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Exploring the Potential of Low-Intensity Focused Ultrasound Stimulation (LIFUS)
Targeting the Nucleus Accumbens:
A Causal Study of Cognitive and Affective Outcomes, and a Methodological
Proof-of-Concept

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Abstract

Objective: This proof-of-concept study investigates whether Low-intensity focused ultrasound (LIFUS) modulation of the Nucleus Accumbens (NAc) causally influences cognitive flexibility (CF), mood, and hedonic processing in healthy individuals.

Relevance: The NAc is an integrative hub in the brain. It is located in the basal forebrain, receives inputs from all major neurotransmitter circuits - most notably dopaminergic ones - it primarily sends inhibitory outputs. LIFUS is a method of non-invasive brain modulation that is more precise than comparable methods with the possibility of targeting deeper brain structures which has not been possible before non-invasively. In healthy humans, cognitive and affective effects of LIFUS, targeting subcortical areas, and its effects on subjective mental states have not yet been studied thoroughly.

Method: This research gap was addressed with a within-subject study design (1 group; N = 21) in two levels (NAc-sonication vs. Sham sonication). CF is a key function of creativity and problem solving; it was tested via the Stroop task in a task-switching paradigm. Mood is a multi-faceted mental state that is mainly a subjective experience, tested with the visual analog mood scale (self-evaluation). Hedonia - the ability to experience and seek joy - is a key construct of well-being and was measured via a novel music-task.

Results and conclusion: While the results were non-significant, this study might provide valuable information for future studies. Especially since it shows that our implemented LIFUS protocol may not affect cognitive and subjective mood-related outcomes in the expected time frame.

Key words: Low-Intensity Focused Ultrasound, Nucleus Accumbens, Subcortical Neuromodulation, Affective Processing, Cognitive Flexibility

Zusammenfassung

Zielsetzung: Diese Proof-of-Concept-Studie untersucht, ob eine Modulation des Nucleus Accumbens (NAc) durch Low-Intensity Focused Ultrasound (LIFUS) kognitive Flexibilität, Stimmung und hedonische Verarbeitung bei gesunden Personen kausal beeinflusst.

Relevanz: Der NAc stellt ein integratives Zentrum im Gehirn dar. Er befindet sich im basalen Vorderhirn, ist in sämtliche Hauptneurotransmitterkreisläufe eingebunden – insbesondere in dopaminerge Netzwerke – und erhält umfassende kortikale Eingänge, wobei seine Ausgänge vorwiegend inhibitorisch sind. LIFUS ist eine Methode zur nicht-invasiven Hirnmodulation, die im Vergleich zu anderen Verfahren eine höhere Präzision aufweist und erstmals eine gezielte Stimulation tieferliegender Hirnstrukturen ohne invasive Verfahren ermöglicht. Die kognitiven und affektiven Effekte von LIFUS auf subkortikale Areale sowie deren Einfluss auf subjektives Erleben wurden bislang in gesunden Personen kaum systematisch untersucht.

Methode: Die Untersuchung erfolgte in einem Within-Subject-Design (eine Gruppe; $N = 21$) mit zwei Bedingungen (NAc-Sonikation vs. Sham-Sonikation). Kognitive Flexibilität (CF), eine zentrale Funktion kreativen Denkens und problemlösenden Verhaltens, wurde mithilfe des Stroop-Tests in einem Task-Switching-Paradigma erfasst. Stimmung, als mehrdimensionaler und vorwiegend subjektiver Zustand, wurde mittels einer visuellen Analogskala zur Selbstbeurteilung erhoben. Hedonie – die Fähigkeit, Freude zu suchen und zu empfinden – ist ein zentrales Konstrukt für *Well-being*, wurde über eine neu entwickelte Musikaufgabe erfasst.

Ergebnisse und Schlussfolgerung: Da sich in keiner der getesteten Hypothesen signifikante Ergebnisse zeigten, liefert diese Studie primär Anhaltspunkte für zukünftige Untersuchungen. Die vorliegenden Befunde legen nahe, dass das eingesetzte LIFUS-Protokoll sowie der gewählte zeitliche Rahmen keine messbaren Effekte auf verhaltensbezogene oder subjektive affektive Zustände durch eine NAc-Sonikation hervorrufen konnten.

Schlagwörter: Niedrig-intensive fokussierte Ultraschall Stimulation, Nucleus Accumbens, Subkortikale Neuromodulation, Affektive Verarbeitung, Kognitive Flexibilität

Glossary of Abbreviation

<i>Abbreviation</i>	<i>Full Term</i>
<i>ACC</i>	Anterior Cingulate Cortex
<i>Amyg.</i>	Amygdala
<i>BOLD</i>	Blood-Oxygen-Level-Dependent (signal)
<i>CF</i>	Cognitive Flexibility
<i>COWAT</i>	Controlled Oral Word Association Test
<i>DBS</i>	Deep Brain Stimulation
<i>dIPFC</i>	Dorsolateral Prefrontal Cortex
<i>DMN</i>	Default Mode Network
<i>EEG</i>	Electroencephalography
<i>Fig.</i>	Figure
<i>fMRI</i>	Functional Magnetic Resonance Imaging
<i>FSL</i>	FMRIB Software Library
<i>GLM</i>	General Linear Model
<i>H1–H4</i>	Hypotheses 1 through 4
<i>IES</i>	Inverse Efficiency Score
<i>LIFUS / LIFU</i>	Low-Intensity Focused Ultrasound (Stimulation)
<i>LMM</i>	Linear Mixed Model
<i>mPFC</i>	Medial Prefrontal Cortex
<i>MNI</i>	Montreal Neurological Institute
<i>MRI</i>	Magnetic Resonance Imaging
<i>NAc</i>	Nucleus Accumbens
<i>NIBS</i>	Non-Invasive Brain Stimulation
<i>NICE</i>	Neuronal Intramembrane Cavitation Excitation (Model)
<i>OFC</i>	Orbitofrontal Cortex
<i>PAG</i>	Periaqueductal Gray
<i>PFC</i>	Prefrontal Cortex
<i>PET</i>	Positron Emission Tomography

<i>RNG</i>	Random Number Generation Task
<i>ROI</i>	Region of Interest
<i>S1</i>	Primary Somatosensory Cortex
<i>S2</i>	Secondary Somatosensory Cortex
<i>TMS</i>	Transcranial Magnetic Stimulation
<i>tDCS</i>	Transcranial Direct Current Stimulation
<i>tES</i>	Transcranial Electrical Stimulation
<i>TUS / tFUS</i>	Transcranial (Focused) Ultrasound Stimulation
<i>VAMS</i>	Visual Analog Mood Scale
<i>VP</i>	Ventral Pallidum
<i>VTA</i>	Ventral Tegmental Area
α	Alpha level (significance threshold)
η^2	Eta squared (effect size)
<i>CI</i>	Confidence Interval

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1 Introduction

Contemporary neuroscience research relies heavily on correlational neuroimaging approaches such as functional magnetic resonance imaging (fMRI) and electroencephalography (EEG). During behavioral tasks, these methods can identify brain regions that are activated. Although neuroimaging methods can provide profound insights into brain–behavior relationships, they remain fundamentally correlational and therefore cannot establish causality between neural activity and behavioral outcomes. Establishing such causal links requires direct manipulation of neural systems. To advance our understanding of the causal relationship between cognition – which refers to the entire set of mental processes, involving acquisition, storage, manipulation, and retrieval of information, and involves functions, such as attention, perception, memory, reasoning, and problem solving (Pessoa, 2008) - and affect – which is defined in this thesis as the (neuropsychological, subjective and conscious) experiential component of emotion (Davidson & Irwin, 1999) – researchers require methods that can actively manipulate brain function while measuring behavioral outcomes.

Currently available neuromodulation techniques present a trade-off between precision and invasiveness. Invasive approaches like deep brain stimulation (DBS), where electrodes are surgically implanted in target regions such as the nucleus accumbens (NAc), demonstrate good spatial precision and can effectively modulate subcortical structures (i.e., Yan et al., 2013). However, their requirement for neurosurgical intervention renders them irreversible and limits their use to severe, treatment-resistant psychiatric and neurological cases, while also carrying risks of infection and other complications. Non-invasive brain stimulation (NIBS) methods, including transcranial magnetic stimulation (TMS) and transcranial electrical stimulation (tES), avoid these surgical risks and are reversible, but their utility is constrained by limited spatial precision and for TMS, a limited ability to reach subcortical targets (Bestmann & Walsh, 2017; Deng, Lisanby & Peterchev, 2013). tES can reach subcortical targets with a novel approach called *temporal inference* (Grossman et al., 2017) but the spatial precision remains limited.

Low-intensity focused ultrasound (LIFUS) has emerged as a promising alternative that combines the precision of invasive methods with the safety profile of non-invasive approaches. LIFUS offers several key advantages: (1) the ability to target subcortical structures with millimeter-scale precision (Bystritsky et al., 2011; Legon et al., 2018), (2) non-invasiveness, by not requiring surgical intervention (Darmani et al., 2022; Folloni et al., 2019), and (3) reversible modulation of neural activity (Mahdavi et al., 2023). While human studies have demonstrated LIFUS's capacity to modulate blood-oxygen-level-dependent (BOLD) signals in target regions

(Ai et al., 2016), its psychological effects, particularly for cognitive and affective processes, remain largely unexplored.

The NAc represents an ideal target for a LIFUS based investigation, given its central role in multiple neural systems (Floresco, 2015): As a key node in the mesolimbic dopamine (DA) system (Bear, Connors & Paradiso, 2016), the NAc integrates inputs from prefrontal cortical regions (involved in cognitive control), limbic areas (processing affective information), and midbrain DA neurons (modulating motivation and reward). Functionally, the NAc has been implicated in: (1) cognitive flexibility (CF) and behavioral adaptation (Duan, 2025; Eijssker et al., 2020), (2) mood regulation (Giordana et al., 2015), and (3) hedonic processing (Auerbach et al., 2017; Wacker, Dillon & Pizzagalli, 2009). Clinically, NAc modulation via DBS has shown therapeutic potential for treatment-resistant depression (Bewernick, 2010; Bewernick, 2012), anxiety (Sturm et al., 2003), and obsessive-compulsive disorder (Torres-Diaz et al., 2021; Sturm et al., 2003).

