The Nucleus Accumbens: A Comprehensive Review

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Abstract

There is increasing interest among functional neurosurgeons in the potential for novel therapies to impact upon diseases beyond movement disorders and pain. A target of increasing interest is the nucleus accumbens (NAc), which has long been studied as a key brain region mediating a variety of behaviors, including reward and satisfaction. As such, focal modulation of the biology of the NAc with deep brain stimulation or novel biological therapies such as gene therapy or cell transplantation could have a major impact upon disorders such as depression and drug addiction. In order to both develop appropriate therapies and then deliver them in an effective fashion, a thorough understanding of the biology, physiology, and anatomy of the NAc is critical. Here, we review the existing literature regarding several areas critical to the development of new therapies, including the known pharmacology, physiology, and connectivity of the NAc, as well as evidence supporting the potential for various NAc surgical therapies in animal models. We then review the relevant anatomy of the NAc, with particular attention to the surgical anatomy, imaging, and targeting necessary to facilitate a proper localization and de-

livery of new agents to this region. The NAc is a fascinating and potentially rich target for stereotactic neurosurgical intervention, and analysis of existing information regarding all aspects of this structure should help potentiate therapeutic advances and reduce complications from future studies of neurosurgical intervention in this region for a variety of disorders.

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Introduction

The nucleus accumbens (NAc) is a major component of the ventral striatum and has long been thought to be a key structure involved in mediating motivational and emotional processes, the limbic-motor interface, and the effects of certain psychoactive drugs. The NAc has been implicated in numerous neurological and psychiatric disorders, including depression, obsessive-compulsive disorder, bipolar disorder, anxiety disorders, Parkinson's disease, Alzheimer's disease, Huntington's disease, obesity, and in drug abuse and addiction. As a result, there has been a great deal of interest in stereotaxic targeting of the NAc for delivery of potentially therapeutic devices or agents. Furthermore, neurosurgical intervention into the NAc has led to encouraging outcomes in pilot studies for a range of disorders, including addiction,

Tourette's syndrome, depression, and obsessive-compulsive disorder. Given the increasing interest in this brain region, a comprehensive understanding of the structural, biological, and clinical features of the NAc is critical. In the present report, we review the anatomical, pharmacological, and physiological attributes of the NAc, with an emphasis on those features most relevant to surgeons who may consider the NAc as a target for future therapeutic studies.

History

The first use of the term 'nucleus accumbens' is accredited to Ziehen [1] (1904) more than 100 years ago, although it has been reported [2, 3] that the area was first described by a number of different authors prior to this, with perhaps the earliest description emerging in 1872. The NAc was initially an extension of the caudate nucleus, distinguishable from the rest of the striatum because of its topographic relationship with the septum, leading it to be dubbed 'nucleus accumbens septi' ('nucleus leaning against the septum') by Kappers and Theunissen [4] (1908). This terminology was rejected a few years later by Johnston [5] (1913) who, after suggesting that the structure was instead a part of the olfactory center, concluded that it should be classified as part of the septum and proposed a new name ('nucleus lateralis parolfactorius'). Johnston eventually recanted and once again called the area the 'nucleus accumbens septi', but still emphasized that this area must be recognized as an olfactory center separate from the rest of the striatum [6]. This notion originated from the hypothesis that the accumbens was predominantly related to the medial forebrain bundle (an area considered to consist largely of fibers of the olfactory system) and was furthered by Herrick [7] (1926), who dubbed the area the 'olfacto-striatum'.

However, studies from the latter half of the century found reason to challenge this terminology. While there had been evidence of olfactory input to the NAc in rodents, a dearth of afferents from the olfactory bulb or secondary olfactory regions in monkeys or cats led Heimer et al. [8] (1982) to conclude that the term 'olfactory-striatum' was misleading. Coupled with new data that found similarities between the afferent and efferent connections of the NAc and those of other striatal tissues (see Nauta et al. [9]), Heimer et al. [8] suggested that considering the NAc part of the ventral striatum was more appropriate. While the striatal nature of the NAc was still contested, evidence was accumulating to show that the NAc was

similar to the striatum in terms of enzyme histochemistry [10], opiate receptors distribution [11–13], acetylcholine levels [14, 15], dopamine (DA) levels [16], neural connections [9, 17], and ontogeny [17, 18]. While differences between the NAc and the rest of the striatum have been documented, it is now the general consensus that the accumbens is an integral, but specialized, part of the striatal complex, closely related the caudate-putamen (striatum) and separate in function and composition from the septum [19].

