

Trends

in Psychiatry and Psychotherapy

JOURNAL ARTICLE PRE-PROOF **(as accepted)**

Review Article

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<http://doi.org/10.47626/2237-6089-2025-1046>

Original submitted Date: 14-Jan-2025

Accepted Date: 24-Apr-2025

This is a preliminary, unedited version of a manuscript that has been accepted for publication in Trends in Psychiatry and Psychotherapy. As a service to our readers, we are providing this early version of the manuscript. The manuscript will still undergo copyediting, typesetting, and review of the resulting proof before it is published in final form on the SciELO database (www.scielo.br/trends). The final version may present slight differences in relation to the present version.

Association between Nucleus Accumbens Volume and Substance Use Disorder: A Narrative Review

Short Title: Nucleus Accumbens Volume in Substance Use Disorder

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Abstract

Introduction: The nucleus accumbens (NAc) is central to the brain's reward circuitry, mediating motivation and emotional processes. Emerging evidence suggests that structural and functional changes in the NAc, including volume alterations, may contribute to the neuropathology of substance use disorder (SUD). This review evaluates current findings on the association between NAc volumetric changes depicted by magnetic resonance imaging (MRI) and SUD.

Methods: A literature search was conducted in PubMed, EMBASE, BVS, Web of Science, Scopus, Cochrane Library, and PsycINFO. Terms used in searches included Nucleus Accumbens, Mental Disorder, Substance Use Disorder, Drug Addiction, and Magnetic Resonance Imaging (MRI). The main findings from the selected studies were synthesized in a table.

Results: The initial database searches yielded 3686 articles. After screening, duplicate articles, non-English/Spanish/Portuguese articles, animal studies, and studies that did not address SUD were excluded. Additional exclusion criteria included studies involving only familial risk of substance use or abstinence, as well as studies without NAc analysis or structural MRI analysis. 52 cross-sectional studies regarding associations between NAc volumes and SUDs were selected.

Conclusion: The reviewed studies suggest that NAc may play a pivotal role as an associated factor in addiction, with strong associations mainly to cigarette smoking and alcohol use. Other substances show inconsistent findings. Discrepancies in results may reflect differences in study designs, type of volumetric analysis employed, and control over confounding variables. Future studies with multimodal approaches and control of confounding variables are required to strengthen these associations.

Keywords: nucleus accumbens, volume, MRI, substance use disorder.

Introduction

The nucleus accumbens (NAc) is part of the ventral striatum and composes the limbic-motor interface (1,2). According to medical literature, it is the principal input nucleus of the basal ganglia (3). NAc neurons receive direct glutamatergic projections from the amygdala, hippocampus, thalamus, and prefrontal cortex (PFC) and receive indirect mesolimbic dopaminergic projections from the ventral tegmental area (VTA) and substantia nigra. NAc neurons send output mainly to the mesencephalon and basal ganglia, in the form of medium spiny neurons (1–3). The NAc plays a pivotal role in mediating motivation and emotional circuitry, as well as the effect of psychoactive drugs (1).

The nucleus accumbens (NAc) was historically named for its location. Its original name, *nucleus accumbens septi*—literally, "the nucleus leaning against the septum"—reflects its anatomical position, as the region where the putamen and caudate nucleus appear to merge leans against the base of the septum pellucidum (4). The NAc extends dorsolaterally to the putamen and dorsomedially to the caudate nucleus, with no

distinct boundary between these two nuclei (Figure 1) (4,5). Anatomical studies suggest that the NAc is longest along the anteroposterior axis and shortest along the dorsoventral axis. According to the literature (4,5), the proposed boundaries of the NAc are as follows: **Posterior boundary**: the posterior edge of the anterior commissure; **Anterior boundary**: the rostral edge of the internal capsule, where it begins to separate the caudate from the putamen; **Medial boundary**: the sagittal plane passing through the inferior border of the lateral ventricle; and **Lateral boundary**: a line extending downward and laterally to the rostral edge of the internal capsule.