Despite these advances, critical gaps remain in our understanding. First, at the time of writing no studies have systematically examined whether LIFUS modulation of the NAc produces measurable effects on cognitive or affective processes in healthy humans. Second, the behavioral specificity of LIFUS-induced NAc-modulation remains unknown. Third, the potential clinical applications of LIFUS for NAc-targeted interventions remain unexplored.

The current study addresses these gaps through a proof-of-concept investigation with three primary aims: (1) to establish whether LIFUS can modulate NAc-function sufficiently to significantly alter CF, mood, and hedonic processing; (2) to provide a causal test of the NAc's role in these psychological processes; and (3) to evaluate LIFUS's potential as a non-invasive alternative to DBS.. Using a within-subjects design with active and sham stimulation conditions, we examine LIFUS-NAc effects on: (a) CF measured through a Stroop task-switching paradigm, (b) self-reported mood states assessed via a visual analog mood scale, and (c) changes in subjective hedonic experiences via an approximation through measuring hedonic responsiveness with a novel music task. Also, (d) a more extensive explorative model – formalizing the NAc's influence on cognitive and affective processes which were postulated to show interactions of any kind – is proposed.

The structure of the thesis will be as follows: Chapter 2 provides theoretical background for LIFUS and the NAc. First, the comprehensive overview of LIFUS research shows its relevance in non-invasive causal investigations, aiming to link neural correlates of cognitive and affective outcomes. This is followed by a comprehensive summary of how NAc-activity is currently understood to influence human behavior and why this is relevant to research causally and how

DBS of the NAc demonstrates its relevance as a target for NIBS, such as LIFUS. Chapter 3 introduces the three constructs – CF, mood and hedonia – and why they were chosen to analyze how LIFUS influences the NAc. Additionally, a larger statistical model, including cognitive and affective effects, is proposed. This larger model was supposed to exploratively analyze how changes in affective constructs, like mood and hedonia, might influence cognitive performance and how the NAc – as a key hub in affective and cognitive processes – could provide valuable information on this hypothesis. In chapter 4, the research questions that drove the research on this topic are explicitly formulated and the hypotheses derived from these questions are formalized. The methods are discussed in chapter 5. It provides a comprehensive overview on LIFUS implementation, study design and the operationalization of the constructs, including a data analysis plan showing which statistical methods were used for analysis, including statistical reasoning. In chapter 6, the analysis and the results are described and visualized. Finally, chapter 7 provides a discussion of the results, and the limitations, what future studies should focus on and a conclusion of the study.

2 Literature Review

In this chapter, a literature review is provided. First, on the LIFUS method: Its relevance, the empirically proven biomechanical processes it causes, and its effects on the human brain. Then, the NAc will be reviewed: Its neuroanatomical properties, then the associated functions, followed by an overview of causal NAc-stimulation-studies . This provides key factors to consider when conducting a LIFUS-based study, targeting the NAc. This clarifies the research gap, regarding behavioral, cognitive and affective effects in LIFUS-studies targeting subcortical areas.

2.1 LIFUS: A Promising Method

For cortical areas, there are well established NIBS methods such as tMS, transcranial direct current stimulation (tDCS) as a famous example of tES. However, although routinely used, these methods are limited in their spatial precision and in their ability to target subcortical areas (Bestmann & Walsh, 2017; Deng, Lisanby & Peterchev, 2013).

In contrast, *LIFUS* – also referred to as LIFU, transcranial (focused) ultrasound stimulation (TUS; tFUS), or transcranial pulse stimulation (TPS) (i.e., Truong, Guillen & Datta, 2023) – offers greater spatial accuracy (Bystritsky et al., 2011; Legon et al., 2018) and the unique ability to reach subcortical targets (Cain et al., 2021b; Folloni et al., 2019; Cox, Connolly, Peng & Badran, 2025). In fMRI experiments, the influence of LIFUS on subcortical areas and connected larger-scale cortical networks could be proven (i.e., Barksdale et al., 2024; Cain et al., 2021b). LIFUS seems to be a promising approach to modulate complex neuronal circuits due to its spatial precision and the possibility of targeting brain areas deep inside the brain. However, its limitations and mechanisms of action are not yet fully understood and require further research (Arulpragasam et al., 2022).

2.1.1 LIFUS – LIFUS-Caused Biological Processes

Recent research has begun to elucidate how ultrasound modulates neuronal activity. Yoo et al. (2022) suggest that LIFUS activates mechanosensitive ion channels (e.g., TRPP1/2, TRPC1, Piezo1), leading to intracellular calcium influx. This influx subsequently activates calcium-sensitive sodium channels (e.g., TRPM4), triggering depolarization and the opening of

voltage-gated calcium channels such as T-type channels. This cascade unfolds within 70–300 milliseconds, aligning with observed response times in animal models (Qiu et al., 2019).

Importantly, enhanced expression of these mechanosensitive channels increases neuronal sensitivity to LIFUS, suggesting potential for targeted neuromodulation (Yoo et al., 2022). Notably, this mechanism of action is mechanical (since it activates mechanosensitive channels) rather than thermal (temperature-related) and does not involve traditional neurotransmitter release mechanisms. However, thermal effects might play a role (Truong, Guillen & Datta, 2023) in LIFUS's mechanisms of action. This indicates that these cellular processes are multiple and yet too complex to fully integrate into a neuroscientific model that can predict how LIFUS works. This indicates that, at the neural level, empirical evidence primarily supports specific hypotheses in isolation and cannot yet be integrated into a broader, generalizable understanding. Because neuroscientific findings remain ambiguous and difficult to generalize, behavioral studies are needed to assess if and how LIFUS affects individuals in the “real world”.

A crucial limitation for directing hypotheses in LIFUS studies is the unpredictability of whether LIFUS *excites* or *inhibits* the neurons of the target regions. LIFUS is capable of doing both: In some studies, it excited the targeted brain regions (i.e., Lee et al., 2015 – Somatosensory cortex; Lee et al., 2016 – Visual Cortex; Ai et al., 2018 – Motor Cortex; Liu et al., 2021a – Somatosensory Cortex), in some it did the opposite (Legon et al., 2018a – Thalamus ; Legon et al., 2018b – Motor Cortex; Fomenko et al., 2020 – Motor Cortex; Cain et al., 2021b – left globus Pallidus) (for more detailed information, see: [Appendix A: LIFUS exciting or not?](#)). Notably, the same brain region can be excited and inhibited with limited ability to predict the direction of effect previously. Thus, this difference in direction of effect cannot be explained by the direction of effect that the outputs of the targeted brain region spark.

2.1.2 LIFUS – Application to the Human Brain

Although the underlying cellular mechanisms of LIFUS are not yet fully understood, a growing body of evidence consistently demonstrates its potential. As discussed, LIFUS can both activate and suppress brain regions. The most targeted brain region in human studies researching LIFUS was the primary Motor Cortex (M1), followed by the primary and secondary somatosensory cortex (S1/S2) (Cox et al., 2025). These findings show how the general potential in humans - increasing motor inhibitory control, decreasing reaction times and improving pain thresholds (Zhang et al., 2021; Fomenko et al., 2020; Legon et al., 2018b) can be induced by LIFUS (see [Appendix B: Sensory and Motor effects of LIFUS](#) This study specifically addresses

the existing gap in the literature regarding the influence of LIFUS on cognitive, affective, and behavioral processes. Especially, in non-clinical population, there is little data.

2.1.2.1 Cognitive Effects of LIFUS

The effect of LIFUS has rarely been tested in healthy populations. The only peer reviewed article, the author is aware of is the Yaakub et al. (2023) nature paper which found interesting effects regarding neuroplasticity and functional connectivity. Apart from that, most assumptions we can draw from previous LIFUS research is from clinical populations. Effects on cognition for example needs to be inferred from clinical effects:

LIFUS has shown potential for enhancing cognitive function, memory and neurological recovery in dementia and Alzheimer's patients (Nicodemus et al., 2019; Popescu, Pernet, & Beisteiner, 2021). Sonication of the thalamus has led to significant increases in behavioral responsiveness in patients with disorders of consciousness, with some exhibiting novel behaviors or even attempting to walk following treatment (Monti et al., 2016; Cain et al., 2021a).

In populations with Alzheimer's disease, LIFUS targeting the frontalis, parietal, and precuneus cortices has resulted in improved memory and language function, with effects persisting for several months. These enhancements have been linked to increased cortical thickness and connectivity within memory-related networks (Beisteiner et al., 2020; Popescu et al., 2021). Additionally, LIFUS applied to the Hippocampus has been associated with improvements in cognitive performance and increased cerebral glucose metabolism – significantly affecting multiple brain areas (the superior frontal gyrus, middle cingulate gyrus, and fusiform gyrus) (Jeong et al., 2021). These results demonstrate the potential of LIFUS to alter cognition, while also revealing its complex, network-wide effects, underscoring the need for further research to predict and optimize its outcomes.

Similarly, stimulation of the right frontal gyrus led to functional connectivity changes, particularly within the default mode network (DMN), suggesting a potential role for LIFUS in modulating large-scale brain networks (Sanguinetti et al., 2020). Since the DMN is involved in most cognitive processes, no clear conclusion can be drawn from this. However, the information provided in this paragraph is evidence in favor of LIFUS being a suitable tool for neuromodulation in several brain areas can lead to profound cognitive effects. However, there is a gap regarding specific cognitive processes. This gap needs to be addressed, by investigating specific LIFUS-induced effects of a healthy population in cognitive tasks.

