

Nucleus accumbens: a systematic review of neural circuitry and clinical studies in healthy and pathological states

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OBJECTIVE The nucleus accumbens (NAcc) of the ventral striatum is critically involved in goal- and reward-based behavior. Structural and functional abnormalities of the NAcc or its associated neural systems are involved in neurological and psychiatric disorders. Studies of neural circuitry have shed light on the subtleties of the structural and functional derangements of the NAcc across various diseases. In this systematic review, the authors sought to identify human studies involving the NAcc and provide a synthesis of the literature on the known circuitry of the NAcc in healthy and diseased states, as well as the clinical outcomes following neuromodulation.

METHODS A systematic review was conducted using the PubMed, Embase, and Scopus databases. Neuroimaging studies that reported on neural circuitry related to the human NAcc with sample sizes greater than 5 patients were included. Demographic data, aim, design and duration, participants, and clinical and neurocircuitry details and outcomes of the studies were extracted.

RESULTS Of 3591 resultant articles, 123 were included. The NAcc and its corticolimbic connections to other brain regions, such as the prefrontal cortex, are largely involved in reward and pain processes, with distinct functional circuitry between the shell and core in healthy patients. There is heterogeneity between clinical studies with regard to the NAcc indirect targeting coordinates, methods for postoperative confirmation, and blinded trial design. Neuromodulation studies provided promising clinical results in the context of addiction and substance misuse, obsessive-compulsive disorder, and mood disorders. The most common complications were impaired memory or concentration, and a notable serious complication was hypomania.

CONCLUSIONS The functional diversity of the NAcc highlights the importance of studying the NAcc in healthy and pathological states. The results of this review suggest that NAcc neuromodulation has been attempted in the management of diverse psychiatric indications. There is promising, emerging evidence that the NAcc may be an effective target for specific reward- or pain-based pathologies with a reasonable risk profile.

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KEYWORDS neuromodulation; nucleus accumbens; review; reward; functional neurosurgery

THE nucleus accumbens (NAcc) is the ventral portion of the striatum, which is the main input into the basal ganglia, receiving both direct input via excitatory glutamatergic projections from the amygdala, hippocampus, thalamus, and prefrontal cortex (PFC), as well as indirect input via dopaminergic projections from the

ventral tegmental area (VTA) and substantia nigra.^{1–4} The main efferent neurons from the NAcc project to several areas of the mesencephalon and basal ganglia and terminate in the diencephalon or pallidal complex.¹ On the basis of neurochemical and connectivity criteria, the NAcc can be divided into two anatomically and functionally distinct

ABBREVIATIONS ACC = anterior cingulate cortex; ALIC = anterior limb of the internal capsule; ASD = autism spectrum disorder; BOLD = blood oxygen level-dependent; CSTC = cortico-striatal-thalamo-cortical; DBS = deep brain stimulation; DTI = diffusion tensor imaging; FA = fractional anisotropy; fMRI = functional MRI; HDRS = Hamilton Depression Rating Scale; JBI = Joanna Briggs Institute; MD = mean diffusivity; MTL = medial temporal lobe; NAcc = nucleus accumbens; OCD = obsessive-compulsive disorder; OFC = orbitofrontal cortex; pACC = pregenual ACC; PFC = prefrontal cortex; PRISMA = Preferred Reporting Items for Systematic Reviews and Meta-Analyses; ROI = region of interest; SUD = substance use disorder; TBI = traumatic brain injury; TPv = ventral temporal pole; VTA = ventral tegmental area; Y-BOCS = Yale-Brown Obsessive-Compulsive Scale.

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subregions: the outer shell and central core.^{1,5} Information is generally transmitted from shell to core, whereby the shell is more related to the limbic system and the core to the extrapyramidal motor system.¹

The therapeutic effect of the NAcc is often attributed to its role in modulating the cortico-striatal-thalamo-cortical (CSTC) circuit, as it regulates emotion perception, cognitive flexibility, self-awareness, and executive function.^{1,6,7} The NAcc is central to goal- and reward-based behavior.¹ Structural and functional abnormalities of the NAcc or its associated neural systems have been shown to be involved in neurological and psychiatric disorders such as generalized anxiety, depression, and addictive behaviors,^{1,8} generating interest in the NAcc as a target for neuromodulation. Moreover, circuitry studies continue to shed light on the subtleties of the structural and functional derangements of the NAcc across various diseases, further contributing to an understanding of their pathophysiology. Given the complex circuitry involving the NAcc, neuromodulation of this one target can result in several behavioral changes.^{1,9} Single case reports for unique indications are often cited in reviews, exaggerating the therapeutic ability of the NAcc. NAcc neuromodulation has been reported to treat obsessive-compulsive disorder (OCD), depression, addiction (to alcohol, heroin, nicotine, and opium), Tourette syndrome, central pain syndrome, and both obesity and anorexia nervosa.^{1,8} In this paper, we present a review of human studies pertaining to clinical outcomes and neural circuitry of the NAcc in health and disease. These studies leveraged a broad range of tools, including structural and functional imaging, volumetric analyses, and network-based modeling. The goals of this study were to identify human studies involving the NAcc and provide a synthesis of the literature on the known clinical outcomes and circuitry of the NAcc in healthy and diseased states.

