed.). New York: McGraw-Hill Medical. pp. 147–148, 367, 376. ISBN 9780071481274. VTA DA neurons play a critical role in motivation, reward-related behavior (Chapter 15), attention, and multiple forms of memory. This organization of the DA system, wide projection from a limited number of cell bodies, permits coordinated responses to potent new rewards. Thus, acting in diverse terminal fields, dopamine confers motivational salience ("wanting") on the reward itself or associated cues (nucleus accumbens shell region), updates the value placed on different goals in light of this new experience (orbital prefrontal cortex), helps consolidate multiple forms of memory (amygdala and hippocampus), and encodes new motor programs that will facilitate obtaining this reward in the future (nucleus accumbens core region and dorsal striatum). In this example, dopamine modulates the processing of sensorimotor information in diverse neural circuits to maximize the ability of the organism to obtain future rewards. ...

The brain reward circuitry that is targeted by addictive drugs normally mediates the pleasure and strengthening of behaviors associated with natural reinforcers, such as food, water, and sexual contact. Dopamine neurons in the VTA are activated by food and water, and dopamine release in the NAc is stimulated by the presence of natural reinforcers, such as food, water, or a sexual partner. ... The NAc and VTA are central components of the circuitry underlying reward and memory of reward. As previously mentioned, the activity of dopaminergic neurons in the VTA appears to be linked to reward prediction. The NAc is involved in learning associated with reinforcement and the modulation of motoric responses to stimuli that satisfy internal homeostatic needs. The shell of the NAc appears to be particularly important to initial drug actions within reward circuitry; addictive drugs appear to have a greater effect on dopamine release in the shell than in the core of the NAc.

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attenuates this behavior (Hedges et al, 2009; Pitchers et al., 2010b). Further, viral overexpression of delta FosB enhances the conditioned place preference for an environment paired with sexual experience (Hedges et al., 2009). ...
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of abuse induce neuroplasticity in the natural reward pathway, specifically the nucleus accumbens (NAc), thereby causing development and expression of addictive behavior. ... Together, these findings demonstrate that drugs of abuse and natural reward behaviors act on common molecular and cellular mechanisms of plasticity that control vulnerability to drug addiction, and that this increased vulnerability is mediated by ΔFosB and its downstream transcriptional targets. ... Sexual behavior is highly rewarding (Tenk et al., 2009), and sexual experience causes sensitized drug-related behaviors, including cross-sensitization to amphetamine (Amph)-induced locomotor activity (Bradley and Meisel, 2001; Pitchers et al., 2010a) and enhanced Amph reward (Pitchers et al., 2010a). Moreover, sexual experience induces neural plasticity in the NAc similar to that induced by psychostimulant exposure, including increased dendritic spine density (Meisel and Mullins, 2006; Pitchers et al., 2010a), altered glutamate receptor trafficking, and decreased synaptic strength in prefrontal cortex-responding NAc shell neurons (Pitchers et al., 2012). Finally, periods of abstinence from sexual experience were found to be critical for enhanced Amph reward, NAc spinogenesis (Pitchers et al., 2010a), and glutamate receptor trafficking (Pitchers et al., 2012). These findings suggest that natural and drug reward experiences share common mechanisms of neural plasticity

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