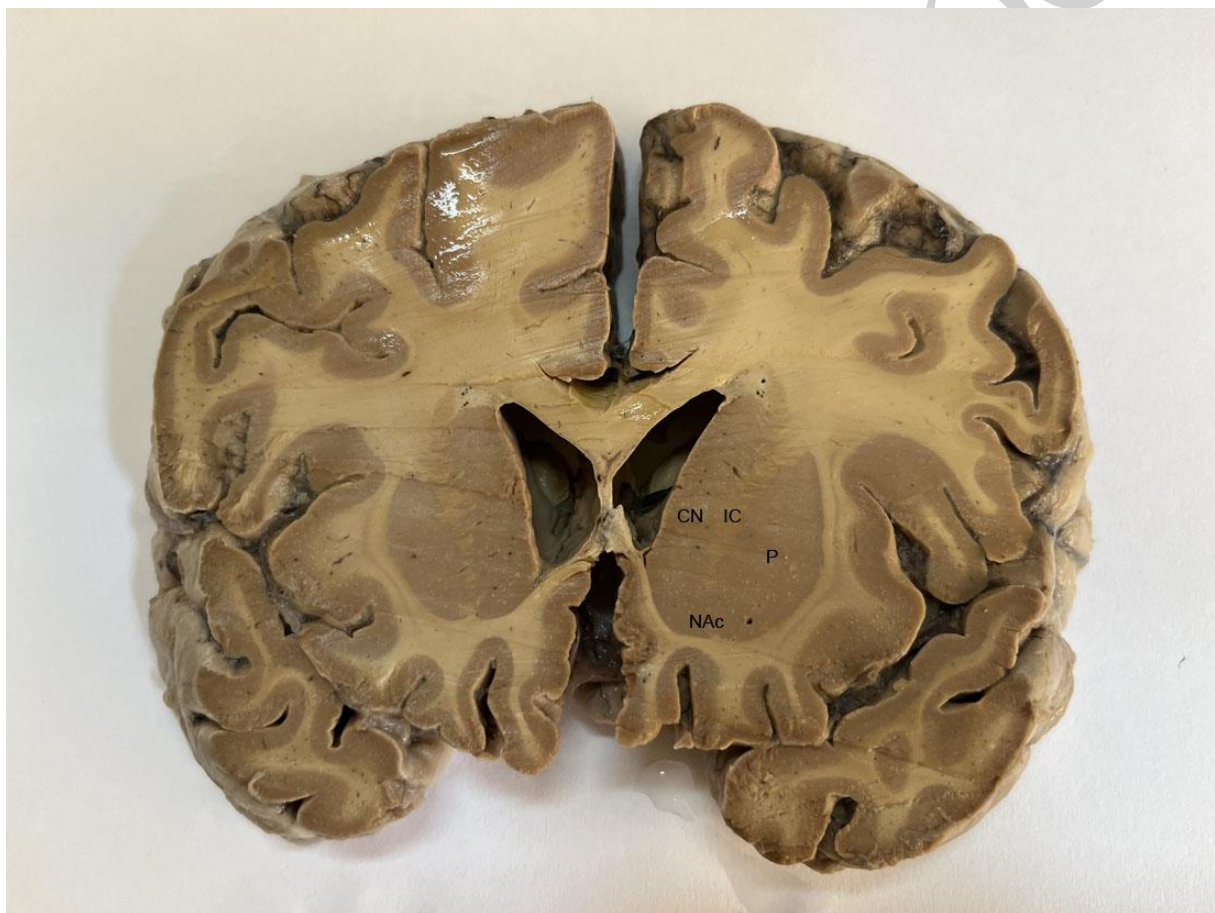


Figure 1. Frontal section of the human brain through the rostral end of the corpus striatum and the rostrum of the corpus callosum. **CN**, caudate nuclei; **IC**, internal capsule; **P**, putamen; **NAc**, nucleus accumbens.

The anatomy of NAc can be evaluated through Magnetic Resonance Imaging (MRI). Mavridis et al. (2011) found that this nucleus is best visualized in coronal MRI slices, as shown in Figure 2. They were able to identify NAc's precise limits with the caudate

nucleus and putamen, specifically with the use of T2-weighted MRIs, due to the slightly more intense MR signal of this nucleus compared to the adjacent nuclei (6). MRI can also be used to measure the NAc volume. The mean raw NAc volume was determined as 473.3 mm³ (SD=±106.8) and the normalized mean as 0.00032 mm³ (SD=±0.00007) (7).