Methods

Search Strategy

A systematic review was performed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 statement to investigate the NAcc.¹⁰ PubMed MEDLINE (National Library of Medicine), Embase (Elsevier), and Scopus (Elsevier) databases were searched in January 2021 using search terms specified in the *Appendix*. The search strategy combined terms related to the NAcc and either neuromodulation treatments for any indication (DBS, Gamma Knife, radiofrequency, etc.) or imaging studies (diffusion tensor imaging [DTI], fractional anisotropy [FA], etc.). No restrictions on date of publication, article type, or language were used. No protocol was prepared or registered.

Screening and Study Selection

After the search was performed, duplicates were removed. The remaining articles were screened by title and abstract for relevance. Then, articles progressing to full-text review were screened based on prespecified inclusion and exclusion criteria. The inclusion criteria were: 1) studies written or translated into English; 2) full-text

availability; 3) human studies involving neurocircuitry or clinical outcomes of neuromodulation related specifically to the NAcc; and 4) sample size greater than 5 patients. The exclusion criteria were: 1) animal studies; 2) conference abstracts, reviews, and commentaries; and 3) studies reporting nonprimary data. Each title and abstract were independently examined by two authors (N.A.S., K.K.Z.) to identify eligible studies. Similarly, the two authors independently reviewed full texts. At both stages, a third author (H.Y.) resolved any discrepancies after group discussion and consensus.

Data Extraction and Analysis

Within the studies that met the inclusion criteria, a review of study characteristics including bibliographic data, aim, design and duration, participants, and neurocircuitry details and outcomes was conducted. The Joanna Briggs Institute (JBI) quasi-experimental assessment tool was used to specify the risk of bias for each included study (Supplementary Table 1).¹¹ Four authors (N.A.S., K.K.Z., Y.J., and H.Y.), in groups of two, independently reviewed the 123 studies included in the analysis based on the nine outlined JBI metrics of potential bias; any discrepancies were resolved with discussion. The overall risk of bias for this systematic review was determined by considering the risk of bias of all included studies.

Results

Included Studies

The search strategy identified 3591 records, of which 2416 studies underwent title and abstract review, and 304 studies received full-text review (Fig. 1). There were ultimately 34 studies reporting on NAcc neuromodulation with clinical outcomes and 89 studies reporting on neural circuitry of the NAcc. Most studies had a moderate quality, with only 15 of 123 studies meeting all nine JBI criteria (Supplementary Table 1). The risk of bias for most included studies was moderate, predisposing this systematic review to a moderate risk of bias overall.

Overview

Among the included studies regarding NAcc neurocircuitry, 7 described anatomy and physiology, 15 focused on reward, and 10 examined pain, all in healthy patients. The remainder of the articles investigated the NAcc in the context of addiction ($n = 15$), OCD ($n = 6$), schizophrenia ($n = 5$), autism spectrum disorder (ASD; $n = 4$), mood disorders ($n = 4$), traumatic brain injury (TBI; $n = 4$), neurodegenerative diseases ($n = 9$), epilepsy ($n = 3$), obesity ($n = 3$), and miscellaneous others ($n = 3$). Among the included clinical studies regarding NAcc neuromodulation, there were 18 reporting on deep brain stimulation (DBS) for the treatment of OCD, 9 reporting on ablation or DBS for substance use disorders (SUDs), 2 reporting on radiofrequency ablation or DBS for anorexia, 3 reporting on DBS for depression, and 1 study of DBS to treat epilepsy. These studies are outlined in Supplementary Tables 2–4 and 6. There were 16 studies that reported on indirect targeting coordinates of the NAcc based on preoperative imaging (Table 1).^{7,12–26}