2.1.2.2 Affective Effects of LIFUS

Studies focusing on affective states in healthy individuals showed that the application of LIFUS to cortical and subcortical brain regions induce promising effects on mood regulation and psychiatric symptoms. Prefrontal cortex (PFC) stimulation has been shown to produce various effects: It has been linked to increased happiness ratings over time (Reznik, 2020) and mood-enhancing effects. LIFUS to the PFC could also increase approach behavior and reduce withdrawal responses (withdrawal from difficult tasks resembling *anxiety-like* behavior) in complex decision-making tasks (Ziebell et al., 2023). Targeting the dorsolateral prefrontal cortex (dlPFC) resulted in significant reductions in depressive symptoms and improved functional connectivity in mood-related brain regions, including the subgenual anterior cingulate cortex (Oh et al., 2024).

LIFUS of the Amygdala was associated with marked reductions in anxiety severity, with over 60% of participants experiencing meaningful clinical improvement (Mahdavi et al., 2023). Consequently, affective states can be altered and clinically improved by sonication of a subcortical brain area.

Collectively, these findings suggest that applying LIFUS to multiple brain structures may offer a novel, noninvasive approach for modulating mood, affect, and cognitive-emotional processing. Table 1 provides a summary of relevant LIFUS studies with human subjects, including the targeted brain areas and the supposed effects that were found. The link to this study is provided by the fact that subcortical areas can influence affective processes. Yet, there is a gap regarding sonication of subcortical structures and researching cognitive processes and also how general mood is influenced by LIFUS sonication. The next chapter will show why the NAc is a promising subcortical area for a LIFUS study on cognitive and affective processes.

Table 1

Summary of studies conducted with LIFUS on the Human Brain

Brain Region	Observed Effect	Study
Primary Motor Cortex (M1)	↑ Inhibitory control, ↑ motor speed	Zhang et al., 2021; Fomenko et al., 2020
Somatosensory Cortex (S1/S2)	↑ Pain threshold, ↑ tactile sensations	Legon et al., 2018b; Liu et al., 2021
Hippocampus, Substantia Nigra	↑ Memory & motor recovery (dementia, Parkinson's)	Nicodemus et al., 2019
Thalamus	↑ Behavioral responsiveness (coma patients)	Monti et al., 2016

Amygdala	↓ Anxiety, ↓ BOLD in emotional circuits	Mahdavi et al., 2023; Barksdale et al., 2024
Prefrontal Cortex (dlPFC, frontal gyrus)	↓ Depression symptoms, ↑ happiness, ↑ DMN connectivity	Oh et al., 2024; Reznik, 2020
Nucleus Accumbens (NAc) (see section 2.3.3.1)	↓ Craving, ↑ mPFC-NAc connectivity, modulation of reward network	Peng et al., 2024; Mahoney et al., 2023

2.2 The Nucleus Accumbens

Given that LIFUS has been shown to affect BOLD levels, functional connectivity, and behavior in humans, it holds strong potential to inform causal biopsychological models. An interesting brain area to study is the NAc, a subcortical brain structure located in the ventral striatum (Fig. 1). It is mainly associated with its central role in reward-related processes (i.e., LeGates, 2018), especially in motivational and behavioral adaptation contexts (Becker-Krail, 2022). It is part of the mesolimbic dopaminergic system (i.e., Schultz, 1997), and particularly associated with incentive anticipation (Knutsen, Adams, Fong, & Hommer, 2001).

Fig. 1

Location of the NAc in the human brain.



2.2.1 Neurophysiology of the NAc

The NAc is anatomically divided into core and shell subregions, which differ slightly in their neurophysiological properties. For this study, these subdivisions will not be distinguished, as the NAc is too small to selectively target either subregion (for further understanding of this potential limitation: [Appendix C; comparison of NAc core and shell](#)).

The NAc receives excitatory glutamatergic input from several key brain regions. These include the basolateral amygdala (BLA), which processes emotional salience, particularly for threat or reward (Wang et al., 2020); the hippocampus, providing spatial and contextual information (LeGates et al., 2018); and specific prefrontal cortex (PFC) subregions, which transmit executive control signals such as value assessment, cost-benefit decision-making, and goal selection (Floresco, 2015).

Importantly, glutamatergic inputs are further modulated by dopaminergic projections from the ventral tegmental area (VTA). Dopaminergic signaling within the NAc occurs in two primary modes: phasic and tonic. Phasic DA release, triggered by unexpected rewards or conditioned cues, encodes reward prediction errors and supports associative learning (Schultz, 1997, 1998; Oleson et al., 2012), whereas tonic DA reflects ongoing reward availability and motivational value over longer timescales, modulating the responsiveness of broader populations of NAc neurons (Niv, 2007; Floresco, 2015). Recent evidence suggests that this phasic/tonic distinction may oversimplify NAc DA function. Liu et al. (2021) showed that DA release is spatially and temporally structured, occurring at sparse active sites with domain-overlap dynamics, while there are arguments that conventional phasic/tonic categorizations may reflect limitations of slow-measuring techniques rather than distinct functional modes (Berke, 2018). DA primarily acts through D1- and D2-receptors: D1 generally enhances neuronal excitability and reward-related signaling, whereas D2 reduces excitability to suppress competing inputs and dynamically gate information (Song, 2024). Taken together, these findings indicate that dopaminergic signaling in the NAc is highly dynamic and context-dependent, with structured DA release shaping glutamatergic inputs, receptor-mediated excitability, and motivational and learning processes, even though precise patterns remain difficult to measure with current imaging methods (Howes & Nour, 2016). This underscores the need for causal investigations, such as NAc-targeted neuromodulation with LIFUS or DBS,

to directly test how manipulating these circuits influences affective and cognitive processes in humans.

The contextual excitability of NAc neurons determine the nature and magnitude of its effects; DA regulates the strength of incoming excitatory inputs via presynaptic mechanisms, effectively acting as a gating system to filter, amplify, or suppress specific afferent signals depending on their salience (Floresco, 2015). Through this intricate integration of glutamatergic and dopaminergic signals, the NAc plays a critical role in prioritizing behaviorally relevant information, particularly under conditions of uncertainty.

Once inputs are integrated, the NAc relays its output to a network of motor and autonomic control regions, including the ventral pallidum (VP) – which projects mainly to the Thalamus (i.e., Zhou et al., 2022), a core region in almost all perceptive (except smelling), cognitive, and affective processes (Bear, Connors & Paradiso, 2016), indicating NAc-influenced modulation of those vast processes – hypothalamus, and midbrain; creating a feedback loop to the VTA and other motor effectors (Floresco, 2015). The vast majority of NAc neurons – in most humans, over 90% – are GABAergic, meaning they project inhibitory signals to downstream targets (Floresco, 2015). These projections influence both the initiation and vigor of behavior, modulating whether and how intensely an organism engages with a reward or avoids a threat, indicating an influence on multiple cognitive and affective processes.

2.2.2 Functionality of the NAc

The NAc's broader functionality arises from its neurophysiological integration within the described systems. As mentioned, these include emotional (limbic), cognitive (prefrontal), motor, sensory, and autonomic circuits (Floresco, 2015; Salgado & Kaplitt, 2015). A core function of the NAc is to bias action selection, facilitating context-appropriate responses by modulating information flow to motor structures (Khamassi & Humphries, 2012). It may also provide outcome-based feedback to the PFC via polysynaptic pathways (connections via intermediate stations) through the VP and medial thalamic nuclei, helping update behavioral strategies based on action outcomes (Zahm, 2008; Floresco, 2015). These mechanisms highlight the NAc's role as not only a driver of behavior but also a key modulator of adaptive learning.

To further delineate the NAc's integrative role in motivated behavior, a growing body of functional circuit-level studies underscores its diverse input-output dynamics and their relevance for distinct behavioral domains ([Appendix Table D1: Overview of studies about NAc involving circuits and functionality](#)). Reward processing, for instance, seems to rely on

convergent input from VTA, PFC, amygdala, and hippocampus, with outputs to the VP and onward to the thalamus – forming a pathway critical for encoding reward salience and hedonic valuation (Bayassi-Jakowicka et al., 2021). Similarly, motivational drive emerges from VTA, insular cortex, and orbitofrontal cortex (OFC) input to hypothalamic- and VP-outputs, supporting goal-pursuit and effort-allocation (Salamone et al., 2005). In addition, these circuits form closed-loop reinforcements involving the PFC and Thalamus, modulating cue reactivity and drug-seeking (Kalivas & Volkow, 2005a).

Consequently, dysregulation of NAc activity has been consistently implicated in addiction-related behaviors, with its impaired functioning contributing to the loss of behavioral control in substance use disorders (Kalivas, Volkow, & Seamans, 2005b). More recently, the NAc has been linked to a broader range of neuropsychiatric and neurodegenerative disorders, including depression, schizophrenia, and Alzheimer’s disease, suggesting its involvement in multiple affective and cognitive processes (Bayassi-Jakowicka, Lietzau, Czuba, Patrone, & Kowianski, 2022).

In addition to these circuit-level mechanisms, recent models refine our understanding of how dopaminergic signaling shapes NAc function. Rather than diffuse transmission, dopamine release appears to be spatially and temporally structured, with sparse active release sites, domain-overlap dynamics, and modulatory influences from regions such as the amygdala (Liu, Goel, & Kaeser, 2021). These mechanistic insights align with the conceptualization of the NAc as a key hub of motivation central to evaluating effort and reward (Berke, 2018), and extend its role to adaptive cognition through processes such as belief updating, which can be disrupted by alterations in D2/D3 receptor signaling (Mikus et al., 2023). While still under investigation, these perspectives provide a theoretical foundation for targeting the NAc with neuromodulatory interventions such as LIFUS, offering novel opportunities to probe its role in affective and cognitive processes (see [Appendix E: Re-Thinking Dopamine](#)).