Embryology

During development, the prosencephalon becomes subdivided into the diencephalon and telencephalon, which continue to expand both dorsally and along the rostrocaudal axis. The basolateral aspects of the telencephalic walls eventually develop into ventricular ridges (also called ganglionic eminences). The rostral portion of these ventricular ridges [18, 20] – specifically, an inner layer of cells related to olfactory invagination [21] – develop into the NAc and the olfactory tubercle. [³H]Thymidine-based analysis of primate neurogenesis suggests that the accumbens develops similarly to the neostriatum. Accumbal neurons are generated over a 50-day period beginning around embryonic day 36 [22], with rodent studies noting that neurogenesis briefly continues postnatally [23–25], a notion that may apply to humans as well [21]. Interestingly, [³H]thymidine-based analysis in primates found no spatio-temporal gradients in the neuronal positioning during development [22], whereas similar analyses in rodents have had mixed findings, with studies identifying ventral-dorsal gradients [25], lateral-medial gradients [25], as well as rostrocaudal gradients [18]. This difficulty in determining a universal spatio-temporal gradient may be partially explained by the hypothesis that the accumbens arises from two distinct germinal zones along the inferior horn of the lateral ventricle, the neuroepithelium and the subependymal zone [25].

The primary neurons of the NAc are medium spiny neurons, the development of which can be influenced by environmental factors. For instance, studies have demonstrated that both prenatal and postnatal stress in animals heightens the complexity of dendritic morphology of the accumbens, altering the branching, length, and spine density of the medium spiny neurons [26–28]. Functionally, in humans, the NAc appears to have adult-like response patterns in adolescence, whereas differences can

Fig. 1. Schematic representation of major afferent (a) and efferent (b) connections of the NAc. SNc = Substantia nigra pars compacta; BNST = bed nucleus of the stria terminalis; GPi = globus pallidus internus; SNr = substantia nigra pars reticulata; ctx = cortex.

still be observed in the prefrontal cortex and the dorsal striatum [29, 30]. This difference in development has led to the suggestion that the activation of the subcortical system is disproportionately weighted during development, which may lead to a focus on immediate over long-term gains during adolescence [30].

Anatomy

A round, but dorsally flattened structure, the NAc is located anterior to the posterior border of the anterior commissure (AC) and lies parallel to the midline. An early 20th century anatomical study found the NAc indistinguishable from the surrounding tissue, with the only clearly defined boundary being the zona limitans, which separates the medial NAc from the septum [5]. While subsequent anatomical studies allowed for further definition, certain boundaries appeared so diffuse and transitional to merit controversy; for instance, whether the rostral pole was a distinct area [19] or an extension of the shell of the accumbens [31] (see Zahm [32], 1999). However, more modern anatomical analyses have suggested that the boundaries of the NAc are as follows: (1) posterior limit: the posterior border of the AC [33, 34]; (2) anterior limit: where the rostral limit of the internal capsule starts separating the caudate from the putamen [34]; (3) medial limit: the sagittal plane passing by the inferior border of the lateral ventricle; (4) lateral limit: a line extending downwards and laterally to the rostral edge of the internal capsule; (5) dorsal limit: the horizontal plane pass-

ing under the caudate nucleus head from the inferior border of the lateral ventricle to the inferior limit of the internal capsule, and (6) ventral limit: the external capsule (lateral side) and Broca's diagonal band (medial side) anteriorly, the anterior hypothalamic nucleus posteriorly [34].

The NAc extends dorsolaterally into the putamen and dorsomedially into the caudate nucleus but lacks any sharp demarcation between the two areas [34]. Anatomical studies have suggested that the morphology of the NAc is such that the nucleus is longest on the anterior-posterior axis and shortest along the dorsal-ventral axis, suggesting that the NAc is more visible in coronal than sagittal and in sagittal than transverse magnetic resonance imaging (MRI) slices [35] (fig. 1). Previously, the NAc was thought to be less well-defined by MRI than by anatomical techniques due to a lack of a distinct signal intensity [34], but a more recent study has suggested that discerning the NAc limits with the caudate nucleus and putamen is easier by T2-weighted MRIs due to the more intense signaling that the NAc presents compared with the caudate nucleus and putamen [35].

Unique to the rest of the striatum, the accumbens can be divided into a central core surrounded medially, ventrally, and laterally by a shell [36]. This division between core and shell can only be distinguished in the caudal parts of the accumbens, which has led to the more rostral part to be referred to as the 'rostral pole' of the accumbens [37]. The differences between the shell and the core are defined by various histochemical, electrophysiological, connectional, and cellular criteria [38] but are difficult to

discern in gross anatomical studies [34, 35], except perhaps at the midrostrocaudal level of the ventral striatum [39]. The AC is surrounded by the core, which in turn is surrounded, on its medial, ventral, and ventrolateral sides, by the shell [19].

Morphometric studies examining dimorphisms based on location and sex have been controversial, with studies indicating the NAc is larger on the left [40], the right [34], in males [40], and with [41] or without [35, 42] sexual or hemispheric differences. The presence of an age-based dimorphism is also contested, with some studies suggesting a decrease in volume with age [35, 41, 42], while others maintain that the NAc does not suffer any age-related atrophy [34].