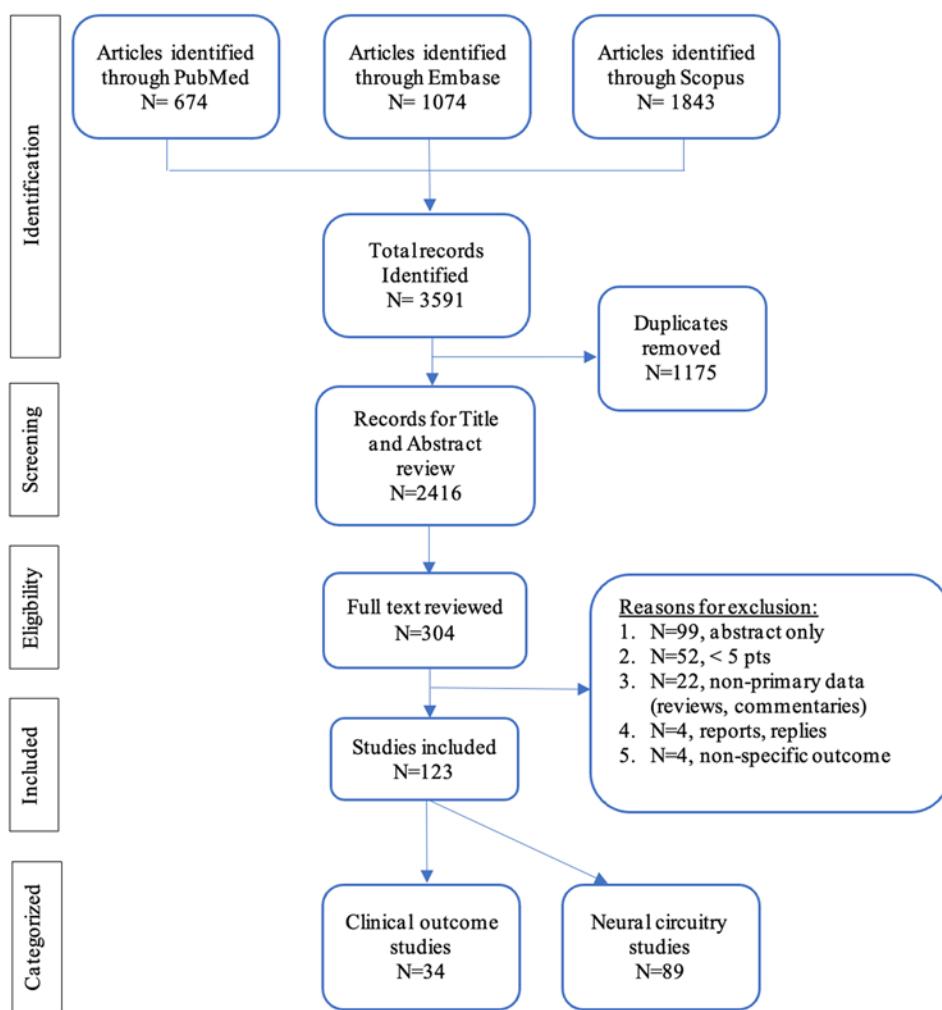


FIG. 1. PRISMA flowchart. This flowchart details the process for database searches and screening used to identify articles for inclusion in this systematic review. Figure is available in color online only.

Anatomy and Physiology in Healthy Patients

In healthy patients (Table 2), the average NAcc is estimated to be $10.5 \times 14.5 \times 7.0$ mm on MRI.⁵ Gillespie et al.²⁷ reported that genetics accounted for 54% of the variation in bilateral NAcc volume and mean diffusivity (MD). The NAcc core and shell can be visualized by clustering individual voxels of connectivity profiles from diffusion-based probabilistic tractography (Fig. 2).⁹ Using this method, it was found that the NAcc core has greater connectivity to the frontal pole and orbitofrontal cortex (OFC), while the shell has greater connectivity to the temporal pole, amygdala, and anterior cingulate cortex (ACC).²⁸ The NAcc is part of a broader network involving the PFC, striatum, and medial temporal lobe (MTL), during both resting states and picture recall tasks.^{28–31} It also produces and regulates emotional laughter through its connections within the network consisting of the pregenual ACC (pACC), ventral temporal pole (TPv), and ventral striatum.³⁰

In studies of reward-related NAcc functional connectivity, the robustness of white matter microstructure con-

nnecting the NAcc and OFC is positively correlated with bilateral NAcc reward-related activation, delayed gratification, and sensitivity to reward cues.^{32–34} The blood oxygen level-dependent (BOLD) signal—a measure of brain activity—of the NAcc is selectively increased bilaterally during moments of high curiosity, perception of pleasant or emotionally arousing cues, and reward processing.^{32,34–39} Generally, NAcc activation during reward-based tasks increased with the age of the participants.^{36,38,40} Three studies^{40–42} examined the effects of pharmacological interventions on the NAcc during reward-based tasks: BOLD signals increased in the right NAcc upon exposure to pleasant reward cues and levodopa or arginine vasopressin hormone.

In understanding the role of the NAcc in relation to pain, several studies described pain-related connectivity of the NAcc to the PFC (Supplementary Table 6). Functional connectivity—measured by FA—between the NAcc and bilateral medial PFC is thought to be significantly increased among individuals who recovered from pain when compared to those who experience chronic pain.^{43–46}