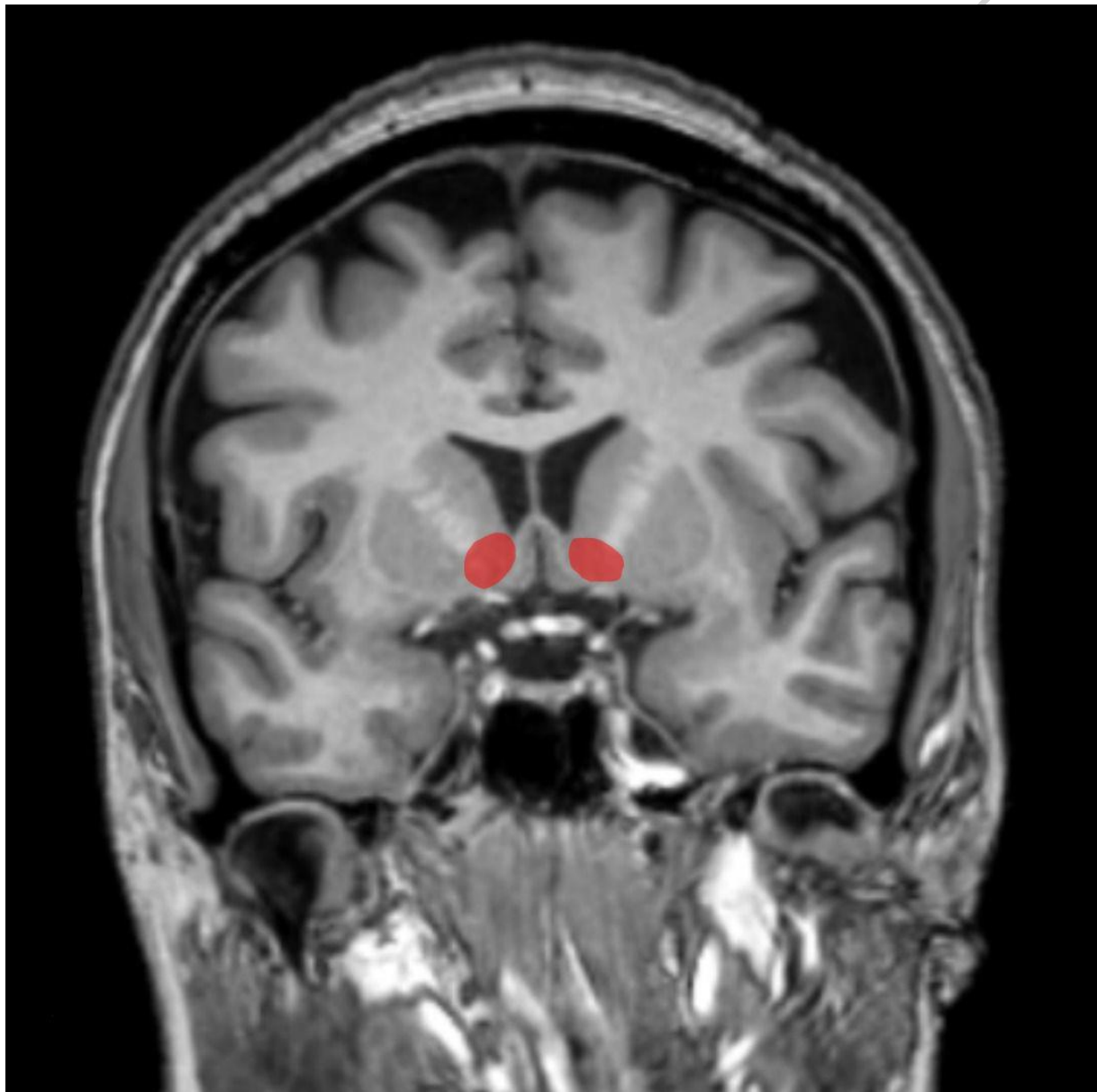


Figure 2: T1-weighted MRI frontal slice showing the Nucleus Accumbens (NAc) and its limits with the caudate nucleus and putamen.

The division of the NAc is based on the mosaic arrangement of the patch-matrix organization, as well as on the anatomical and morphological compartmentalization of the core and shell. The patch-matrix system pervades the entire striatum, including the NAc, and is defined by the differential expression of neurochemical markers. Patches (or striosomes) exhibit high mu-opioid receptor (MOPr) expression and low calbindin and acetylcholinesterase content, whereas the surrounding matrix, comprising most of the tissue, displays high acetylcholinesterase activity and calbindin density. Unlike other striatal regions, the NAc is divided into a central core and an outer shell, distinguished by neuronal density, neurochemical distribution, and mRNA expression. In the medial shell, patches are more abundant than the matrix, inverting the typical ratio. This unique organization has been implicated in functional differences between the core and shell: the core, with a more matrix-like structure, connects primarily to motor-related areas such as the frontal pole and orbitofrontal cortex (OFC), whereas the shell, enriched in patches, exhibits stronger connectivity with limbic structures, including the amygdala and anterior cingulate cortex (ACC). These anatomical and neurochemical distinctions suggest an information flow from the shell to the core, integrating limbic and motor signals in a manner distinct from other striatal regions. However, these divisions are not strictly segregated, as both compartments receive converging limbic and sensorimotor inputs. Recent evidence challenges a rigid functional dichotomy, indicating that the patch-matrix system interacts dynamically with broader neural circuits, complicating direct anatomical and functional correlations (8,9). The NAc is part of the brain's reward circuitry, constituted by three synaptically connected neuronal elements. There is a descending link from the anterior bed nuclei of the medial forebrain bundle to the ventral tegmental area (VTA), an ascending link running from the VTA to the NAc, as well as a further ascending link originating from NAc towards the ventral pallidum. Dopamine is the primary neurotransmitter involved in the ascending fiber that connects the VTA and NAc. Gamma-aminobutyric acid (GABA), substance P, and enkephalin are the neurotransmitters involved in the link projecting from NAc to the ventral pallidum. Although evidence suggests that glutamate participates in the descending myelinated fiber tract, the exact neurotransmitter type involved in this tract is still unknown (10). In healthy individuals, studies of reward-related NAc functional connectivity showed that bilateral NAc reward-related activation is positively correlated with the robustness of the white-matter microstructure connecting the NAc and OFC. Reward processing is correlated to an increase in the

activity of NAc, measured through a blood oxygen level-dependent (BOLD) signal (2). Recent evidence on lateralization within subcortical structures suggests that the right NAc tends to be larger in volume compared to the left, similar to other basal ganglia subregions. Furthermore, diffusion tensor imaging (DTI) analyses have demonstrated notable left-right microstructural differences between hemispheres. However, the impact of NAc laterality on neuropsychiatric processes remains to be determined (11). All abused drugs increase dopamine transmission in the NAc, through different mechanisms (12,13). It is known that multiple substances can influence the NAc, such as alcohol, opiates, heroin, methamphetamine, ethanol, and nicotine (1,2). Several neuroimaging studies using resting-state functional magnetic resonance imaging (fMRI) have reported connectivity changes in cases of SUD and addiction (2). In comparison with healthy controls, individuals with a family history of alcohol use disorder have shown reduced radial diffusivity in white matter tracts, depicted in diffusion tensor imaging (DTI), connecting the NAc and the OFC (14,15). High-dependent smokers have shown greater connectivity between the right amygdala and the left NAc, in comparison with low-dependent smokers (16). In terms of opioid addiction, it has been reported that addicted individuals show increased connectivity between the NAc and both ACC and OFC, as well as reduced connectivity between NAc and both the anterior insula and inferior parietal cortex, in comparison to healthy controls (17). NAc involvement due to substance abuse includes changes not only in synaptic plasticity but also in volume (18). Seifert et al. (2014) demonstrated a reduction in the structural volume of the left nucleus accumbens (NAc) in patients addicted to heroin as compared to healthy controls, utilizing the segmentation technique FIRST (19). Ceceli et al. (2023) demonstrated a reduction in ventromedial prefrontal cortex (vmPFC) and NAcc/putamen gray matter volumes in individuals with heroin addiction using voxel-wise general linear models and non-parametric permutation-based tests (20). Moreover, Korponay et al. (2017) demonstrated a positive correlation between abstinence duration and volume in the NAc in alcohol and cocaine users (21). However, the exact effects of different substances on the volume of NAc are not fully known.