Organization

While historically, there has been disagreement whether the NAc belongs to the septal system or the basal ganglia, decades of research utilizing a variety of tract-tracing, immunohistochemical, and receptor-binding methods have suggested that the accumbens is a specialized part of the striatal complex [19, 8], similar, but not exactly parallel, to other striatal structures such as the caudate-putamen [37, 43]. The NAc has typically been divided by two different sets of criteria: (1) the mosaic arrangement of the patch-matrix organization as well as (2) anatomical and morphological compartmentalization of the core and shell. However, it should be noted that studies have also demonstrated additional levels of NAc organization, separate from the well-documented patch-matrix and core-shell differences. These include gradients of rostrocaudal differentiation in terms both of structure and function of the NAc [44–47] as well as organizational structures based upon differences in immunostaining and signaling molecules in the ventral and medial areas [48, 49].

The Patch Matrix

Similar to other striatal tissue, the NAc is characterized by a 'striosomal' or a 'patch-matrix' organization, which is a mosaic arrangement consisting of two distinct compartments [48, 50–52]. The patches are characterized by dense μ -opiate receptor-binding sites [37, 53–55], while the matrix consists of weaker opiate receptor binding, high acetylcholinesterase activity, strong calcium-binding protein immunoreactivity, and a rich plexus of somatostatin fibers [37, 56–58]. This striosomal organization can also be recognized on the basis of the immunohisto-

chemical distribution of several markers, including enkephalin, substance P, DA, and calcium-binding protein [48, 59, 60].

The Accumbal Core and Shell

Unlike the rest of the striatal complex, the NAc can be divided into two distinct areas: a central core surrounded by an outer shell, each of which have unique features (some studies also consider the rostral pole, which lacks an apparent boundary separating it from the caudate-putamen and olfactory tubercle [61] and consists of uneven histochemical and immunostaining for a number of substances [37], to be a third division of the accumbens). While throughout the accumbens, the cell bodies are small to medium in size, in humans, the core region has been found to contain a low density of impregnated neurons consisting predominantly of pyramidal-like neurons with spines on secondary branches, and to a rarer extent, some multipolar neurons [62]. In contrast, the shell region has a high cell density [62, 63] consisting primarily of groups of well-arborized fusiform and multipolar neurons, all of which are rich in spines on secondary and tertiary dendritic branches [62]. Interestingly, morphological studies in rats have reached the seemingly opposite conclusion, determining that the shell contains smaller cells with fewer dendrites and dendritic spines than those found in the core [64, 65].

On a molecular level, studies have noted core-shell differences in the distribution of a number of neuroactive substances and receptors, including substance P [39], calcitonin [39], DA [66], serotonin [66], and serotonin receptors [67], with a tendency for these substances to be preferentially located in the shell than the core. Substances that are preferentially located in the core include calbindin [39, 48, 68], enkephalin [45, 47, 63], GABA_A receptors [69], and limbic associated membrane protein [39]. Furthermore, there are core-shell differences in mRNA expression [47, 70, 71], with differences in Fos-like immunoreactivity leading to the notion that the shell of the accumbens may be a site of antipsychotic drug action [72].

Some histological and tract tracing studies have suggested that the shell of the NAc not only harbors characteristics similar to those of striatal tissue, but also contains features analogous to the extended amygdala. These include immunohistochemical similarities, such as the presence of areas rich in neurotensin, cholecystokinin, and opioid peptides, as well as connectional similarities, including efferents to the lateral hypothalamus and afferents from the basolateral complex of the amygdala (see [19, 73, 74]). This has led to the notion that the shell area

of the accumbens could be conceived as a transitional zone between the striatum and the extended amygdala [75]. These similarities have even raised the question of whether the NAc shell would be more appropriately classified as part of the extended amygdala, but sufficient network differences exist such that the two should most usefully be regarded as separate, interacting functional-anatomical entities [76].

Afferents

There is evidence to suggest that the NAc is the main input nucleus of the basal ganglia [77], as it receives both indirect input via the mesolimbic dopaminergic projections from the ventral tegmental area (VTA) and substantia nigra [78–80] as well as direct input in the form of glutamatergic projections from the subiculum and amygdala [80–83], hippocampus [84–88], thalamus [63, 80, 89], prelimbic [90] and prefrontal cortex [80, 91–96]. Animal studies have further elucidated that the accumbens, similar to the caudate-putamen and olfactory tubercle, receives input from the allocortical and periallocortical areas as well as from the medial and lateral preisocortical areas [73, 89] (fig. 1a).

There is also evidence that the patch and matrix receive different afferents from the cortex and midbrain, with animal tracing studies determining that the patches receive innervations from the prelimbic cortex and the substantia nigra, while the matrix is innervated by the prefrontal, motor, and sensory cortical areas [57]. The prelimbic area has also been found to project mainly to the rostral half of the NAc, whereas only the lateral region of the caudal half receives frontal cortical fibers [97]. Afferents from the entorhinal and perirhinal cortices reach the NAc by way of the external capsule and terminate mainly in a ventral zone of the NAc. Those from the entorhinal area are distributed to the entire accumbens, whereas the termination field of the perirhinal afferents is largely restricted to the lateral part of the NAc [97]. Furthermore, the matrix is innervated by cortical laminae from the midline and intralaminar thalamic nuclei, which avoid the patches [11].