TABLE 1. Indirect targeting of the NAcc

| Authors & Year | Preop Imaging | Frame/Navigation | Reference Point | Coordinates, mm | | | Verification |
|---|---|--|------------------|-----------------|----------------|----------------|---------------------------|
| | | | | X (lat) | Y (ant/pst) | Z (sup/inf) | |
| Barcia et al., 2019 ¹² | CT + MRI (2.3-mm slices, 0-mm interval) | Medtronic StealthStation Treon Navigation System | Ant border of AC | ± 6.5 | + 4.5 | + 2.5 | Intraop x-ray & postop CT |
| Bewernick et al., 2012 ¹³ | MRI | Leksell stereotactic frame | Ant border of AC | ± 7.5 | + 1.5 | + 4.0 | Intraop x-ray & postop CT |
| Chen et al., 2019 ⁷ | MRI (2-mm slices, 0-mm interval) | Leksell stereotactic frame | MCP | ± 6–9 | + 16–18 | + 4–6 | Postop MRI |
| Conen et al., 2018 ¹⁵ | MRI | Leksell stereotactic frame | AC | NA | + 5 | NA | Periop MRI |
| Denys et al., 2010 ¹⁶ | MRI | NA | Ant border of AC | ± 7 | + 3 | + 4 | Postop CT/x-ray |
| Fang et al., 2012 ¹⁴ | CT or MRI | Leksell G stereotactic frame | NA | ± 10 | + 1 | + 2 | NA |
| Figuee et al., 2013 ¹⁷ | MRI (1-mm slices) | NA | Ant border of AC | ± 7 | + 3 | + 4 | Postop CT |
| Gao et al., 2003 ¹⁸ | CT (3-mm slices, 2-mm interval) | CRW stereotactic frame | MCP | ± 4–10 | + 19–23 | + 7–9 | NA (ablation) |
| He et al., 2008 ¹⁹ | CT (3-mm slices, 2-mm interval) | CRW stereotactic frame | MCP | ± 4–10 | + 19–23 | + 7–9 | NA (ablation) |
| Li et al., 2013 ²⁰ | MRI (2- to 3-mm slices, 0-mm interval) | CRW stereotactic frame | AC | ± 6.0–6.5 | + 5–6 | + 5.5–6.0 | NA (ablation) |
| Liu et al., 2020 ²² | MRI | Leksell stereotactic frame | AC | ± 4 | + 3 | + 6 | Postop MRI |
| van den Munckhof et al., 2013 ²¹ | MRI (1-mm slices) | NA | Ant border of AC | ± 7 | + 3 | + 4 | Postop CT |
| Schmitt et al., 2014 ²³ | MRI | NA | AC | ± 6–8 | + 3–4 | + 2 | Intraop x-ray & postop CT |
| Voges et al., 2013 ²⁴ | MRI | NA | AC | ± 6–8 | + 3–4 | + 2 | Intraop x-ray & postop CT |
| Wang et al., 2013 ²⁵ | MRI, 3-mm slices, 0-mm interval | CRW stereotactic frame | MCP | ± 4–10 | + 19–23 | + 7–9 | NA (ablation) |
| Wu et al., 2010 ²⁶ | MRI, 3-mm slices, 0-mm interval | CRW stereotactic frame | MCP | ± 4–10 | + 19–23 | + 7–9 | NA (ablation) |

AC = anterior commissure; Ant = anterior; CRW = Cosman-Roberts-Wells; inf = inferior; lat = lateral; MCP = midcommissural point; NA = not applicable; pst = posterior; sup = superior.

Addiction and SUD

SUD (alcohol or illicit drug dependence or abuse) is a pervasive neuropsychiatric condition. The dopamine-driven NAcc plays a critical role in addictive behaviors as it mediates the reinforcing properties of reward and drug relapse (Supplementary Table 2).

Fifteen neuroimaging studies, including 473 patients with a personal or family history of substance use, reported on the involvement of the NAcc in the context of addictive behaviors. These studies revealed that a number of substances can influence the accumbens, including alcohol,^{47–49} opiates,⁵⁰ heroin,⁵¹ methamphetamine,^{52,53} and nicotine.^{54–57} Individuals with methamphetamine or alcohol addiction generally exhibit reduced FA in tracts projecting from the NAcc to the frontal cortex relative to healthy controls.^{48,52}

Although no significant volumetric differences were reported, a study of DTI data revealed reduced MD and radial diffusivity in white matter tracts connecting the NAcc to the OFC in individuals with a family history of alcohol use disorder, when compared to controls.^{58,59} With regard to smoking addiction, high-dependent smokers demon-

strated significantly enhanced left NAcc–right amygdala connectivity, whereas low-dependent smokers had reduced bilateral NAcc–right amygdala, -ACC, and -VTA connectivity.⁵⁵ DTI studies have also reported reduced FA in tracts projecting from the bilateral NAcc to the frontal cortex.^{54,56} Similarly, individuals with opioid addiction present with increased NAcc connectivity to the ACC and OFC, but reduced connectivity to the anterior insula and inferior parietal cortex, when compared to healthy controls.⁵⁰ In contrast, individuals with methamphetamine addiction demonstrated significant FA reduction in the NAcc,^{52,53} whereas lower-right NAcc FA was associated with a longer duration of methamphetamine use.⁵² Individuals with heroin addiction were found to have reduced NAcc volume relative to healthy controls,⁵¹ thus highlighting the importance of further analyzing NAcc volumes in different SUDs to improve precise neuromodulatory targeting.