Drug use disorders result in personal disability, as well as problems in family, social, educational, and occupational activities. They represent high costs to society, as the cause of premature mortality and detriment in social welfare. In 2021, it was estimated that 296 million people aged 15-64 used psychoactive drugs and that 39.5 million

people were affected by drug use disorders. About 0,6 million deaths annually can be attributable to drug use (22). Several studies have reported functional alterations in brain connectivity due to the use of substances. Nevertheless, a deeper understanding of NAc volumes in different SUDs is important to improve precise neuromodulatory targeting (2,8) and treatment identification by primary drug of abuse (20). Therefore, this review aims to assess whether the volumetric alteration of the NAc can be associated with SUD.

Materials and methods

The search strategy and selection process of this review were made according to the guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) 2020. A literature search was performed using Medical Subject Headings (MeSH) and keywords in the following databases: PubMed, Embase, BVS, Web of Science, Scopus, Cochrane Library, and PsycINFO. The search was limited to English, Spanish and Portuguese language literature; the term “Nucleus Accumbens” or its synonyms was combined with “AND” and the term “Mental Disorder” or its synonyms; synonyms for “Mental Disorder” were accounted for by combining that expression with “OR” and the following terms: “Substance Use Disorder”, “Drug Addiction”, “Mood Disorders”, “Crack Cocaine”; these terms were combined with “AND” and the term “Magnetic Resonance Imaging” or its synonyms. The search strategies used in this review are available in Supplementary Table 1. The search was not limited to the publication dates. The last literature search was performed in September 2024. The following were first excluded from the review: Studies that did not address Substance Use Disorders, Longitudinal studies, Meta-Analyses, Review Articles, Clinical Trials, Case Reports, and Theses. The remaining reports were filtered using other exclusion criteria, such as “Familial Risk of Substance Use”, “Abstinence Only”, “No Nucleus Accumbens Analysis”, and “No Magnetic Resonance Imaging Analysis”. The data were extracted from the article text, tables, and figures. Two investigators (BLINDED FOR PEER REVIEW) independently reviewed the full text of all eligible studies, and a third investigator, together with two experienced physicians, was responsible for solving the conflicts between the included articles. The data extracted from the articles included: the number of participants, type of population, type of substance use addiction, presence of comorbidities, exclusion criteria, methodology, type of scan used in the study, NAc volumetric alteration, other structures analysis, and time of exposure and

abstinence. Rayyan, a platform for systematic review management, was used to select articles.

Results

A narrative review of the literature

Our electronic search yielded 3686 studies. After removing duplicates and applying the inclusion criteria, exclusion criteria, and full-text examination, 52 articles were included in the analysis, regarding different substances: alcohol, nicotine, cannabis/marijuana, crack-cocaine, heroin, ketamine, and opioids, as well as polysubstance use. A PRISMA flow diagram specifying the data collected and evaluated is provided in Figure 3. The data corresponding to this literature review are summarized in Supplementary table 2 (number of participants, type of population, type of substance use addiction, presence of comorbidities, exclusion criteria, methodology, type of scan used in the study, NAc volumetric alteration, other structures analyzed and time of exposure and abstinence). In the included studies, samples ranged from $n = 20$ to $n = 3805$ participants (23). Main volumetric analysis techniques included FreeSurfer ($n = 34$), Voxel-Based Morphometry ($n = 11$), and FSL-FIRST ($n = 9$). Of the included studies, some of them analyzed participants only subject to prenatal exposure ($n = 7$). Both significant and nonsignificant alterations in NAc volume were reported in the included studies. A narrative synthesis is presented below.