Additionally, there appear to be differences between the cortical origin of afferents entering the core of the NAc versus the medial shell, with the dorsal peduncular, infralimbic (the rodent equivalent of human Brodmann area 25), and posterior piriform cortices projecting to the medial shell, while the dorsal prelimbic, anterior agranular insular, anterior cingulate, and perirhinal cortices

project to the core [89]. The ventral medial prefrontal cortex, in particular, sends glutamatergic projections to the shell [98, 99] and is thought to play a role in the reinstatement of drug-seeking behavior [100, 101]. The afferents from the VTA also appear to extensively innervate the shell compartment of the NAc [102], whereas the substantia nigra predominantly innervates the core [103]. The caudal dorsomedial extremity of the shell (the ‘septal pole’ of the NAc) has been observed to be innervated by a variety of structures in the ventral forebrain, including lateral hypothalamus, deep temporal lobe, and brainstem [89]. The area between the septal pole and the most ventral ‘temporal pole’ contains afferents from the subiculum [97], but these terminations are inhomogeneously distributed [104]. Afferents from the dorsal agranular insular area and the intermediodorsal thalamic nucleus appear to avoid the shell of the lateral NAc, which instead receives inputs from the magnocellular basal amygdala [38].

Efferents

The main output neurons from the NAc are medium spiny neurons that project to various areas of the mesencephalon and basal ganglia. Similar to other striatal tissue, many of the efferent fibers terminate in the diencephalon or the pallidal complex, with projections reaching the stria terminalis, preoptic region, nucleus parataenialis, nucleus mediodorsalis thalami, lateral habenular nucleus, substantia nigra-ventral tegmental area, the lateral hypothalamus, cingulum, thalamus, globus pallidus, and subpallidal region [9, 17, 75, 105–109]. There also appear to be projections to the amygdala [110, 111] and septum [9, 112–114], although this is not a universal finding [19] (fig. 1b).

Evidence suggests differences in efferent projections from the patches versus the matrix as well as from the core versus the shell. The patches project to the substantia nigra pars compacta, while the matrix projects to the substantia nigra pars reticulata. While both the core and shell project to the entopeduncular nucleus (the rodent equivalent of the human globus pallidus internus), only the shell appears to project diffusely throughout the rostro-caudal extent of the lateral hypothalamus and to the extended amygdala [19, 115]. Both areas also innervate pallidal areas, but the precise locations of the projections vary depending on shell or core origin. The core projects to the dorsolateral compartment of the ventral pallidum, which lacks an appreciable amount of neurotensin, whereas the

neurotensin-rich ventromedial ventral pallidum is innervated predominantly by the shell [19, 36, 68].

The rostral pole of the accumbens appears to share efferents with both the core and the shell. The lateral rostral pole gives rise to core-like projections (to the rostromedial globus pallidus, subcommissural ventral pallidum, entopeduncular nucleus and an adjacent part of the lateral hypothalamus, lateral VTA, dorsal pars compacta, and structures in the lateral mesencephalic tegmentum and central grey), while the medial part of the rostral pole is more shell-like in its innervations (projecting to the subcommissural ventral pallidum, lateral preoptic region, lateral hypothalamus, VTA, dorsalmost pars compacta, retrorubral field, lateral midbrain tegmentum, and central grey) [61].

Furthermore, there appear to be differences in the efferents from the lateral and medial accumbens. The lateral accumbens has been found to project to the ventral pallidum, the subcommissural part of the globus pallidus, the entopeduncular nucleus, the substantia nigra, and the retrorubral nucleus [113]. The medial NAc has been found to project to a multitude of areas, including the ventral pallidum, the rostral part of the lateral hypothalamus, the lateral septum, the bed nucleus of the stria terminalis, the medial preoptic and hypothalamic areas, the VTA, the retrorubral nucleus, the central superior nucleus, the nucleus tegmenti pedunculoopontinus, and the central gray [113]. However, other studies [19, 116] have been unable to replicate similar results, especially the projections to several medial hypothalamic areas, leading to the suggestion that since the medial accumbens largely contains the shell region, some of the reported connectional differences may be due to the differences between core and shell projections rather than medial-lateral differences.

Circuitry

Previous work has noted a pattern of connectivity between the patch and matrix compartments of the basal ganglia and NAc. The afferents, efferents, and dendritic processes of the neurons are compartmentally segregated and are restricted [11, 57, 58, 117, 118] suggesting that the patch and matrix compose segregated, parallel systems [57]. Furthermore, it has been demonstrated that regions of the cortex that project to the NAc receive input from midline thalamic and basal amygdaloid nuclei, which also project to the same part of the NAc as their cortical target [38, 68].