Evidence for the vast affective effects connected to NAc-activity is based mostly on clinical data: Depressive symptoms like anhedonia correlate with impaired signaling from medial PFC (mPFC), amygdala, and hippocampus to VP and thalamus to the NAc (Zhou et al., 2022). Additional circuits highlight the NAc’s involvement in effort-based cost-benefit analysis (Salamone et al., 2007), aversive learning (Verharen & Adan, 2020), decision-making under uncertainty (Diekhof et al., 2008; Haber, 2011), pain modulation (Harris & Peng, 2020), and the contextual grounding of goal-directed actions via hippocampal and OFC inputs (Xu et al., 2024). These findings substantiate the NAc’s role as a highly adaptive neural hub, capable of dynamically regulating behavior based on complex internal and external contingencies.

Although these circuits are thought to support the functions described, there is currently no comprehensive biopsychological model explaining how these complex processes interact or what mechanisms underlie them. Notably, both cognitive rigidity and mood disturbances are symptoms of disorders such as depression, which has been linked to NAc activity (Zhou et al., 2022). The NAc, its causal investigation especially, contains the potential to understand the underlying biopsychological mechanisms behind the mentioned effects and might even allow for consistent biopsychological models in the future (i.e., how NAc-stimulation affects cognition, affective processes and behavior).

Consequently, the NAc plays an integrative role in multiple circuits in the brain. Especially, the mentioned biopsychological mechanisms should be interpreted with caution, since such processes are highly complex, depend on multiple brain areas, and the outcomes of their scientific investigation depend on the design of the respective study. Different studies might show different outcomes, and again, causality of these effects and NAc-activity is yet to be established. This section, however, highlights the complex effects a stimulation of the NAc might cause in humans and shows the necessity to causally link distinct cognitive and affective processes to NAc-activity (Summary-table of NAc functionality in [Appendix Table D1: Overview of studies about NAc involving circuits and functionality](#)). As of now, only causal DBS-studies were able to highlight distinct psychological outcomes of targeted neuromodulation.

2.2.3 Stimulation studies of the NAc

To establish a causal link, the NAc must be directly stimulated or inhibited, allowing researchers to observe the effects of targeted modulation. Some evidence exists from direct NAc stimulation studies, primarily in clinical or pre-clinical (animal) models. As previously mentioned, DBS involves the neurosurgical implantation of electrodes to modulate specific neural populations – functioning analogously to a pacemaker, but for neural circuits (Herrington, Cheng & Eskander, 2016).

NAc-DBS in rats has been shown to reduce excitatory neurotransmission by decreasing glutamate and increasing GABA levels in morphine-treated animals, suggesting a dampening effect on mesolimbic reward circuit hyperactivity (Yan et al., 2013). It has also been found to enhance long-term memory, mimic dopaminergic novelty signals, and produce antidepressant-like effects, indicating a role in both cognitive enhancement and emotion regulation (Kale et al., 2021).

Due to the irreversibility and invasiveness of DBS, most human data stems from treatment resistant psychiatric or neurological cases. In treatment-resistant depression, for

instance, NAc-DBS can reduce depressive symptoms in human individuals, and can induce a hedonic effect (Bewernick, 2010), with significant long-term improvement (Bewernick, 2012). In a single-case psychiatric study, invasive DBS of the NAc resulted in an improved mood in a patient suffering from major depressive disorder (Giordana et al., 2015). Also, in obsessive-compulsive disorder patients, there is evidence for similar effects (Torres-Diaz et al., 2021; Sturm et al., 2003), as well as in anxiety disorder patients (Sturm et al., 2003). The underlying process may be explained by increasing γ -aminobutyric acid (GABA) outputs from the NAc to the VTA, which inhibit VTA-GABA neurons. This disinhibits (increases) dopaminergic neuron activity in the VTA; enhancing VTA dopaminergic outputs to D1-expressing (excitatory DA) neurons in the NAc (Song, 2024). Behaviorally, a clinical population of OCD-diagnosed individuals showed an improvement in behavioral adaptation while the NAc was being inhibited with DBS. Those findings indicate that changes of the NAc can lead to profound effects regarding mood and CF (OCD as rigid cognitive patterns in humans (i.e., Gu et al., 2008); behavioral adaptation (“flexibility of motor action control” in this case) as a cognitive flexible effort (Eijsker et al., 2020)).

2.2.3.1 LIFUS and the NAc

In addition to the already discussed evidence investigating effects of NAc - DBS, recent research has proven that LIFUS can affect the NAc on a neural level. A study by Peng et al. (2024) demonstrated that sonication of the left NAc resulted in bilateral decrease in activity of the NAc and increased functional connectivity between the NAc and medial prefrontal cortex (mPFC), suggesting two points: (1) LIFUS of one side of the NAc can induce bilateral effects; (2) LIFUS may modulate reward-related nodes & circuits implicated in affective processes and decision-making.

Mahoney et al. (2023) conducted a study applying LIFUS on the NAc, reporting that bilateral stimulation attenuated cue-induced substance cravings, with effects of an increased dose persisting for up to 90 days. Although the study’s sample was very small, with only four participants with clinical conditions, which limits the generalizability of the findings, these findings suggest that NAc-LIFUS is safe and can produce clinically meaningful effects. Importantly, the study included psychological measures, demonstrating that subjective states can be influenced long-term by NAc stimulation.

This not only shows that the NAc is reachable through LIFUS but also reinforces the NAc’s role in both motivation and flexible cognitive adaptation, supporting the potential of LIFUS as a neuromodulation tool for i.e., health psychological interventions, or disorders

marked by mood instability and cognitive rigidity. Importantly, both studies confirmed that LIFUS targeting the NAc was well tolerated and did not result in adverse structural brain changes, further underscoring its feasibility as a non-invasive intervention for improving affective states and CF.

In summary, while animal and clinical studies implicate the NAc in CF, mood, and hedonia, causal evidence from non-invasive LIFUS modulation in healthy humans remains absent. Critically, the behavioral specificity of LIFUS effects on subcortical targets like the NAc is unknown, and the interplay between these constructs (CF, mood, and hedonia) lacks empirical testing. The following sections will (1) define the core constructs under investigation (chapter 3), (2) formalize hypotheses bridging these gaps (chapter 4), and (3) detail a methodological approach designed to isolate NAc-specific effects (chapter 5).

3 Constructs

To evaluate LIFUS as a potential method to alter cognitive and affective states, the NAc is a strategic choice. Chapter 2 showed that the NAc plays a crucial role in multiple neural circuits related to a variety of cognitive and affective processes. We will further discuss why its role in CF, mood, and hedonia is especially crucial to evaluate. All constructs are linked to NAc activity.

3.1 Cognitive Flexibility

CF – “the ability to appropriately adjust one’s behavior according to a changing environment” (Dajani & Uddin, 2015) – is often defined as a core aspect of creative cognition (alongside fluency and originality) (i.e., Guilford, 1967; Hennessey & Amabile 2010). Thus, it is no surprise that CF has been linked to creative achievement in adulthood (Chen et. Al, 2014), as well as heightened levels of resilience to stress and negative life events (Genett & Siemer, 2011). In older women, set shifting (one aspect of CF, see section 2.2.1) and working memory were independently associated with higher quality of life (Davis, Marra, Najafzadeh & Liu-Ambrose, 2010). CF has a significant influence on the executive control network (ECN) (i.e., Dajani & Uddin 2015), which is relevant in basically all complex cognitive tasks, especially tasks including the so-called executive functions (it is even considered to be an executive function itself. I.e., Gullstrand, Cladière, Fagot, 2024). This shows on one hand how vast CF is neuroscientifically connected to large-scale networks, on the other hand, it shows how fatigue

in participants might influence CF outcomes. CF is also essential for appropriate behavioral responses – as shown in clinical impairment (Dajani & Uddin, 2015). Thus, the research of this “obvious core of creativity and problem solving” (Guilford, 1970) seems to be essential in a lot of cognitive processes that are not only important in everyday life throughout the whole lifespan but also hold clinical relevance. Neuromodulation has been shown to improve CF significantly on multiple instances (full review on this topic: Sachse & Widge, 2025).

An issue in evaluating literature about the concept of CF is that it is a heterogeneous construct, with multiple approaches of operationalization (Dias et al., 1996). In some studies, CF is defined by the processes required to shift attention; in other studies, it is defined by the task used to measure it (Dajani & Uddin, 2015). The main approaches to measure CF in a task are either *set-shifting*, which is the ability to shift attention from a learned strategy to a new strategy (i.e., Konishi et al., 1998), and *reversal learning* – the ability to actively adapt reward–stimulus related contingencies (i.e., Ghazinouri, Cheng, Krichmar & Brock, 2025). Propositions to unify the concept (i.e., Dajani & Uddin, 2015) have not yet been successful in the sense that CF is still a concept that is defined heterogeneously; sometimes it is not even clearly distinguished from concepts that are closely related to CF. Operationalization is often similar in i.e., behavioral flexibility (Ghazinouri, Cheng, Krichmar, Brock, 2025) and attentional flexibility (Vilgis, Silk & Vance, 2015). In the following, only research that implemented task-switching and set-shifting tasks will be regarded.

The NAc, especially through its connections with the medial PFC (mPFC), is essential for behavioral flexibility. Activation of the mPFC-NAc pathway improves performance on set-shifting tasks and reduces repetitive errors, highlighting its role in adapting to new rules or strategies (Duan et al., 2025). In addition, dopaminergic projections from the NAc modulate activity across multiple neural clusters, including prefrontal and striatal circuits, which are implicated in CF at the neural level (Ding et al., 2014). Specifically, this modulation likely influences the balance between excitatory and inhibitory inputs within these circuits, facilitating the updating of behavioral strategies and adaptive responses. Supporting this, clinical trials have demonstrated causal improvements in CF following NAc stimulation (Eijsker et al., 2020). Therefore, CF represents a theoretically grounded construct for this proof-of-concept study.