Radiofrequency ablation has been used to treat severe opioid,^{18,19,60} heroin,^{14,20} and alcohol²⁶ addiction in six unique patient cohorts based in China. Although no consistent outcome measure was reported, several studies reported nonrelapse rates at different follow-up times.^{18,20}

TABLE 2. Neurocircuitry of the NAcc in healthy states

| Authors & Year (country) | Participants | Imaging | Structure | Setting | Findings |
|---|---|---|---|---|---|
| Neto et al., 2008 ⁵ (Portugal) | 12 healthy | MRI | Bilat NAcc | Postmortem histology | 10.5 × 14.5 × 7.0 mm |
| Kahn et al., 2013 ²⁹ (Israel) | 994 healthy | fMRI (ROI-based) | Bilat NAcc | Resting state | Part of a broad PFC-striatal-MTL network |
| Lucas-Neto et al., 2015 ²⁸ (Portugal) | 10 healthy | DTI (voxel-based, probabilistic tractography) | Bilat NAcc | Resting state | NAcc divided into core & shell division |
| | | | Bilat NAcc core | Resting state | Greater connectivity to frontal pole & OFC |
| | | | | Resting state | Greater connectivity to temporal pole, amygdala, & anterior cingulate |
| Coynel et al., 2017 ³¹ (Switzer- land) | 664 healthy | DTI (volumetric analysis) | Lt NAcc | Episodic memory task, successful picture recall | Structural connectivity w/ insula, superior temporal lobe, temporal pole, fusiform, inferior temporal lobe |
| Gillespie et al., 2017 ²⁷ (USA) | 387 healthy twins (83 MZ, 55 DZ, 111 incomplete) | DTI (volumetric analysis) | Bilat NAcc | Resting state | 54% volume & mean diffusivity variation accounted for by genetics |
| Cartmell et al., 2019 ⁹ (USA) | 245 healthy | MRI (volumetric analysis & probabilistic tractography) | NAcc ventral posteromedial & dorsal anterolateral | Resting state | ≥91% overlap across all subjects |
| Gerbella et al., 2020 ³⁰ (Italy) | 15 healthy | DTI (probabilistic tractography) | Bilat NAcc | Resting state | Connected to brainstem via hypothalamus & mammillo-tegmental tract Connections to TPv in 15/15, NAcc-TPv overlaps w/ uncinate fasciculus Connections to pACC in both hemispheres (lt 12/15, rt 13/15) & NAcc-pACC overlaps w/ anterior cingulate bundle |

DZ = dizygous; MZ = monozygous.

^{26,60} Between 12 and 15 months, the nonrelapse rate was approximately 75%, and between 5 and 8 years,^{18,26} the nonrelapse rate was approximately 62%,^{20,60} an improvement on the 50% nationwide 5-year nonrelapse rate.²⁰

DBS of the NAcc has also shown some efficacy in managing alcohol use disorder. Notably, in a small German

cohort, 2 of 5 patients with alcohol use disorder demonstrated improvements in the Alcohol Urge Questionnaire, decreased craving for alcohol, and remained completely abstinent for more than 4 years.⁶¹ In an open-label pilot study, Chen et al.⁷ also reported improvement in addiction symptoms, in which 5 of 8 patients with alcohol use

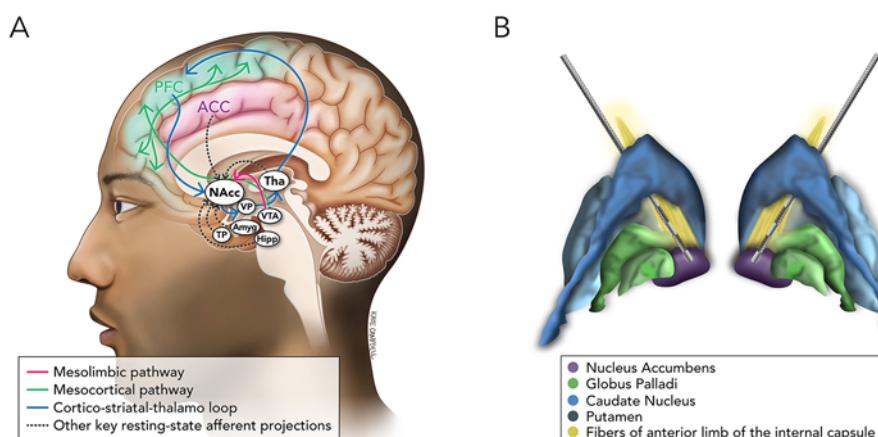


FIG. 2. NAcc circuitry and anatomy. **A:** Schematic of the major cortical and limbic connections to and from the NAcc. Amyg = amygdala; Hipp = hippocampus; Tha = mediiodorsal nucleus of thalamus; TP = temporal pole; VP = ventral pallidum. **B:** Illustration of the relative anatomy of the NAcc in relation to the ALIC, globus pallidi, caudate, and putamen. © Han Yan, published with permission. Figure is available in color online only.