Also of interest are the differences between the core and shell projections. The core connectivity eventually leads to premotor and supplemental motor areas of the cortex, while the shell connects to the prefrontal cortical areas as well as a range of subcortical motor areas, including the extended amygdala and lateral hypothalamus [37, 119, 120]. Further examination reveals the presence of two distinct dopaminergic circuits based on the topography of the NAc [19, 66]. The NAc core projects to the dorsolateral ventral pallidum, which in turn projects to the subthalamic nucleus and substantia nigra, the origin of dopaminergic innervation of the striatum. On the other hand, the NAc shell projects through the ventromedial ventral pallidum to the mediodorsal nucleus, which contains a reciprocal connection with the prefrontal cortex, and the VTA, which sends dopaminergic projections to mesocortical sites [19, 61, 68, 121–123]. The similarity between these projections and those of the amygdala supports the notion that the shell may represent a transitional zone between the striatum and amygdala.

These projections have been found to form networked connections within the neuronal framework, leading to the concept that the functional architecture of the basal ganglia is parallel in nature, innervating a number of structures, but following the general pattern of a cortico-striato-pallido-thalamo-cortical loop [124, 125] (for example, the prefrontal cortex projects to the NAc which, in turn, innervates the ventral pallidum; the ventral pallidum, via the mediodorsal nucleus of the thalamus, then sends afferent fibers back to the prefrontal cortex, completing the circuit) via a number of re-entrant pathways [125, 126]. There are currently five major circuits recognized, with the NAc playing a major role in the anterior cingulate circuit [125, 126], among other, smaller loops. The cortical circuits that link these systems may play a key role in feeding behavior [127], motivated behavior [128], and addiction [129].

Function

While immunohistochemistry and histology commanded much of the attention in the early history of the NAc research, more recent functional studies have illuminated the role of the NAc in behavior, which as a result has opened the NAc as a therapeutic target. Due to its input from the limbic system as well as output and cytochemical similarity to the motor nuclei of the basal ganglia, the accumbens has been said to be the functional interface between the limbic and motor systems [78, 130],

suggesting that the accumbens is an important player in controlling the biological drives necessary for survival and reproduction. Indeed, studies have demonstrated that the NAc plays crucial roles in locomotion [131–135], learning (including both conditioned place preference [136, 137] and avoidance [138, 139]), impulsivity [140], risk-taking behaviors [141], feeding behavior [127] (in animals [142–147] and humans [148]), sexual motivation (in animals [149] and humans [150]), as well as incentive and reward [151–154], especially unpredictable reward [155].

There appears to be a point of contention in the literature whether the NAc is involved in modulating goal-oriented behavior [156–159], only motivation [160, 161], or part of a more complicated circuit connecting multiple independent functional systems [162, 163]. Overall, however, the NAc appears to be a key structure in the natural reward system, which includes modulation of motivation and incentivized learning [154]. Coupled with connectional studies, these findings have led to the suggestion that the NAc plays a central role in a positive emotional response pathway, counterbalanced by a negative emotional response pathway mediated by the amygdala [164], although others believe the NAc itself may play a vital role in aversive motivation [165].

There also appears to be a division of labor between the NAc shell and core. The shell, especially the medial shell, is suspected to mediate the reinforcing properties of novelty [166], feeding behavior [167], rewarding substances [168], and drug relapse [169, 170]. The core seems to play a crucial role in spatial learning [171], conditioned responses [172–174], responses to motivational stimuli [166, 175], and impulsive choices [176], likely operating in tandem with the anterior cingulate via a corticostriatal circuit [172]. Even more precise functional segregation of the accumbens can also be justified, with studies showing behavioral differences in feeding behavior after alterations in neuronal firing in the medial versus lateral shell [177, 178].

Pharmacology

Dopamine

The NAc first became a structure of interest among behavioral neuroscientists with the discovery that DA [179, 180] and DA agonist injections [181] into the NAc enhanced locomotor activity in rats, suggesting that a motor stimulant is partly mediated by D1 receptors. Further study of the accumbens has resulted in a strong body

of evidence demonstrating that DA in the NAc plays a key role in the natural reward system of the brain, as well as in addiction (see below).

Dopaminergic neurons from the substantia nigra and the VTA project to the matrix, while the patches are innervated mainly by the substantia nigra [58]. Each nigral neuron appears to influence a large number of striatal neurons [182], and this signal amplification may be a key function of the nigrostriatal system in DA-based learning. The projections from the VTA, a part of the mesolimbic DA pathway, appear to extensively innervate the NAc shell [183]. Together, this has led to the hypothesis that dopaminergic innervation of the NAc core is associated with the nigrostriatal system, while that of the NAc shell is related to the mesolimbic system [66]. This is further supported by 6-OHDA lesioning, which has demonstrated that the mesostriatal DA cells innervating the patch and matrix are distinct [184].

DA turnover is higher in the accumbens than the rest of the striatum, but not significantly different between the core and shell [66]. However, there are noticeable core-shell differences in regard to DA. The shell contains a larger number of DA receptors [71], but the core has a greater DA utilization [66] and contains more DA transporters [185]. There are conflicting reports on whether the basal concentration of DA is greater in the shell [66] or core [186, 187], but it appears that opiate drugs increase extracellular DA in the shell more than in the core [188, 189]. Drug-induced 5-HT₂ receptor occupancy favors DA release in the shell (clozapine, amperozide, risperidone, and ritanserin) [190], whereas high D2 receptor occupancy favors DA release in the core (haloperidol and raclopride) [66, 190]. Separate from the core-shell differences, there also appears to be a rostrocaudal gradient for D1 and D2 receptors and a lateral-to-medial gradient of D2 receptors [191].