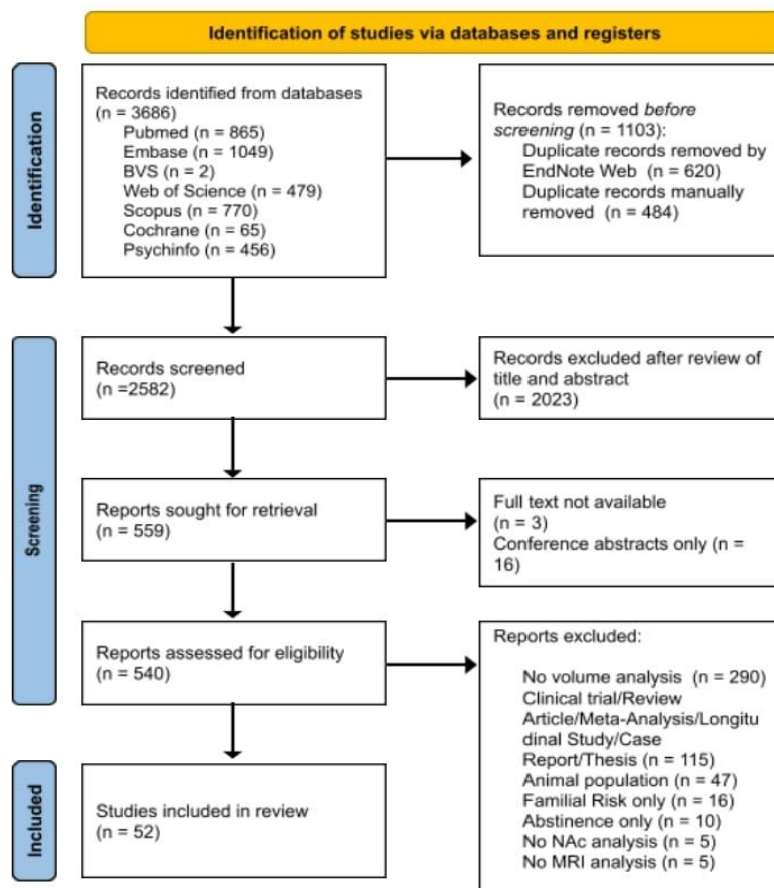


Figure 3: PRISMA 2020 flowchart

Alcohol Abuse

Some studies highlighted a trend of volumetric reductions in the NAc associated with alcohol abuse ($n = 6$) (24–29). In these studies, samples ranged from $n = 42$ participants (21 alcohol-dependent and 21 controls) (24,26) to $n = 986$ participants (660 with alcohol dependence and 326 controls) (27). The observed effect was bilateral for most of the included studies ($n = 3$) (24,27–29), though only right ($n = 2$) (25,26) and predominantly right ($n = 2$) (24,27) NAc volume reductions were also observed. Additionally, a significant volume increase on the left NAc associated with depression and anxiety comorbidities in individuals with alcohol dependence was reported. Most of the studies used Functional Source License (FSL) software for the volumetric analysis ($n = 4$) (24–26,28), while others used FreeSurfer ($n = 2$) (27,30) and manual segmentation ($n = 1$) (29). Some studies have shown no significant NAc volumetric alteration associated with alcohol abuse ($n = 6$) (31–36), which used different methodologies of volumetric analysis: custom Unix-based software ($n = 1$) (31), semi-automated segmentation ($n = 1$) (33), Statistical Parametric Mapping ($n = 2$) (32,34), Voxel-Based Morphometry (VBM) ($n = 1$) (34), FSL and VBM software ($n = 1$) (35) and FreeSurfer ($n = 1$) (36). In these studies, samples ranged from $n = 48$ participants (24 alcohol-dependent and 24 healthy controls) (34) to $n = 120$ participants (60 alcohol-dependent and 60 controls) (33). Moreover, studies analyzing prenatal alcohol exposure (PAE) have reported no significant NAc volume alterations ($n = 4$) (37–40). These studies used FreeSurfer as the main volumetric analysis methodology.

Cigarette smoking

Studies using FreeSurfer have reported negative associations between lifetime cigarette smoking (measured in pack-years) and NAc volumes ($n = 2$) (41,42). Both bilateral (41) and only left (42) NAc volume reductions were reported. In these studies, samples ranged from $n = 83$ participants (40 smokers and 43 non-smokers) (41) to $n = 315$ participants (123 smokers and 192 non-smokers) (42). However, one study reported no significant differences in NAc volumes between young smokers and non-smokers (43). This study analyzed $n = 120$ participants (60 smokers and 60 non-smokers) (43). Additionally, no significant differences in NAc volumes in prenatally exposed participants compared to controls were reported (44).

Cannabis/Marijuana

Significant left NAc volume increase ($n = 2$) (45,46) and significant right NAc volume increase ($n = 1$) were reported (47). The samples from these studies ranged from $n = 40$ participants (20 cannabis-users and 20 non-users) (45) to $n = 184$ (92 cannabis-users and 92 non-users) (46). Conversely, some studies described no significant volumetric alterations in cannabis users compared to healthy controls ($n = 5$) (48–52). In these studies, samples ranged from $n = 142$ (14 cannabis users and 28 healthy controls underwent VBM analysis, and 14 cannabis users and 100 healthy controls underwent subcortical volumetric analysis) (49) to $n = 1096$ (622 young Australian adults and 474 middle-aged US males) participants (50). The main methodologies used for image analysis in the studies were FreeSurfer ($n = 7$) (45–48,50–52), FSL-VBM ($n = 3$) (45,48,49), and FIRST ($n = 3$) (45,48,49).

Crack-cocaine and cocaine

Significant left NAc volume reduction ($n = 1$) (53), significant right NAc volume reduction ($n = 1$) (54), and bilateral NAc volume reduction were reported ($n = 1$) (55). In these studies, samples ranged from $n = 30$ participants (15 crack-cocaine and 15 controls) (55) to $n = 58$ participants (18 with pathological gambling, 19 with cocaine dependence, **and 21** healthy controls) (54). One study focused on the association between cocaine use disorder and HIV, showing a significant reduction in NAc volume in HIV-positive participants (56). Moreover, some studies reported no significant volumetric alterations in cocaine users compared to controls using FreeSurfer ($n = 2$) (57,58), FSL-VBM ($n = 1$) (20), and MAGeT-Brain pipeline ($n = 1$) (59). In these studies, samples ranged from $n = 67$ (45 cocaine-dependent and 22 healthy controls) (58) to $n = 76$ (36 cocaine addicts and 40 healthy controls) (59) participants. Additionally, prenatal cocaine exposure has not been associated with NAc volumetric alteration (60).

Heroin

Studies analyzing heroin-dependent individuals reported significant NAc volume alterations in comparison with controls ($n = 3$) (19,20,61). Both an increase in right NAc volume ($n = 1$) (61) and a decrease in left NAc volume ($n = 2$) (19,20) were reported. The samples from these studies ranged from $n = 50$ (30 heroin-dependent patients and 20 controls) (19) to $n = 96$ (32 heroin users, 32 cocaine users, **and 32** controls) (20).

As volumetric analysis methodology, Wang et al. (2021) used FreeSurfer 6.0 (61), whilst Seifert et al. (2014) (19) and Ceceli et al. (2023) (20) used FSL-FIRST and FSL-VBM, respectively.

Ketamine

Chronic ketamine users have been reported to exhibit lower gray matter volume in NAc compared to poly-drug-using controls ($n = 1$). In this study, the sample was $n = 36$ (17 chronic ketamine users and 19 polydrug-using controls). This study used FreeSurfer as a volumetric analysis methodology (62).