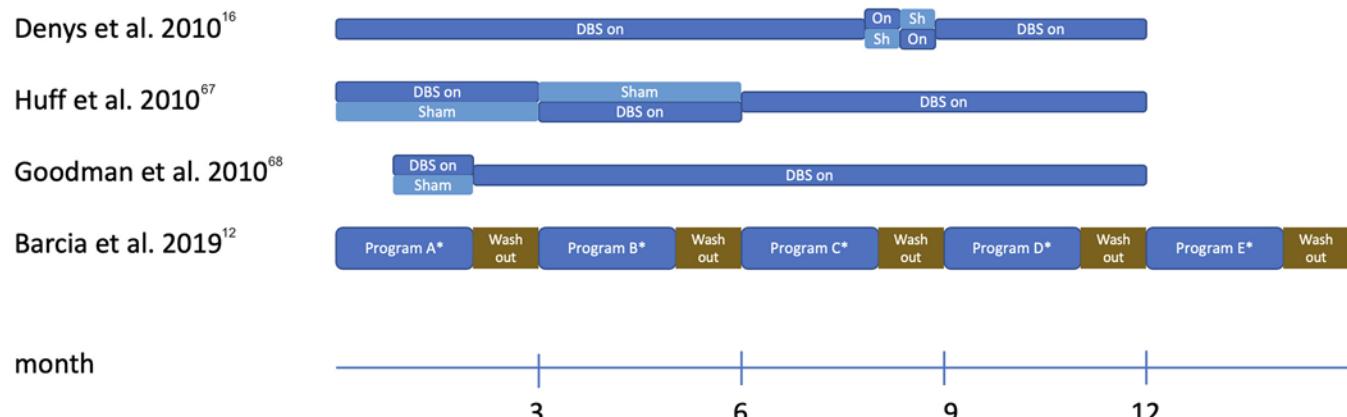


FIG. 3. Timeline of blinded DBS studies observing the outcomes of patients with OCD. Sh = Sham. *Randomized sequence of contact activations (C0, 1, 2, 3) including sham activation of 0 V. Figure is available in color online only.

disorder treated with NAcc and anterior limb of the internal capsule (ALIC) DBS became abstinent for more than 3 years. Positron emission tomography in these patients found that after 6 months of active stimulation, glucose metabolism increased in the left anterior lobe of the cerebellum, left angular gyrus, both sides of the middle temporal gyrus, bilateral inferior frontal pars opercularis, right supramarginal gyrus, left inferior frontal gyrus, and right precuneus; the latter two structures are known to be critically involved in decision-making.

OCD

Six articles involving 134 patients with OCD and 113 controls examined neurocircuitry (Supplementary Table 3). No significant differences in NAcc volume have been reported between OCD patients and matched healthy controls.^{17,62–66} However, Narayanaswamy et al.⁶⁴ revealed a significant negative correlation between the right NAcc volume and Yale-Brown Obsessive-Compulsive Scale (Y-BOCS) score. Three OCD-related studies reported reduced NAcc activity among patients with OCD in comparison to healthy controls.^{17,62,63} Using region of interest (ROI)-based functional MRI (fMRI), it was found that the NAcc of OCD patients had heightened connectivity to the lateral PFC and left ventral striatum and reduced connectivity to the OFC.^{17,63,66} It is also thought that drug-resistant patients with OCD have significantly reduced left NAcc FA than non-drug-resistant patients, which is negatively associated with patient symptom severity.⁶⁵

An additional 18 studies with 7 unique cohorts, comprising 73 patients aged 21–59 years, described DBS of the NAcc for the treatment of OCD.^{12,16,67–71} Of the 73 patients, 40 (54.8%) were classified as DBS responders, although this definition varied from 35% to 50% reduction in Y-BOCS score between studies. In total, 17 studies targeted the bilateral NAcc. In the study by Huff et al.,⁶⁷ 5 of 10 patients with right NAcc DBS experienced a ≥ 25% improvement in Y-BOCS score at 12 months. Analysis of the baseline and follow-up means of the Y-BOCS in 6 studies presenting unique cohorts demonstrated a fixed-effects size of -1.63 (95% CI -2.10 to -1.18, $p < 0.001$) and a random-effects size of -1.66 (95% CI -2.25 to -1.07, p

< 0.001), with a heterogeneity $I^2 = 0.0\%$ (95% CI 0.0%–69.6%).^{12,16,67–69,71} Four studies,^{12,16,67,68} 3 of which were randomized controlled trials,^{12,16,68} utilized a double-blind study design to examine differences in symptomatology between active and sham stimulation. Although all 4 studies were blinded sham stimulation designs, four completely different protocol schedules were developed to measure the same outcome (Fig. 3). Only the study by Denys et al.¹⁶ demonstrated a significant 25% Y-BOCS score difference between sham stimulation and control in a 4-week phase following 8 months of stimulation.