GABA/Glutamate

GABAergic neurons are a primary component of the major efferent projection from the NAc to the ventral pallidum [19, 37, 106–108] and structures such as the globus pallidus [192]. GABAergic projections originating from the NAc modulate cortical acetylcholine efflux in the basal forebrain, which has been linked to context-dependent arousal [193] and may play a role in schizophrenia [194]. Similar to DA administration, GABA_A antagonists [78, 195] increase locomotion, but interestingly, GABA injection into the NAc produces both hyperactivity (after low doses) and hypoactivity (after high doses) [195, 196]. These findings may be partially explained by the notion

that GABA antagonists facilitate DA-induced hyperactivity, while high levels of GABA depress this effect [197]. Furthermore, DA-induced hyperactivity could be blocked by preventing GABAergic stimulation of neurons in the globus pallidus [78], indicating that the DA-mediated effects on locomotion can be modulated by other neurotransmitter systems.

Locomotion behavior can also be influenced by alterations in accumbal glutamate neurons, with glutamate agonists (AMPA [198] and N-methyl-aspartate [199]) inducing hyperactivity. Administration of glutamate antagonists appears to reduce locomotion [200, 201], although this hypoactivity has not been seen universally [202]. These behavioral findings may be due to an increase in DA release after exposure to glutamate agonists [203–206], a notion that is further supported by the finding that DA antagonists mitigate the stimulatory effects of glutamate agonists [207]. However, the finding that AMPA, but not amphetamine, induced hyperactivity after 6-OHDA lesions or blocked D1/D2 receptors [208] suggests a more complicated picture, in which the locomotor effects of accumbal glutamate do not solely depend on DA-mediated effects and perhaps act through other mesoaccumbal fibers. This decoupling of the dopaminergic and glutamatergic systems in the accumbens has also been suggested by animal models of cocaine relapse [209]. Animal models of addiction have also demonstrated the importance of accumbal glutamate in response reinforcement learning [210], which may play a role in nicotine reward [211], and dissociable differences in drug-seeking behavior mediated by core and shell glutamate neurons [212].

Acetylcholine

There appear to be two main cholinergic pathways that influence the reward pathways: (1) a forebrain projection from the nucleus basalis magnocellularis to the basolateral amygdala [213] that has been linked to drug relapse [214] and (2) a hindbrain projection from the mesopontine cell groups [213] (specifically the pedunculopontine tegmental nucleus (Ch5) and laterodorsal tegmental nucleus (Ch6) [215]) to the VTA and substantia nigra that modulates accumbal DA neurons [216, 217] and has been linked to psychosis and schizophrenia [218].

High levels of acetylcholine and choline acetyltransferase are found in the NAc, especially in the patch compartments [64] and the medial accumbens [219]. Cholinergic neurons in the striatum appear critical for long-term potentiation [220, 221] and conditioning [222]. Accumbal cholinergic activity has been linked to cessation of feeding and satiety [143–145], with more acetylcholine being re-

leased after normal feeding and less release after a feed-purge regimen [143] (DA release, in contrast, seems to be independent of purging and instead based on taste). Cholinergic interneurons may be particularly important modulators of overall NAc functioning. Optogenetic inhibition of ChAT neuronal activity reduces addictive behavior in rodents [223]. Furthermore, mice lacking the gene for the small receptor-binding protein p11 exhibit depression-like behaviors, and relative inhibition of p11 using gene therapy only in NAc ChAT neurons yields similar depression-like behaviors, while a very small percentage of NAc neurons, cholinergic interneurons, clearly play a major role in NAc-regulated behaviors.

Pathology

Role in Addiction

Evidence (see above) has suggested that the NAc modulates the brain's natural reward system, likely through changes in accumbal DA. Naturally rewarding stimuli – food, for instance – increase DA release in the accumbens, but importantly, the DA response wanes with repeated access [146, 147, 224]. However, it appears that the functioning of this reward system can be overwhelmed by drugs of abuse, which do not exhibit the same waning DA release with repeated exposure [225, 226]. Furthermore, studies have demonstrated that a number of substances can influence the accumbens, including cocaine [227–231], opiates [232] (for review, see [233, 234]), ethanol [235], nicotine [236, 237], THC [238], heroin [238], and PCP [239, 240]. Given the role of NAc DA in conditioned behavioral activation and discrimination of behavioral responses [241], it has been proposed that a DA transmission in the NAc regulates the effort expended to achieve a goal [242]; hence, alterations in accumbal DA may play a central role in abuse and addiction. This notion has led to the hypothesis that the mesolimbic DA system is hypo-functional in the addicted brain, resulting in a decreased interest in non-drug-related stimuli and increased sensitivity to the drug of choice [243].