3.2 Mood

There are multiple ways to define what mood is: According to the American Psychological Association (APA), mood is “disposition to respond emotionally in a particular way that may last for hours, days, or even weeks, perhaps at a low level and without the person

knowing what prompted the state. Moods differ from emotions in lacking an object; for example, the emotion of anger can be aroused by an insult, but an angry mood may arise when one does not know what one is angry about or what elicited the anger. Disturbances in mood are characteristic of mood disorders.“ (APA, n.d., "Mood"). In cognitive psychology, mood is defined as a persistent group of feelings that shape one's evaluative and cognitive states, thereby modulating future thoughts and behaviors (Amado-Boccaro et al., 1993). Clark (2005) further characterizes mood as a prolonged emotional tone that impacts one's mental landscape, including health perceptions, self-confidence, and environmental interpretations.

Notably, mood is a heterogenic construct. There are different types of mood and ways to address mood scientifically which are not yet congruently unified into one construct. (i.e., generally, in everyday life there is the dimension of “good” and “bad” mood, but one can also be in a “sociable” or “reserved” mood, or be “(in)attentive” etc. which does not necessarily align with the one-dimensional perspective of “good” vs “bad” mood .). For this study, we will not define mood in a specific way. The broad APA-definition serves as a working definition and the operationalization of mood (see section 5.2.2) will address multiple dimensions of mood.

Mood can influence well-being (Cummins, 2010), and the mood-behavior model even proposes mood impacts most behavioral outcomes (Gendolla, 2000). Evidence also shows a mood-based effect on cognitive processes like cognitive control, decision-making and working memory (Martin & Kerns, 2011), indicating an influence on CF as well. The underlying neural pathways of different types of mood lack causal investigation in healthy individuals. Such causal investigations (i.e., with LIFUS) could clarify which brain areas are involved in different moods and potentially, how malleable they are. The NAc, as mentioned, influences many mood-related states and conditions: Most notably, reward and motivation, which are central to processing pleasure. In addition, the NAc is involved in most major neurotransmitter systems (DA, Serotonin, Acetylcholine, GABA, Glutamate) indicating involvement in the modulation of most mood states (Floresco, 2015). Additionally, in mood disorders, chronically dysregulated affective states like apathy or mania have been associated with altered activity in the NAc (Kale et al., 2021). In order to also investigate affective phenomena that can be more precisely operationalized and are closely tied to the NAc, we included hedonia (see section 3.3).

3.3 Hedonia

Hedonia – the pursuit of pleasure, comfort, and the experience of positive emotion (Huta & Ryan, 2010) – serves essential adaptive functions and is tightly linked to mesocorticolimbic systems, prominently involving the NAc (Berridge & Kringelbach, 2015; Höflich et al., 2019). It is a fundamental form of positive affect (Berridge & Kringelbach, 2015). Unlike eudaimonia, which concerns meaning and long-term fulfillment (Huta et al., 2010), hedonia reflects more immediate and measurable affective experiences, making it particularly well-suited for experimental research. Music-induced pleasure offers a compelling and ecologically valid way to operationalize hedonia: it elicits robust activation in reward-related brain areas, including the NAc, and can be manipulated systematically in controlled tasks (Jenkins et al., 2018).

Notably, music-based paradigms capture both anticipatory and consummatory phases of hedonic response while providing a non-invasive and repeatable method for assessing individual differences. In line with this, the construct of musical anhedonia has emerged as a specific marker of diminished hedonic responsiveness, characterized by an inability to experience pleasure from music despite intact reward sensitivity to other stimuli (Martínez-Molina et al., 2016). Crucially, this condition has been linked to reduced NAc activation during music listening, underscoring the centrality of this structure in music-evoked hedonic states. Compared to broader constructs such as mood or CF — which rely on distributed brain networks — hedonic responses to music are more directly linked to NAc function (Malik, Chanda & Levitin, 2017; Martínez-Molina et al., 2016). As such, music-based tasks represent a highly targeted approach for evaluating the feasibility of neuromodulation techniques like LIFUS, aimed at modulating NAc activity and altering hedonic processing.

While the current study focuses on hedonic function, it is closely intertwined with its counterpart, anhedonia – the reduced ability to experience or pursue pleasure – which has been far more extensively characterized in affective neuroscience and clinical psychology (Rømer Thomsen et al., 2015) than hedonia. Integrating findings from the anhedonia literature is therefore essential for establishing the relevance and validity of the hedonic construct examined here. Anhedonia was introduced by Ribot (1897), it is a hallmark of several psychiatric disorders, including major depressive disorder, bipolar disorder, and anxiety (Rizvi, Lambert & Kennedy, 2018; Steinmann et al., 2022; Winer et al., 2017). However, anhedonia-related traits also appear in non-clinical populations and have been linked to structural and functional alterations in the NAc, such as reduced volume (Auerbach et al., 2017) and diminished responsivity (Wacker, Dillon & Pizzagalli, 2009; Dillon & Pizzagalli, 2009). Stress-related neuroadaptations in this region, including those affecting D1-receptor-expressing neurons (Lim

et al., 2012), further support the NAc's critical role in hedonic regulation. Moreover, individual differences in NAc connectivity have been shown to distinguish between forms of anhedonia (Hu et al., 2023; Liu et al., 2021b), reinforcing the link between hedonic function and NAc circuitry. These findings provide a translational rationale for using hedonic response – particularly in the musical domain – as a sensitive readout in studies targeting the NAc with LIFUS.

3.4 Linking the Constructs

CF, mood and hedonia, even though distinct psychological concepts might be linked by neural underpinnings (Anacker & Hen, 2017). Especially, the link between mood and CF seems to be crucial for understanding how neuromodulation might affect CF. CF plays a role in resilience (Genett & Siemer, 2011), its improvement has a therapeutic effect on affective disorders (Dajani & Uddin, 2015), and its impairment, being prevalent in most affective disorders – such as depression (Zhang et al., 2024) – indicates the importance of looking at the interactions of CF and mood in general. Also, CF – in this case, switch costs (in set-switching experiments) – were larger in patients with mood disorders versus healthy controls (Piguet et al., 2016), indicating a correlation between impaired mood processing and CF. There are limited findings on mood and CF in healthy participants. While not necessarily generalizable, this suggests that emotional processing can influence cognition. Thus, there is need to evaluate a causal link between these concepts.

A common neural underpinning of mood and CF seems plausible: There is compelling evidence that the VTA-NAc dopaminergic pathway is linked to CF (Radke et al., 2019), and mood (Elmaghraby, Nobari, Schreiner, & Cullen, 2018). The modulation of such pathways can be relevant in understanding – and modelling – CF, mood and especially their interactions. Thus, linking these concepts causally seems to be valuable research.

Extending this line of reasoning beyond mesolimbic dopamine, downstream plasticity mechanisms provide an additional substrate through which mood and CF may interact. Neurogenesis mechanisms in the hippocampus are heavily influenced by mood and CF (Anacker & Hen, 2017), indicating that mood, CF, and memory could be causally related.

Complementing these neural findings, behavioral research on mood-related beliefs and performance further underscores the functional significance of this interaction. Hirt, Devers & McCrea (2008) found positive effects of mood-related belief systems (mood is perceived as changeable vs. not changeable) and CF, mood, and self-reported creative abilities, as well as

good mood (“being happy”) and performance in a task regarding CF. These findings indicate that being in a good mood is a crucial component to evaluating findings on CF (as well as creativity and related concepts).

A lot of studies regarding mood in relation to the NAc, the dopaminergic system and CF were clinical trials (linked to *mood disorders* rather than *mood* in healthy individuals). Part of the affective disorders addressed in these studies is hedonia: Its deficit is linked to a deficit in reward processing and to various affective disorders, including major depressive disorders and mood disorders (Keren et al., 2018; Whitton, Treadway, & Pizzagalli, 2015). Therefore, hedonia is an affective state that might explain the correlation between CF and affective disorders. To support that, hedonic orientation has been shown to moderate the relationship between cognitive control and affect in adolescent boys (Klipker et al., 2017). Otherwise, a link between affect, cognition, and hedonia has not yet been empirically established to our knowledge.

This study seeks to bridge the gap between several implications drawn from clinical studies by causally analyzing the NAc’s role in hedonia. Since, a direct link between CF and hedonia has not yet been established. As mentioned, due to neural similarities – including NAc-involvement and both constructs being involved in affective disorders, such a link seems plausible, suggesting that all three constructs might be connected and the NAc as an integrational hub might be part of the neural underpinnings of such a connection.

3.5 Causal Data-Driven Model

In neuroscientific experiments, there is usually the issue of not getting enough test power because sample sizes are usually low (i.e., Grady et al., 2020). This is most likely due to the large number of resources needed to gather data in cognitive neuroscience, since one usually needs to assess each participant individually in a rather complex setup (i.e., MRI, LIFUS etc.). Low sample sizes hold implications for the informational value of most neuroscientific experiments (i.e., Grady et al., 2020; Lakens, 2021). This can affect the outcome of neuroscientific research (i.e., Vozzi et al., 2021), since it leads to smaller statistical models and low overall test power, meaning that only large effects are likely to reach significance. Larger models, potentially showing meaningful connections between constructs, require either simulated (artificial) data or sample sizes that are usually not affordable.

For this reason, an exploratory analysis was aimed at using a bootstrap method to simulate data. Such an exploratory simulation of a larger model would have only been justified

if the data of the study looks promising (i.e., large effect sizes and / or significant results in the rather simple statistical tests of the other hypotheses). This data was supposed to be used to assess a more complex model of the involvement of the NAc in cognition and mood. Data selection will be exploratory and was aimed at generating models testable in future research. This procedure would have been in accordance with previously proposed models to enhance test power in neuroscientific research (i.e., Eckel & Eckstein (2019)).