Mood Disorders

Four studies investigated the NAcc in 68 patients with depression and 51 controls (Supplementary Table 4). No differences in NAcc FA were observed between patients with melancholic depression, nonmelancholic depression, and controls.⁷² In a study examining connectivity patterns of two common targets for DBS in intractable major depression, Gutman et al.⁷³ indicated that both the subcallosal cingulate white matter and ALIC had connections to the NAcc, among other regions. Furthermore, DBS-responsive patients with treatment-resistant depression were found to have connections between the bilateral NAcc and subgenual ACC, but only minimal connections to the pACC.⁷⁴ Two studies examined NAcc structural and functional connectivity across 54 patients with bipolar disorder and 67 controls.^{75,76} Haller et al.⁷⁵ found that individuals with bipolar disorder had a lower gray matter concentration in the NAcc, while Caseras et al.⁷⁶ noted increased BOLD signals in the NAcc in patients with bipolar I and II disorder compared to healthy controls.

Three studies described the effect of NAcc-DBS on depression, providing clinical outcomes on 18 different patients through two unique cohorts.^{13,15,77} The ages of patients ranged from 31 to 65 years, and both the Hamilton Depression Rating Scale (HDRS) and the Montgomery-Asperg Rating Scale of Depression were utilized as primary outcomes. Bewernick et al.^{13,78} demonstrated that 5 of 11 patients were responders to DBS, achieving 50% reduction in the HDRS-28. The same group demonstrated cognitive safety of NAcc-DBS through serial neuropsychological

tests performed over 12 months.⁷⁷ Conen et al.¹⁵ implanted 4 electrodes targeting both the subcallosal cingulate gyrus and the NAcc in 7 patients, stimulating independent and combinations of electrodes within these targets. Five of 7 patients responded to DBS, although 3 remitted.

Complications From NAcc Neuromodulation

The most commonly reported nonstimulation-related complication was impaired memory or concentration and temporary incisional site pain (Supplementary Table 5). Two patients who received NAcc-DBS for depression subsequently committed suicide, although these acts were judged to be unrelated to the DBS and rather the severe depression for which the DBS was unsuccessful in treating. With regard to stimulation-related adverse effects, new-onset hypomania or psychosis was commonly cited in 22 patients. Only 2 of these patients required mood stabilizing therapy; the majority of patients only experienced transient changes in mood, often related to stimulation changes.⁶⁹

Discussion

Although the NAcc has increasingly been recognized as an important regulator of emotional, motivational, and psychomotor processes,^{1,8} the full scope of its functions remains unknown, necessitating further investigation regarding its role and pathophysiology in healthy individuals and in neuropsychiatric disorders, respectively. Imaging modalities, such as DTI and fMRI, have been particularly useful in these endeavors. We systematically reviewed the existing literature examining volumetric, neurocircuitry, and functional aspects of the NAcc in healthy patients and those with neurological and psychiatric disorders. Furthermore, we reviewed patients undergoing NAcc neuromodulation for a variety of indications. The establishment of causal effects following NAcc neuromodulation is complicated by several factors: 1) the NAcc is targeted for many indications in small case reports, with only 19 studies reporting on 5 or more patients; 2) study designs and measurements of primary outcomes were not standardized; and 3) there is a lack of understanding of the mechanisms leading to clinical response and adverse effects.

Anatomy

The NAcc has been a long-standing target of interest for stereotactic neurosurgical intervention, creating the drive to further characterize its anatomy for optimal surgical planning. It is generally a target with challenging borders, particularly at the anterior and rostral area, where the internal capsule arises between the caudate and putamen. Nonetheless, it remains sufficiently distinct from these neighboring structures to establish constant stereotactic coordinates.⁵ While the oft-touted central core and surrounding shell are not visible with conventional imaging methods,⁵ the two structures have been distinguished using postmortem histological analysis.⁹ Confirming the existence of the shell and core within the human NAcc is significant given the numerous animal studies that have proposed a histological, electrophysiological, and cellular distinction between the two, with subsequent impacts on their

role in various pathologies such as addictive behaviors and mood disorders.¹

Connectivity

Imaging studies of healthy individuals suggest the NAcc is a component of the PFC-striatal-MTL network, with distinct connectivity to other regions between the core and shell.^{28,29,32} The NAcc modulates reward, with increased activation during positive emotions or thoughts following investigative tasks. The integrity of white matter within relevant circuits may influence reward-based learning and responsiveness by altering the efficiency of information transfer.^{32,44,79} Additionally, the NAcc is involved in pain. Although positive phasic NAcc activation at stimulus onset and offset are associated with stimulus salience, responses differ between the shell and core.^{43,79} Greater connectivity is deleterious, representing a risk factor for the persistence of pain.⁴⁶ However, NAcc-PFC connectivity adapts to increased pain modulatory capacity by inhibiting the emotional value of painful stimuli, mediating the effects of cognitive self-regulation of pain.^{45,80}

NAcc Indications for Treatment

Despite the many cited indications of NAcc neuromodulation, the larger studies investigated NAcc-DBS and radiofrequency ablation in the treatment of OCD and substance abuse, respectively. A growing base of evidence has sought to target the NAcc for the treatment of depression and anorexia.