Methamphetamine

Some studies have reported a significant increase in NAc volume in methamphetamine users using manual segmentation and FreeSurfer for volumetric analysis ($n = 2$) (63,64), though a significant decrease has also been observed employing FreeSurfer ($n = 1$) (65). The samples from these studies ranged from $n = 103$ (21 methamphetamine MA-dependent HIV-negative, 30 HIV-negative **nonusers**, 22 MA-dependent HIV positive, and 30 HIV positive non-users) (63) to $n = 124$ (62 methamphetamine users and 62 controls) participants (64). However, some studies using FreeSurfer reported no significant alterations in NAc volumes for methamphetamine users ($n = 2$) (52,66). The samples from these studies ranged from $n = 27$ (10 healthy controls, 9 methamphetamine abusers, and 8 methamphetamine+cannabis abusers) (52) to $n = 64$ (22 with methamphetamine-associated psychosis, 21 methamphetamine users, and 21 healthy controls) participants (66).

Opioids

One study using FreeSurfer reported no significant association between opioid dependence and NAc volume alteration. The sample was $n = 20$ participants (10 prescription opioid-dependent patients and 10 healthy controls) (17). Additionally, one study using FreeSurfer reported that children prenatally exposed to opiates and other substances had significantly smaller NAc volumes compared to controls (67).

Substance-general associations and polysubstance use

Some studies have reported associations between substance general dependence or polysubstance use and volumetric NAc alteration ($n = 3$) (23,68,69). In these studies, samples ranged from $n = 43$ (22 female adolescents with severe substance and conduct problems, and 21 healthy controls) to $n = 3805$ (1535 nondependent controls and 2270 individuals with primary substance dependence) participants (23). These studies used FreeSurfer ($n = 2$) (23,69) and VBM8 ($n = 1$) (68) for volumetric analysis. Conversely, studies also reported no significant NAc volume differences between groups with and without SUD, or between polysubstance users and healthy controls ($n = 2$). In these studies, samples ranged from $n = 51$ participants (12 violent offenders with SUDs, 12 violent offenders without SUDs, 13 nonoffenders with SUDs, and 14 nonoffenders without SUDs) (70) to $n = 111$ participants (27 with alcohol dependence only, 37 with polysubstance use, and 37 healthy controls) (25). These studies used FSL's FIRST (25) and VBM SPM5 (70) for volumetric analysis (25,70).

Discussion

This manuscript summarizes the main associations of substance abuse with NAc volumes, regarding different substances, including alcohol, nicotine, cannabis/marijuana, crack-cocaine, heroin, ketamine, methamphetamine, and opioids.

Alcohol Abuse

Findings suggest a possible association between alcohol abuse and volumetric reductions in the NAc, with bilateral reduction in most of the studies (24,27–29). A volume increase in the left NAc linked to depression and anxiety in alcohol-dependent patients was also reported, although this study did not include a non-alcohol-dependent control group (30). Neuroanatomical changes associated with alcohol appeared to be widespread, as sex-specific changes have been reported in selected regions (27). Rossetti et al. (2021) analyzed data from 986 participants (660 with alcohol dependence and 326 controls), providing more robust statistical power compared to other included studies (27). Recent drinking appears to be a significant factor in NAc atrophy, as recently sober individuals tend to exhibit the greatest NAc volume deficits (29).

In contrast, some studies reported no significant NAc volumetric changes **related to** alcohol abuse (31–36). Deshmukh et al. (2005) and Sullivan et al. (2005) reported that recently drinking alcoholics (< 3 weeks of sobriety) exhibited significantly smaller NAc

volumes compared to long-term abstinent alcoholics, which further suggests recent alcohol exposure as a significant factor in NAc volume reduction (31). Dai et al. (2021) did not report significant volumetric alterations in NAc, although the study reported a significant positive correlation between the right NAc atrophy and cognitive deficits, as measured by the Montreal Cognitive Assessment (MoCA) scores, in individuals with alcohol use disorder (AUD) (32). However, the abstinence duration of the participants included in these studies was heterogeneous, which could introduce heterogeneity in recovery-related structural changes (31,33,36). Studies comparing control groups with patients with a short history of alcohol use (34) or with adolescents with AUD (35) reported no significant NAc volume differences, thus suggesting that more prolonged alcohol exposure is necessary to be associated with structural changes in the brain. Although no significant alterations in NAc volume were observed in cases of prenatal alcohol exposure (PAE), significant associations between PAE and volume reduction in other brain structures have been reported, such as on the corpus callosum, caudate nuclei, pallidum, putamen, amygdala, thalamus, ventral diencephalon, and hippocampus (37–40).

Cigarette Smoking

The evidence suggested a trend toward an association between prolonged exposure to cigarette smoking, or chronic smoking, and reduced NAc volume, either bilaterally or only on the left side. The negative associations between lifetime cigarette smoking and NAc volumes indicate that a greater amount or duration of cigarette exposure rather than nicotine dependence level can be associated with a smaller volume (41,42). The short average time of smoking reported by Yuan et al. (2016) further indicates that structural changes in NAc might emerge only in association with prolonged smoking use (41–43). Das et al. (2012) included an imaging analysis of 315 participants, thus having a more robust statistical power than the other included studies (41–43). As a high prevalence of comorbid smoking and alcohol dependence has been reported (71), alcohol use was controlled in analysis by Das et al. (2012), and was considered not to approach a hazardous level in participants analyzed by Durazzo et al. (2017) and was an exclusion criterion for participants in Yuan et al. (2016) (41–43).

Cannabis/Marijuana

Despite reports of significant correlations between NAc volume alterations and cannabis use, the results remain inconsistent across studies, since both volume increase and no volumetric changes in NAc volume were observed. Çolak et. al (2019) report that variations in the chemical composition of synthetic cannabinoid products may help explain the differing effects on brain volume (47). The age of first cannabis use was negatively correlated with both left and right NAc volumes, which suggests that earlier use is associated with larger NAc volumes (46). Additionally, both left and right NAc volumes were positively correlated with a greater frequency of cannabis use (46).