4 Research Question and Hypotheses

Insights into the LIFUS of the NAc could expand not only knowledge about a key structure of the dopaminergic system (Boot et al., 2017; Salgado & Kaplitt, 2015) but also show how LIFUS might replace DBS in future clinical applications, making brain stimulation interventions more accessible and non-invasive. Since the NAc is involved in many cognitive processes related to cognitive control, CF, reward processing and mood, an investigation of healthy individuals seems to be relevant to determine how LIFUS sonication of the NAc affects healthy brain function. These findings may have implications for clinical models and could further inform neuroscientific conceptualizations of the NAc and could hold more generalizable psychological implications.

The overarching research question arises from the LIFUS's potential as a form of NIBS, which can reach subcortical areas with unprecedented precision, and from the current research gap in applying this method to alter cognitive and affective processes: Does LIFUS sonication of a subcortical brain area alter cognitive and affective processes in humans?

A more concise question was derived out of the mentioned neuronal connectivity of the NAc, along with the clinical implications of NAc-DBS, indicating that NAc sonication should alter CF and affective states, like hedonia (see Chapter 3). In addition to that, the constructs of CF and mood are concepts that are quite broad and highly complex and psychologically relevant in multiple regards. Altering these constructs through sonication would have important implications for clinical and preventive psychological / psychiatric use cases. Hedonia is more directly linked to NAc activity and engages fewer additional brain regions than the other two, making it particularly suitable for testing the proof-of-concept of LIFUS. Thus, the more directed research question is: How does LIFUS sonication of the NAc alter CF, mood and hedonia?

The hypotheses had to be adjusted to the expected sample size of $N \sim 20$, which is why the effect of NAc – LIFUS application on the three constructs were investigated in individually testable hypotheses. Exploratively, a larger scale model was hypothesized, since – as mentioned – the three constructs might be related by neural underpinnings. Mood or hedonia could, for instance, have moderated the effect on CF. However, a confirmatory model was not available, as testing this hypothesis would have required a fully data-driven approach by using a bootstrapped based simulation to achieve a greater sample size. This explorative hypothesis, however, would have only made sense if clear trends would have become apparent in the confirmative hypotheses. As a summary, these are the hypotheses of this study

Confirmatory Hypotheses:

1. H1: LIFUS sonication of the NAc leads to changes in cognitive flexibility
2. H2: LIFUS sonication of the NAc leads to changes in mood
3. H3: LIFUS sonication of the NAc leads to changes in hedonia

Explorative hypothesis:

H4: A simulation of the study's data will show that LIFUS of the NAc can explain an explorative model of mood and cognitive flexibility

The research gaps that these hypotheses address are multiple: Notably, they are a proof-of-concept of the LIFUS method, since psychological effects (not “only” effects on neural connectivity) due to subcortical LIFUS-sonication have not yet been evaluated enough to prove such mechanisms (a). Insights into the causal relationship between NAc and cognitive & affective processing would inform future studies and potential therapeutic mental health applications/interventions (i.e., Qiao et al., 2020; Beda, Smith & Orr, 2020) by providing models of causal effects (b). Finally, if significant effects were found, the direction of effect would hold valuable information on whether our LIFUS-parameters (see table 2) stimulate or inhibit the NAc (c). The following chapters present the methods, operationalization, and data analysis (chapter 5), followed by the results (chapter 6) and a discussion of the findings, limitations, and implications for future research (chapter 7).

5 Methods

We utilized a randomized, controlled experimental design to investigate the effects of LIFUS on cognitive and mood-related measures (full study design as a diagram: [Figure 2: Study Design](#)). A within-subject, repeated-measures design was employed, with each participant undergoing both active and sham stimulation in separate sessions. The target region for stimulation was the right NAc (rNAc). To minimize carry-over effects, sessions were spaced at least seven days apart (Bergmann & Hartwigsen, 2021). Participants attended three study sessions. In the initial session, anatomical magnetic resonance imaging (MRI) scans (T1, T2, and PETRA) were obtained for neuronavigation and LIFUS sonication simulations. Sessions 2 and 3 involved the administration of LIFUS in either the active or sham condition. The condition order was randomized across participants.

Upon arrival for each stimulation session, participants completed baseline cognitive and mood assessments, including a Visual Analog Mood Scale (VAMS) and a Stroop task (list of all tasks and questionnaires: [Figure 2: Study Design](#)). After the assessments, participants were prepared for sonication by securing their heads in a head and chin rest, and a neuronavigation system was used to position the transducer at the pre-determined target location. The sonication trajectory was actively monitored to ensure accuracy. Following stimulation, a post-sonication pause of 12 minutes was implemented to allow potential effects to manifest (e.g., Dallapiazza et al., 2017; Yaakub et al., 2023). Participants then completed a second round of cognitive and mood assessments, which included the same tests as the pre-sonication phase, along with a music task and a post-sonication questionnaire regarding their subjective experience and perception of the treatment condition. After the final session, participants were debriefed on the study's aims and given an opportunity to ask questions.

We used a single-blind design to make sure participants did not know whether they were receiving active or sham stimulation. The only difference between the two conditions was the type of gel pad used: the active pad was transparent, while the sham pad was white. However, measures were being taken to make sure that participants would not see the gel pad at any time: All gel pads were arranged in the same way on a separate equipment table before each session, and the application was carried out of the participant's line of sight. After stimulation, the pads were cleaned, placed back on the table, and covered with a paper towel to avoid identification based on leftover gel. The transducer emitted a sound that was audible during active and sham sonication, ensuring further that participants couldn't tell which treatment they were receiving based on auditory cues. If a participant accidentally saw one of

the pads, the blinding was still considered intact, since they were not informed about what the different pad types meant.

Prior to data acquisition, each participant was required to complete a questionnaire to confirm their eligibility for the study. To ensure standardization across subjects, selection criteria were chosen accordingly to what our study was designed to measure: Participants had to be between the ages of 18 and 40, to control age-related effects, and right-handed, to maximize the likelihood of participants' brains being as similar as possible. Since questionnaires and instructions for the tasks were presented in German language, each participant needed to be at least at C1-level in German to make sure instructions and items were understood as intended. Participants were excluded if they had a diagnosed neurological or psychiatric disorder, received medical treatment at the time of data acquisition, were non-compliant with the study protocol, were not able to give informed consent, or if any contraindication for MRI and LIFUS was present (i.e., a pacemaker, any chance of pregnancy, or the possibility of metal inside the participants body). MRI-criteria are standardized criteria of the University of Vienna; LIFUS-criteria were adopted from TMS protocols (Rossi et al., 2011), since there exists no established screening questionnaire for LIFUS yet, as to our knowledge (Schmid & Crone, 2025).

Due to time constraints and the aim of completing the thesis within the scheduled period, only a subset of the full study sample was used for this analysis. Specifically, the data analyzed reflects participants tested up until April 1st, 2025 (N = 21). While the overarching study (Schmid & Crone, 2025) continues to collect data and is expected to include a larger sample, this thesis focuses on an interim analysis based on the available data at the time of writing. This decision allowed for a timely proof-of-concept evaluation, but with limited statistical power.

5.1 Model-Based Planning and Sonication Protocol

To ensure accurate and safe targeting with LIFUS, we used individual, simulation-based planning to correct for skull-induced distortion and attenuation of ultrasound waves (Murphy et al., 2024; Pichardo, 2023). The target, the rNAc, was identified using a T1-weighted anatomical scan (a high-resolution structural magnetic resonance imaging scan emphasizing differences in T1 relaxation time), which was first processed with optiBET (Lutkenhoff et al., 2014) and non-linearly registered to Montreal Neurological Institute (MNI) standard space within the FMRIB Software Library (FSL) suite (Jenkinson et al., 2012). A mask in MNI space of the region of interest (ROI; here, the predefined rNAc area) was derived from the subcortical

atlas by Tian et al. (2020) and overlaid on the MNI-normalized T1 image. The T1 image and ROI mask were then merged and transformed back into each participant's native (individual anatomical) space using optiBET, yielding an individualized rNAc target for subsequent procedures.

T1 and T2 scans were resampled to 1-mm isotropic resolution and co-registered. A head mesh was created using SimNIBS (Thielscher et al., 2015). The trajectory was planned in Brainsight (Rogue Research, Montréal), where a virtual transducer was aligned to the scalp and directed, so that a transducer-based trajectory perpendicular went through the ROI. This trajectory was saved for simulation in BabelBrain (Pichardo, 2023). BabelBrain simulations involved three steps: (1) creation of a segmented simulation domain with the carrier frequency (see table 2) as input and a resolution of ≥ 9 points per wavelength (PPW = standard rule to accurately resolve the wave without too much numerical error) (2) acoustic simulation to visualize the beam path and focal point using normalized Spatial-Peak-Pulse-Average-intensity (ISPPA = intensity Distribution of how strong the ultrasound is at each point during the pulse) maps; and (3) thermal simulation that gives information about local temperature rising and sonication parameters (Table 2). Misalignment or insufficient focus prompted either minor corrections or a new trajectory plan. Final outputs, including acoustic maps and thermal estimates, were saved and integrated into Brainsight for guided stimulation (For more detail: Schmid & Crone, 2025).