The role of DA in drug use has been hypothesized for quite some time [244], and while the relationship between DA and reward has been extensively reviewed [245–249], a few points warrant highlighting. Drugs of abuse tend to increase DA in the accumbens [250] or change synaptic plasticity [251, 252], whereas nonabused drugs generally do not affect accumbal DA [250] or plasticity [251, 252]. After an addictive behavior is learned, groups of DA neurons in the accumbens fire to differing degrees (in pro-

portion to the time between drug infusions [253]) and at various times [227], including before drug exposure (anticipatory response), during drug exposure, and in response to paired sensory stimuli (cue-induced drug seeking). However, human neuroimaging studies have made the link between cue-induced reinforcement and the accumbens more obscure, with some studies finding ‘cues’ such as paraphernalia and images leading to increased accumbal activation in heroin [254], cocaine [255, 256], and alcohol abusers [257], smokers [258], and even video game addicts [259], while others have been unable to replicate similar results (for smoking [260] and cocaine [261, 262]). However, it has been noted that this discrepancy may be due to technical difficulties isolating the NAc with current technology [260, 263].

Interestingly, addictive behavior may persist even after subsequent lesions of DA neurons [264, 265] suggesting the involvement of other neurotransmitter systems in learned behavior and reward. While a number of the other neurotransmitters, including norepinephrine [266], serotonin [267, 268], and GABA [269], are likely involved, the role of glutamate is perhaps the most well studied [251, 252, 270–276]. On a molecular level, these changes are likely mediated by a host of transcription factors, but three in particular – the cyclic-AMP response element-binding protein (CREB) [277–281], Δ FosBand [282–287], and CaMKII [288–292] – have often been implicated in addiction (for review, see [293, 294]).

Role in Mood Disorders

Patients with mood disorders have been found to have a reduced accumbal activation on functional imaging [295] and reduced volume on structural imaging [296], and a number of studies have found alterations in the VTA-NAc pathway in animal models of depression (for review, see [297]). On a molecular level, a number of factors have been linked with depression. CREB-mediated transcription in the VTA-NAc pathway may be partly responsible for changes in mood, with studies suggesting that elevations of CREB within the NAc produce anhedonia, lowered affect, and decrease the rewarding effects of drugs of abuse [298–300]. Knocking out p11, a regulator of the cell surface localization of specific serotonin receptor subtypes, has been shown to induce depressive-like behaviors [301], which are reversed by p11 gene therapy in the accumbens [302]. Together, these findings suggest an accumbal role in mood disorders and depression, a notion bolstered by the positive outcomes of treatment-resistant depression in pilot studies of accumbal deep brain stimulation (DBS) [303, 304].

Surgery

Surgical Anatomy

While some studies have used the AC posterior border [305, 306], the posterior commissure (PC) [307], or the mid-commissural point [308, 309] as a reference point for determining DBS coordinates, the most often reported reference point is the anterior border of the AC at the midline [303, 304, 310–314], which has been recognized as the most reliable reference point because it is less affected by ventricular anatomy or the AC-PC distance [35] (see Mavridis and Anagnostopoulou [315]). A comprehensive anatomical examination has been done comparing both gross anatomical specimens and T2-weighted MR images in order to localize the NAc within the ventral striatum [41]. Pathological analysis of 32 cerebral hemispheres localized the NAc to a fairly variable area based upon hemisphere. However, in coronal sections 2 mm anterior to the AC, the NAc was found 6–9 mm anterior to the rostral border of the AC and 1–2 mm inferior to the AC regardless of hemisphere. A similar localization of the NAc was found in sagittal sections 7 mm lateral to the midline, with the NAc found to be 2–4 mm anterior to the rostral border of the AC. Radiologic study of T2-weighted MR images found the location of the NAc to vary depending on sex, age, and hemisphere, but it was determined that in transverse sections 4 mm ventral to the AC-PC plane (an often reported target point for NAc DBS), the NAc was always located between 1.8 and 3.6 mm anterior to the AC, regardless of age, sex, or gender. Coronal examination at sections 2 mm rostral to the border of the AC determined that the NAc was located 3.8–10.7 mm anterior to the rostral border of the AC and 0.8–3.7 mm inferior to the AC, while sagittal sections 8 mm lateral to the midline defined an area –3.8 to 7.0 anterior to the rostral border of the AC and 1.5–3.7 mm inferior to the AC, regardless of sex, age, and hemisphere examined.

Combining both MRI and gross anatomical findings, it was determined that in a coronal slice 2 mm anterior to the rostral border of the AC (another often cited target coordinate for NAc DBS), the area within 6–8 mm lateral to the midline and 0.8–2.0 mm inferior to the AC contained the NAc in every gross specimen and radiologic image analyzed. This finding, by identifying a reliable, standard localization of the NAc, presents an ideal target for the positioning of electrodes for DBS of the NAc (fig. 2). These suggested coordinates can be compared to the target coordinates used in previous NAc DBS surgeries (table 1).