The null results regarding NAc volumetric alterations (48–52) could be due to the inclusion of a broader range of confounding variables in the analyses, such as sex, IQ, and alcohol use (48,51). In contrast, Francis et al. (2023) reported significant NAc volume alteration and controlled the effects of alcohol using ANCOVA (46). Methodological differences, such as the use of FreeSurfer or VBM, do not seem to consistently impact the findings, as both techniques were employed in studies reporting the presence and absence of NAc alterations. Furthermore, variations in the duration of cannabis exposure and the age of onset, which differ between studies, may influence outcomes. Weiland et al. (2015) only assessed marijuana use as daily over the past 60 days (adults) or 90 days (adolescents), thus not providing a detailed history, which could partially explain differences in results compared to Gilman et al. (2014) and Francis et al. (2023) (45,46,48). These inconsistencies highlight the necessity for future research with larger, well-controlled samples and standardized measures of cannabis exposure to better elucidate the relationship between cannabis use and NAc morphology.

Crack-cocaine and cocaine

The reviewed studies demonstrated inconsistent findings regarding NAc volumetric alterations in crack-cocaine and cocaine-dependent individuals, showing bilateral NAc reductions (55), but also only-right (54) and only-left (53) volume reductions. No sex-specific effects were analyzed in these studies, as only male (53,55) or predominantly male participants (54) were included. Bittencourt et al. (2021) reported significant left NAc volume reduction in the crack-cocaine group compared to healthy controls using VBM analysis, though no significant NAc findings were observed using the FreeSurfer

analysis (53). The divergent results using the same sample are evidence that the imaging analysis method plays an important role in the findings of the studies in this review. Therefore, methodological differences may explain inconsistencies across studies, emphasizing the need for multimodal approaches. Additionally, comorbid alcohol and/or tobacco use in the patients included in these studies could contribute to explaining the differences in results (53,55). In contrast, sensitivity analyses confirmed that the significant findings of Irizar et al. (2020) regarding the right NAc were not driven by the co-use of other substances, such as alcohol or tobacco (54).

However, some studies reported no significant volumetric alterations (20,57–59). The discrepancies in results are unlikely to be explained by the average time of exposure, as similar durations of crack-cocaine use were reported in studies with significant (55) and non-significant findings (58). Similarly, imaging methodology does not appear to fully account for these differences, as significant findings have been reported using both FreeSurfer (55) and VBM (53), whilst other studies employing the same techniques did not identify significant alterations (20,57,58). Prenatal cocaine exposure has not been associated with NAc volumetric alteration (60).

Heroin

The evidence pointed to a potential association between heroin dependent individuals and NAc volume alterations, both increase and decrease being observed (19,20,61). These studies have relatively small sample sizes, which limits the generalizability of the findings. Wang et al. (2021) matched the Heroin-Dependent Individuals (HDI) and Healthy Controls (HC) groups for nicotine and alcohol use, minimizing possible confounding variables (61). Seifert et al. (2014) controlled for multiple variables using ANCOVA. However, the authors report that the result of the FIRST analysis is statistically weak and will not be significant after correction for multiple comparisons (19). Additionally, polysubstance use and comorbid mental health issues may have confounded the results, as patients were recruited from heroin maintenance programs, which may have more comorbid mental health problems and polydrug use (19). Individuals with heroin use disorder (HUD) reported by Ceceli et al. (2023) had an average lifetime heroin use shorter than reported by Seifert et al. (2014). In this study, the severity of dependence, days since last use, lifetime use in years, and withdrawal showed no significant correlations with gray matter volume (20). Though in partial or

sustained remission during the time of the study, the HUD group presented comorbidities such as marijuana, sedative and meth use disorder, and major depressive disorder, which needs to be considered when interpreting the results (20). Differences in results could be partially explained by imaging techniques and participant profiles. Additionally, Wang et al. (2021) analyzed short-term abstinent heroin users, therefore in an acute phase of recovery (61).

Ketamine

Reductions in NAc volume of chronic ketamine users compared to poly-drug-using controls were reported (62). Nevertheless, the chronic ketamine users included by Chesters et al. (2021) had higher use of other substances, such as cocaine, amphetamines, heroin, cannabis, and alcohol, compared to controls, which complicates associating lower NAc volumes solely with ketamine (62).

Overall, further studies with larger and more controlled samples are needed to confirm this trend.

Methamphetamine

Some studies indicate a potential association between methamphetamine use and significant increases in NAc volume (63,64), although volume reductions (65). and no significant alterations(52,66) were also reported. Jernigan et al. (2005) reported more pronounced increases in NAc volume in younger methamphetamine-dependent individuals, which suggests a possible interaction between methamphetamine exposure and brain maturation processes (63). No sex-specific associations were reported in this study, and a manual segmentation was employed as the volumetric analysis technique (63). Kogachi et al. (2016) found that methamphetamine (METH) users had larger left NAc volumes than the controls, mostly due to the larger volume (both sides) in female METH users than female controls. METH-by-sex interactions only reached significance for the right NAc and could indicate a neuroprotective glial response mediated by estrogen. Morphometric analyses were conducted using FreeSurfer. It is important to note that METH users often use other substances concurrently or have other substance use disorders, which may confound the interpretation of the findings concerning METH use. Kogachi et al. (2016) attempted to minimize confounders by recruiting an equal proportion of tobacco and alcohol use in all groups (64). Hu et al. (2022) observed significantly smaller left NAc volume in males

with methamphetamine use disorder (MUD) compared to male healthy controls, thus precluding conclusions about sex differences (65). Hu et al. (2022) also conducted morphometric analyses using FreeSurfer. The duration of METH use was shorter than in patients analyzed by Kogachi et al. (2016) and Jernigan et al. (2005). The duration of abstinence and the population samples were shorter than in the study by Kogachi et al. (2016).