For sonication, the BXPulsar 1001 ultrasound device (BrainSonix Corporation, Sherman Oaks, California, USA) was used. The sonication sessions lasted nine minutes and 50 seconds. A standard block design was implemented: Ten seconds of LIFUS and ten seconds of no-LIFUS alternating for 30 blocks. The BXPulsar 1001 device allows different transducers (see Table 2) depending on the target region and the subject's anatomical characteristics. The BabelBrain simulation (Pichardo, 2023) made it possible to decide which transducer would work best. The detailed parameter settings for the transducers used are displayed in the table below (Schmid & Crone, 2025):

Table 2*Technical Parameters of the Two Transducers Used in LIFUS Protocol*

Parameter	65 mm Transducer	80 mm Transducer
Carrier wave	650 kHz	650 kHz
Pulse repetition frequency	100 Hz	100 Hz
Pulse width	0.5 ms	0.5 ms
Duty cycle	5%	5%
I_{SPTA}	720 mW/cm ²	661.12 mW/cm ²
Pressure amplitude	0.725 MPa	0.71 MPa

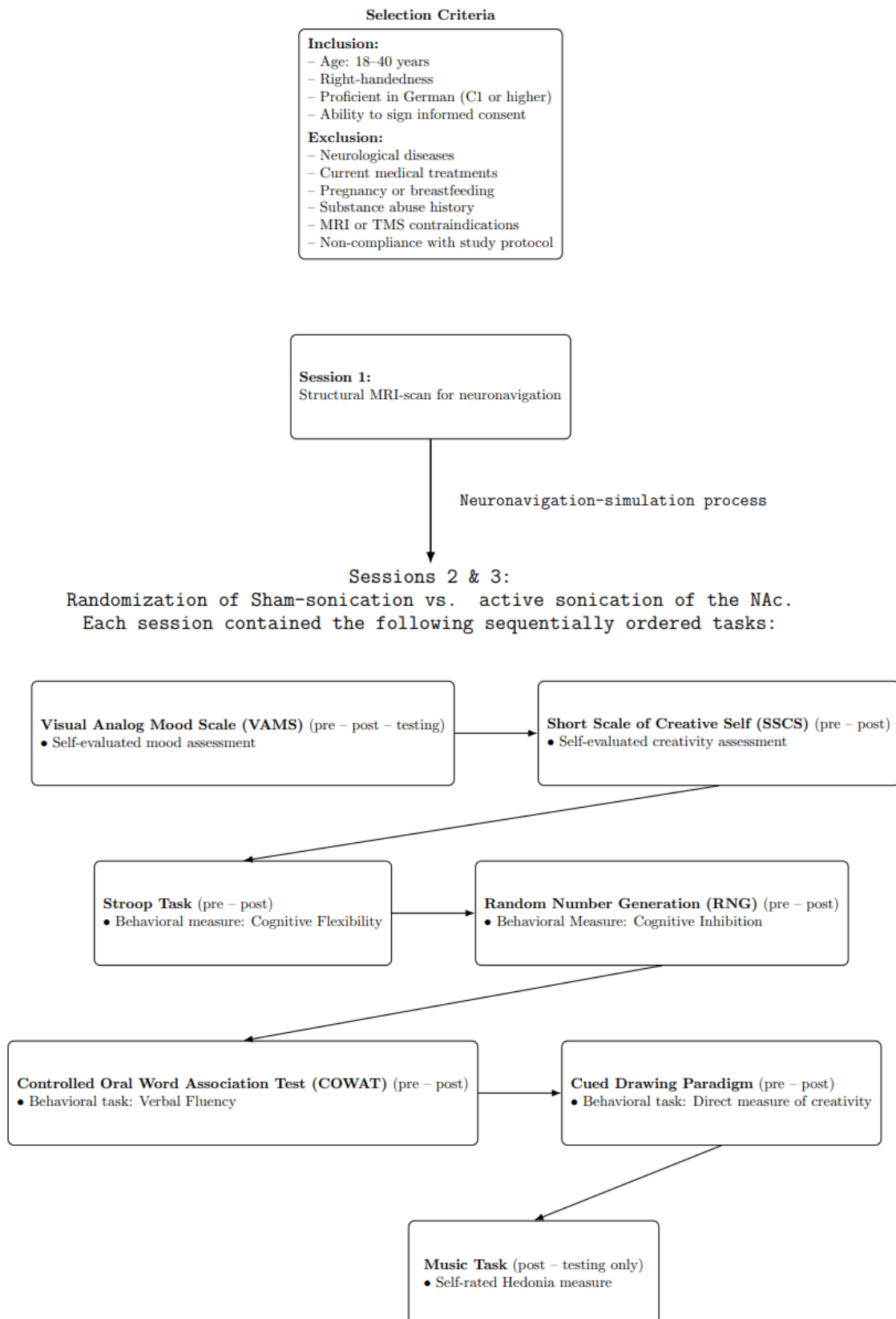
Note: I_{SPTA} = Spatial Peak Temporal Average Intensity; MPa = Megapascal; mW/cm² = milliwatts per square centimeter.

Disclaimer: This table is derived from the pre-registration of Schmid & Crone (2025). It is included to provide technical details for comparison in future studies.

Prior to this study, a pilot study (N = 7) was conducted. In this study, the tasks, except for the music task, were tested. The initial goal of this research was to causally link a dopaminergic key hub to creativity (CF as a more robustly operationalizable proxy). To see which of those brain areas was the most promising to conduct research on, the rNAc and the right Caudate nucleus were targeted in separate sessions. A sham session was included to control LIFUS-specific effects. Thus, the participants underwent three sessions (sham vs. rNAc vs right Caudate Nucleus) in randomized order. Since the NAc showed stronger results in the implemented Stroop task, and a Random Number Generation (RNG) task, it was decided to only sonicate the NAc to maximize efficiency while reducing participant fatigue and stress (each LIFUS-session took about three hours to complete); also, potential training effects were minimized by this decision.

Fig. 2

Diagram of the Study Design



5.2 Operationalization, Scoring and Data Analysis Plan

Due to the low sample size, assumptions for a parametric test according to the general linear model (GLM) (i.e., paired t-test, mixed or repeated-measures ANOVA) had to be evaluated. Non-parametric alternatives would be the Wilcoxon signed-rank test (for comparing two dependent groups) and the Friedman test (alternative to a repeated-measures ANOVA, when analyzing more than 2 groups)). A Linear mixed model (LMM) would have made sense since informative individual variability – especially in the behavioral tasks comparing reaction times (i.e., Stroop task) – was to be expected.

However, due to the research question, a comparison of i.e., Session (pre vs. post) or condition (sham vs. sonication) might hold too little information to justify the complexity of such a model. Even for a robust LMM (*rlmer* from the *robustlmm* package in R would be suitable), the expected sample size might be too small ($n < 25$). Results would therefore need to be cross-checked with a Wilcoxon signed-rank test, if normality in data distribution is not reached. While this test is less informative in terms of model complexity, it is a statistically robust, non-parametric statistic that does not hold many assumptions, which might make it the most suitable test for the data. This is also why outliers will not be excluded from the analysis. The trade-off between test power and statistical robustness of the data will most likely not be sufficient to have excluded outliers systematically.

Missing data in either part of the study led to participant exclusion from the respective analysis, since any kind of imputation can have significant impact on the results in small sample sizes. If any data had been missing in one part of the task, the data set would not have been complete anymore, and its inclusion would have resulted in a distortion of data. This does not apply to any missing Stroop data that implies information on participant performance.

All hypothesized models include random intercepts for subjects to account for repeated measures. Model assumptions were assessed prior to interpretation. These included checks for normality of residuals, homogeneity of variance, and sphericity where applicable. Statistical significance was interpreted at an α level of 0.05. Potential effect sizes (e.g., partial η^2 or Cohen's d , depending on the respective analysis method) have not been reported since there was no case of statistical significance.

5.2.1 Cognitive Flexibility (Stroop)

For this study, CF was evaluated through the Stroop task (Stroop, 1935) in a task-switching design, which requires cognitive control, especially cognitive inhibition of switching

conditions (Wu et al., 2015). The Stroop Task remains one of the most robust paradigms for investigating response inhibition, sustained attention, and cognitive interference in controlled processing tasks (MacLeod, 1991; Smith et al., 2019). In its contemporary computerized adaptation, participants are presented with color words on a laptop screen, which appear either in plain text (e.g., *green*) or enclosed by bars (e.g., *|green|*), with each format serving as a cue to attend either to the font color or to the word. This dual-cue design enables systematic manipulation between two task conditions: the *interference* condition, where participants must inhibit automatic reading and respond to the font color, and the *switch* condition, where they must shift attention and respond to the semantic content of the word. Each trial can further be *congruent* (font color matches the word) or *incongruent* (font color differs), creating varied cognitive load. The task is structured in two phases: the initial phase consists solely of interference trials (54 trials across 6 randomized blocks), while the second includes both interference and switch trials (108 trials in 3 pseudorandomized blocks with a 3:1 ratio). Participants receive instructions and perform a brief training phase before each condition, with short breaks separating task segments to minimize fatigue and preserve attentional consistency. To quantify CF rather than just inhibition, we utilized a score that operationalizes the task-switching aspect in the following way: Performance was indexed using the Inverse Efficiency Score (IES) – a measure that combines reaction time and accuracy by dividing the mean reaction time by the proportion of correct responses (Townsend & Ashby, 1978). This scoring approach provides a sensitive metric for detecting differences in cognitive control demands between switching and non-switching trials, analyzing more information than rather traditional measures, which usually only compare reaction times (RTs) (Hughes et al., 2014; Vandierendonck, 2017), allowing for more nuanced interpretations of executive function engagement in Stroop paradigms. The formula for the IES is:

$$IES = \frac{\text{Mean reaction time}}{\text{Proportion of correct responses}}$$

The final score was calculated with: $\frac{IES_{post} - IES_{pre}}{\sigma(IES_{pre})}$ per participant and condition. This scoring ensured standardization, according to baseline performance.

The first hypothesis was planned to be analyzed by taking the difference of the already discussed IES score (see above) of post-task and pre-task measuring and compare it over both conditions. Thus, if parametric assumptions were met, a LMM would have been the expected model: CF, operationalized via the Stroop Task (post – pre difference in IES):

$$IES \sim \text{condition} + 1 \mid \text{subject}$$

Since parametric assumptions (i.e., normality of distribution of residuals) were not met, the Wilcoxon signed-rank test was most suitable for analysis. This test is appropriate to analyze data of within-subject study designs.