These indications are supported by the perceived role of the NAcc in goal- and reward-based behaviors. Specifically, the repetitive behaviors seen in both OCD and substance use may be associated with altered reward perception and error recognition.^{1,41,62,66} The NAcc became a target of interest for OCD after Greenberg et al. noted optimal ALIC-DBS results with posteriorly implanted electrodes. These posterior electrodes are suspected to be where the CSTC network and corticobasal fibers converge, and the caudal NAcc emerged as a feasible neuromodulation target.⁶

Other indications for NAcc-DBS, such as schizophrenia, TBI, Tourette syndrome, obesity, and self-injurious behaviors, have been reported, but were not included in the systematic review, as they consist of case studies or small sample sizes (i.e., n < 5). The mechanistic underpinnings that subserve the clinical effect of NAcc neuromodulation are not fully elucidated. Neuroimaging studies continue to identify the neural correlates of psychiatric disorders, such as comparisons of NAcc volume, activity, and functional connectivity between patients and controls.

Limitations

This study is limited because only published studies with full-text English manuscripts were included, leading to publication bias. The risk of bias was moderate given that the majority of studies were moderate-quality cohort studies. Many of the studies had low sample sizes, perhaps underpowering them to detect significant differences between patients with a given condition and healthy controls. No meta-analysis was conducted because the

heterogeneity of the studies prevented us from drawing statistically significant conclusions from our results. Regarding the clinical neuromodulation of the NAcc, many included studies also selected patients without accompanying psychiatric comorbidities, limiting the generalizability of these results. The absence of controlled studies also limits the scope of statistical analysis. Notably, there are subtle variations across studies with respect to electrode placement and stimulation parameters, interfering with the accuracy of the results. Nonetheless, we present a comprehensive review of the existing literature on the volumetry, neurocircuitry, function, and neuromodulation of the NAcc. Future studies are necessary to investigate the functions and connections of the NAcc in greater detail, characterize its response to pathological states, and elucidate its role in yet-under-researched conditions.

Conclusions

The clinical results of our review suggest that the NAcc neuromodulation is a feasible target for well-selected patients with OCD and substance abuse, with a favorable side-effects profile; the lack of robust controlled studies precludes more definitive conclusions regarding effectiveness. The NAcc maintains connections to other brain regions such as the PFC and is involved in reward and pain, with differential responses between the shell and core. The volume of the NAcc is reduced in people who experience substance use, have TBI, or have Parkinson's disease. FA is decreased in people with pain, addiction, depression, ASD, multiple sclerosis, Huntington's disease, epilepsy, and Tourette syndrome. Other measures such as MD, axial diffusivity, radial diffusivity, and BOLD signals are infrequently described and vary by condition. The multifunctionality of the NAcc, as a result of its many corticolimbic connections, emphasizes the importance of studying the NAcc of patients in healthy and pathological states.

Acknowledgments

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Appendix

Search terms and search strategy:

PubMed: 673 citations found

("nucleus accumbens"[MeSH] OR "nucleus accumbens"[tiab]) AND ("deep brain stimulation"[MeSH] OR "radiosurgery"[MeSH] OR "deep brain stimulation*"[tiab] OR "dbs"[tiab] OR "neuromodulat*"[tiab] OR "gamma knife"[tiab] OR "radiosurg*"[tiab] OR "thermal ablat*"[tiab] OR "thermoablat*"[tiab] OR "thermo-ablat*"[tiab] OR "diffusion tensor imag*"[tiab] OR "dti"[tiab] OR "fiber tractograph*"[tiab] OR "fractional anisotrop*"[tiab])

Embase: 1074 citations found

("nucleus accumbens"):ti,ab,kw AND ("deep brain stimulation*" OR "dbs" OR "neuromodulat*" OR "gamma knife" OR "radiosurg*" OR "thermal ablat*" OR "thermoablat*" OR "thermo-ablat*" OR "diffusion tensor imag*" OR "dti" OR "fiber tractograph*" OR "fractional anisotrop*"):ti,ab,kw

Scopus: 1843 citations found

TITLE-ABS-KEY(("nucleus accumbens") AND ("deep brain stimulation*" OR "dbs" OR "neuromodulat*" OR "gamma knife" OR "radiosurg*" OR "thermal ablat*" OR "thermoablat*") OR

"thermo-ablat*" OR "diffusion tensor imag*" OR "dti" OR "fiber tractograph*" OR "fractional anisotrop*"))

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Disclosures

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

Author Contributions

Conception and design: Ibrahim, Yan. Acquisition of data: Yan, Shlobin, Jung, Zhang. Analysis and interpretation of data: Yan, Shlobin, Jung, Zhang. Drafting the article: Yan, Shlobin, Jung, Zhang. Critically revising the article: all authors. Reviewed submitted version of manuscript: all authors. Approved the final version of the manuscript on behalf of all authors: Ibrahim. Statistical analysis: Shlobin. Administrative/technical/material support: Ibrahim, Kulkarni. Study supervision: Ibrahim, Kulkarni.

Supplemental Information

Online-Only Content

Supplemental material is available with the online version of the article.

Supplementary Tables and Results. <https://thejns.org/doi/suppl/10.3171/2022.5.JNS212548>.

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