Jan et al. (2012) reported an increase in the left NAc volume in active METH-dependent individuals compared to controls, although this finding did not survive Bonferroni correction for multiple comparisons. Other studies have reported gains in left NAc volume in METH users (63,64), but these studies analyzed abstinent users, which might not be directly comparable to active users (72). This study used FSL's FIRST tool and VBM for volume analysis. Churchwell et al. (2012) and Uhlmann et al. (2016) reported no significant NAc volume changes (52,66). However, both studies had small participant samples, which may affect the reliability of their results.

Differences in findings may reflect variations in sample sizes, abstinence durations, and analysis methods, such as FreeSurfer (64,65) or manual segmentation (63). Small samples and concurrent substance use limit result reliability, highlighting the need for larger and more controlled studies.

Opioids

Upadhyay et al. (2010) reported significantly reduced functional connectivity of the nucleus accumbens (NAc) with subcortical and cortical regions, but no NAc volume alterations (17). However, Walhovd et al. (2007) reported a significant reduction in NAc volume was observed in children with prenatal opioid exposure (67). Different findings of Upadhyay et al (2010) and Walhovd et al. (2007) may be partially attributed to the developmental effects of prenatal opioid exposure, as opposed to the chronic use observed in adult populations. Larger sample sizes and further studies are needed to confirm these associations.

Substance-general associations and polysubstance use

The studies reviewed reveal mixed findings regarding associations between substance use in general, or polysubstance use, and alterations in nucleus accumbens (NAc) volume. Chye et al. (2020) identified lower local thickness and surface area in the right NAc among substance-dependent individuals compared to non-dependent controls,

with alcohol dependence being the primary driver of these effects. This study also highlighted substance-specific effects, with structural differences in the NAc associated with nicotine use, regardless of dependence status, reinforcing the role of cigarette exposure in NAc alterations (23). This follows Durazzo et al. (2017), as it supports the association of NAc volumetric alteration with cigarette exposure, in addition to the association with nicotine dependence (23,41).

In contrast, no significant NAc volume alterations in SUD or polysubstance use groups were reported (25,70). Oh et al. (2021) found smaller left NAc volumes in substance use disorder (SUD) individuals compared to healthy controls, but not when compared to psychiatric controls (PC). Thus, NAc alterations may be linked to common psychiatric comorbidities, such as major depressive disorder (MDD) and post-traumatic stress disorder (PTSD), rather than being specific to SUD (68). This aligns with findings by Dalwani et al. (2015), which associated widespread gray matter volume reductions with behavioral disinhibition (BD), a trait strongly predictive of substance use disorders, and with comorbid conditions such as ADHD and depression (68).

Collectively, these findings emphasize the complexity of interpreting NAc volumetric alterations in substance use, highlighting the influence of substance-specific effects, comorbidities, and polysubstance interactions, while underscoring the importance of using well-matched control groups to isolate substance use-related alterations.

Conclusion

The findings of this narrative review indicated that the nucleus accumbens (NAc) may play a role as an associated factor to substance addiction, with strong associations to specific substances. Cigarette smoking and alcohol use demonstrate the strongest evidence of volumetric alterations in the NAc, with multiple studies reporting reductions in NAc volume compared to healthy controls (24–29,41,42). Recent drinking (29,31) and prolonged smoking exposure (41,42) appear to be important factors in associations between reductions in NAc volumes and substance use. Alcohol abuse appears to have a stronger association with right NAc volume reduction (24–27), while cigarette smoking did not show consistent laterality findings amongst the included studies (41,42). While recent evidence has identified hemispheric asymmetries in the volume of subcortical structures, including the NAc (11), further research is needed to

determine whether these lateralized features contribute to differential responses to drug exposure.

Morphological differences unique to alcohol and nicotine observed in participants with dependence on varied primary substances support that relationships between substance abuse and subcortical brain structures are likely substance-specific (23). Additionally, although the studies in this review suggest a tendency for structural changes in NAc associated with heroin use (19,20,61), these exact changes are not clear. In contrast, substances such as cannabis, methamphetamine, and cocaine show inconsistent findings, with reports of both increased and decreased NAc volumes, or no significant alterations (45–59). Substances such as ketamine and opioids require further studies, with larger sample sizes, to determine more robust associations in this matter (17,62). The findings in this review do not establish a causal relationship and instead suggest correlations that warrant further investigation.

Discrepancies in reported results may reflect differences in study designs, such as sample size, duration of use, abstinence periods, and the methodologies employed for volumetric analysis, including FreeSurfer, VBM, and manual segmentation. Different results obtained using two different imaging methodologies to analyze the same sample provide evidence that the choice of imaging technique may influence the associations drawn (53). Moreover, the lack of uniform control over confounding variables, such as comorbid substance use and psychiatric conditions, likely contributes to the variability in results.

The evidence reviewed here underscores the need for multimodal approaches in future research, combining volumetric, functional, and connectivity analyses to better elucidate the relationship between substance use and NAc alterations. Furthermore, larger and more standardized studies with comprehensive control of confounding variables are required to strengthen the robustness of these associations.

Acknowledgements

E.M. (#303471/2022-0) is the recipient of a CNPq fellowship.

We gratefully acknowledge Rosana Evangelista Poderoso for her assistance with the literature search strategies for this review.

Date of last literature review: September 2024

Conflict of interest declaration: The authors declare no conflicts of interest related to the publication of this manuscript.

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Handling Editor: Dr. Thiago Roza

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Supplementary material

Table S1: Search strategies

Table S2: Literature review