Fig. 2. Radiological localization of the NAc. Coronal (a), axial (b), and sagittal (c) representation of the NAc (*) on reconstructed, thin-cut spoiled gradient recalled (SPGR) sequences. 1 = Caudate; 2 = putamen; 3 = internal capsule.

Table 1. Coordinates used for NAc DBS surgery

Study	Electrode (Medtronic model No.)	Lateral from midline, mm	Rostral to anterior AC, mm	Inferior to AC-PC, mm	Contact(s) activated for therapy
Mantione et al. [313]	3389	7	3	4	2 and 3
Denys et al. [316]	3389	7	3	4	2 and 3
Heinze et al. [326]	3389	6–8	2	3–4	0, 1, 2, and 3
Huff et al. [310]	3387	6.8–7.7	–2.1 to 2.3	2.2–6.5	0 and 1
Malone et al. [305]	3387	6–7	1–2 (measured from postborder of the AC)	3–4	0 and/or 1
Kuhn et al. [311]	3387	6.5	2.5	4.5	0, 1, 2, and 3
Kuhn et al. [312]	3387	7	1	4	1 and 2
Bewernick et al. [303]	3387	7.5	1.5	4	0 and 1
Müller et al. [328]	3387	6.5	2.7	4.5	0 and 1
Schlaepfer et al. [304]	3387	7–8	1.5	4	0 and 1
Voges et al. [317]	3387	6–8	2	3–4	0 and 1

The coordinates indicate the center of the deepest contact (contact 0). To date, the published studies cited above have all used Medtronic electrodes, although electrodes from other manufacturers are being tested currently. The distances between contacts in the Medtronic 3389 and 3387 electrodes are 0.5 and 1.5 mm, respectively.

From a practical standpoint, there appears to be a discrepancy whether the target coordinates refer to the final location of the electrode tip or the center of the deepest contact. Malone et al. [305] and Denys et al. [316] placed the tip of the electrode at the target coordinate, whereas Mantione et al. [313], Bewernick et al. [303], and Voges et al. [317] placed the center of the deepest contact at the target coordinates. This inconsistency highlights the need for a uniform surgical procedure to produce comparable results. However, based on the reported targeted coordinates presented in table 1, coupled with the NAc localization work presented by Mavridis et al. [41], placing the tip of the electrode at these coordinates, rather than the center of the deepest contact, would likely result in a more accurate

placement in the NAc. The trajectory in most cases passes through the anterior limb of the internal capsule, entering just anterior to the coronal suture and slightly lateral to the mid-pupillary line (fig. 3), although the exact trajectory can be influenced by the width of the lateral ventricle.

Ablation Studies

Bilateral ablation of the NAc has been attempted for the treatment of opiate [309, 318] and alcohol [319] addiction with evidence of efficacy, although following surgery, changes in personality characteristics, short-term memory, and attention have been noted [308]. Long-term follow-up notes continued effectiveness [318], but a lack of extensive long-term data has halted the use of ab-

Fig. 3. Representative trajectory for stereotactic neurosurgical access to the NAc. A reconstructed coronal view through the axis of a plane that traverses a cortical gyrus, the corona radiata, and the anterior limb of the internal capsule and finally ends in the NAc.

lative treatments, especially in light of the ethical concerns of intentionally causing irreversible damage to brain structures with as many cognitive and behavioral functions as the NAc.

Deep Brain Stimulation

DBS represents an adjustable and reversible method for the modulation of neural pathway activity. The success of DBS in improving motor function in dystonia, essential tremor, and Parkinson's disease [320, 321], with better stability and fewer adverse effects compared with lesion-

ing, has opened the door for trials evaluating its efficacy in treating a host of neurologic and psychiatric disorders. There have been a number of studies evaluating DBS of the NAc for the treatment of obsessive-compulsive disorder [310, 316, 322], Tourette syndrome [311, 323–325], depression [303–305], addiction to certain drugs of abuse, including alcohol [312, 326–329], heroin [330], and nicotine [313], and central pain syndrome [331, 332]. Given the known connections outlined above, it is not surprising that a recent large animal study supported the influence of NAc DBS on a variety of brain structures which could influence these and other psychiatric disorders [333]. Although the clinical studies are mostly preliminary and have used small numbers of patients, with some being observations of efficacy following DBS for a different indication, the relative safety and encouraging efficacy will likely promote more extensive clinical trials of human NAc DBS for various neuropsychiatric disorders.

Summary

The NAc is a complex and fascinating structure that has great influence over a variety of human behaviors. Clinical applications to date of focal surgical interventions into the NAc have been intriguing but likely represent only the beginning of what may become a very important area of clinical exploration for stereotactic neurosurgeons. A great deal of both animal and human data has provided a very detailed picture of the anatomy and physiology of the human NAc, but that knowledge is not exhaustive. Ongoing research into the role of this region in both normal and abnormal brain function should help facilitate further development of promising therapies targeted at this important region.

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