5.2.2 Mood (VAMS)

To assess participants' *mood*, we employed the Visual Analog Mood Scale (VAMS), a psychometric tool for capturing subtle affective states, validated by Luria (1975). Participants were presented with a horizontal bar anchored by two opposing mood descriptors in German (e.g., *wach (alert) - schläfrig (sleepy)*; *ruhig (calm) - aufgeregt (agitated)*) and were instructed to indicate their mood by marking a point along the bar. This format treated the bar as a continuous, analog scale, allowing participants to place their response at any point along the continuum. Research has shown that analog scales enable finer emotional discrimination than discrete Likert-type scales (Machado et al., 2019). In the current study, the VAMS was administered across 16 consecutive bipolar dimensions (full list, including item reversal in [Appendix G: VAMS – Supplementary Material](#)). The analog scale was implemented with continuous granularity (no discrete points) to capture micro-level distinctions in affective state. From these ratings, we derived four composite scores: *Mental Sedation*, *Physical Sedation*, *Tranquilization*, and *Other Feelings*. These indexes distinguish affective dimensions relevant to mood variability and intervention effects. However, in the manual of this scale (non-published), it is explained, that the authors do not believe that mood can be theoretically cut up in these subscores. They were still used as intended by the authors since they might provide interesting insights about the nature of the NAc's effect on mood. However, also an overall mood score was used to check for overall effects.

For each of these dimensions, scores were first transformed into percentages (ranging from 0 to 100), based on their relative placement on the visual analogue scale. Then, for each session (pre vs. post), the mean score for each subscale was calculated. To capture changes due to the intervention, difference scores (post – pre) for each participant and condition (sham vs. sonication) were computed, resulting in two values per participant per subscale — one for each condition. These were not standardized with the standard deviation of the participant's pre-scoring, as for the first hypothesis, since the VAMS-data is self-evaluated. Thus, the standard deviation shows no behavioral tendency. Also, there is only one score for each dimension which increases the probability of unsystematic tendencies in each participants standard deviation.

Given that the VAMS subscales might be conceptually related, statistically correlation was tested, and multivariable assumed. The approach of individually comparing the four

subscores might have ignored meaningful shared variance between them and risk inflating Type-I-error or losing statistical power due to multiple comparisons corrections. High intercorrelations between the subscales would suggest that the effects of the condition may not act independently across subscales but instead reflect a multivariate effect. To account for this, the intercorrelations were taken into account. Significantly correlated Subscales were combined into an overall multivariate model. Since some data was multivariate, a MANOVA made most sense. Any subscale that was not correlating significantly was tested on its own to increase robustness either with a Wilcoxon signed-rank test or a paired t-test, depending on the normality of distribution.

Formally, the expected MANOVA Model can be expressed as:

$$\mathbf{Y}_i = \boldsymbol{\mu} + \mathbf{C}_i + \boldsymbol{\varepsilon}_i$$

Where:

- $\mathbf{Y}_i$ is the vector of dependent variables (VAMS subscale difference scores) for participant i ,
- $\boldsymbol{\mu}$ is the grand mean vector,
- $\mathbf{C}_i$ represents the effect of the **within-subject condition** (sham vs. NAC),
- $\boldsymbol{\varepsilon}_i$ is the vector of residuals.

5.2.3 Hedonic experience (Music Task)

Hedonia was inferred by measuring hedonic experience. More specifically, the hedonic response towards music was measured. An improvement in hedonic experience is interpreted as a improvement of hedonia.

To measure hedonic experience, a Music Task was implemented. This task was developed in a study that has not yet been published (as of current knowledge). Prior to participating in the LIFUS sessions, participants were required to provide 10 self-selected emotionally moving (favorite) songs and 10 self-selected emotionally neutral songs. Participants also indicated the peak moment of emotional impact for each moving song. This idiographic approach was chosen because previous research has shown substantial inter-individual variability in musical preferences and emotional responses (Salimpoor et al., 2011). Since the focus was not on music per se, but on the hedonic experience, it was critical to ensure each participant would reliably experience this hedonic response.

Using the open-source Python multimedia framework ffmpeg (Tomar, 2006), 70-second audio excerpts were created around each participant-indicated peak for the moving songs. Neutral songs were trimmed to 70-second random segments. All excerpts were volume-normalized, sampled at 44.1 kHz, and had 2-second fade-ins and fade-outs to prevent abrupt transitions and reduce startle effects.

The Music Task was divided into two runs, each with three blocks alternating between positive and neutral music conditions. The order of blocks was counterbalanced across participants. Each trial began with a one-second pictogram instructing participants to close their eyes, followed by the music excerpt. After each excerpt, participants rated: How moving the experience was ("Were you moved?", Scale from 1 to 10); Whether chills were felt ("Did you feel chills?"; scale from 1 to 9). The task lasted approximately 25 minutes per condition and was only conducted post-sonication (active or sham) to reduce burden and prevent fatigue.

The moving experience rating captures the degree to which participants found a musical excerpt emotionally pleasing or moving. This dimension reflects subjective enjoyment and emotional resonance with the stimulus, both central features of hedonia. In the context of anhedonia – the reduced capacity to experience pleasure – lower aesthetic ratings may indicate diminished sensitivity to typically rewarding stimuli (in this case, music that one usually enjoys).

This rating is complemented by the chills response that allows for capturing a broader aspect of musical enjoyment. The chills response – often described as a “pleasurable shiver” or “goosebumps” in response to emotionally powerful music – serves as subjective, psychophysiological marker of emotional arousal and reward sensitivity (de Fleurian & Pearce, 2021). There is evidence that this dimension has a modulatory effect on reward processing in hedonia (Jain et al., 2025) and that chills is directly connected to NAc activity (Sachs, Ellis & Schlaug, 2016). Thus, a combined model of the moving and the chills score might provide valuable information on how the NAc is involved in hedonia.

Scores were computed by subtracting the mean response values after listening to a song they liked with the mean response while listening to a neutral song. This focuses the scoring on the effect that the hypothesis (H3) is looking at. The dimensions are significantly correlated, which makes sense, since they are conceptually linked. A MANOVA was implemented to analyze the (an)hedonic experience. If there is no significance in correlation, both dimensions will be analyzed individually. Either in an LLM or the equivalent for non-parametrically distributed data set, the Wilcoxon signed-rank test, would provide a robust analysis of the data,

while not modelling as much information of the data. The expected model was: Music Task (Hedonic- rating in each condition)

$$\text{Moving Ratings} = \beta_0 + \beta_1(\text{Condition}) + (1 | \text{Subject}) + \epsilon$$

$$\text{Chills Ratings} = \beta_0 + \beta_1(\text{Condition}) + (1 | \text{Subject}) + \epsilon$$

In the case of both variables being significantly correlated (using Pearson's r), the analysis method of choice was a Multivariate Analysis of Variance (MANOVA), since this type of model accounts for the increased Type I error probability associated with conducting multiple univariate tests. MANOVA is particularly suitable when dependent variables (in this case, aesthetic and chills ratings) are theoretically related (which they are) and empirically intercorrelated, as it evaluates the effect of the independent variable (condition) on the combined outcome space.

To examine the multivariate effect of experimental condition on participants' affective responses to music, a two-way MANOVA was conducted. The MANOVA model is specified as follows: The independent variable is the condition in 2 levels (NAC-sonication vs. Sham); while the dependent variables can be specified as: Y_1 = Mean Moving Experience Difference Score (Moving music – Neutral music), and Y_2 : Mean Chills Rating Difference Score (Moving music – Neutral music). With this in mind, the MANOVA model can be specified as:

$$[Y_1 \ Y_2] = \mu + \tau_j + \epsilon;$$

where: μ = overall multivariate mean; τ_j = effect of the j -th condition (LIFUS or Sham); ϵ : multivariate error term.

A significant result would indicate that the condition has a statistically significant effect on the multivariate pattern of responses. Assumptions of multivariate normality, homogeneity of covariance matrices (Box's M test), and linear relationships between DVs were assessed prior to interpretation.

In cases, in which assumptions of normality (evaluated through the Shapiro–Wilk test) and multivariate normality were not met, a non-parametric alternative was applied. , the Wilcoxon signed-rank test was performed for each dependent variable independently. Although this method does not account for covariance between outcomes, it is robust against violations of distributional assumptions and still allows for valid inference regarding within-subject differences across conditions. In this case, the moving experience would be most important, while the chills rating is mainly explorational.

5.2.4 A bootstrap-based simulation of the study's data will show that LIFUS of the NAc can explain an explorative model of mood and cognitive flexibility

This hypothesis is purely exploratory and builds on the findings of the previous analyses. If none of the confirmatory hypotheses yield significant results, this extended model would lack interpretable statistical value. In such a case, pursuing it further would risk drifting into post-hoc theorizing (i.e., hypothesizing after the results are known (HARKing)), which is widely regarded as problematic in psychology, particularly in light of the replication crisis (Ioannidis, 2005).

The primary aim here is to compare different model types and inferential methods to determine which approach provides the best fit for the data, especially when working with a synthetically enhanced sample. If meaningful patterns emerge, the potential relationship between CF and mood would be of particular interest. For instance, it could be examined whether mood, as an affective context for cognition, moderates or mediates CF. If such effects can be modelled, they could provide valuable directions for future studies, which may then investigate these mechanisms with real-world data and potentially even explore causal pathways through LIFUS sonication.

6 Results

In the following, the results of the data analysis, as proposed in the Data Analysis Plan, are presented. The preprocessing and analysis of the data was conducted in Jupyter Notebook with 3.9.13 (main, Aug 25 2022, 23:51:50) [MSC v.1916 64 bit (AMD64)] (Python Software Foundation, 2023). For all analyses, raw data – generated by the participants of the study and saved by a bash script, in data sheets – was preprocessed by combining all datasets (saved separately for each task and participant) into the relevant columns. These combined data frames were the base for scoring and analysis for each hypothesis.

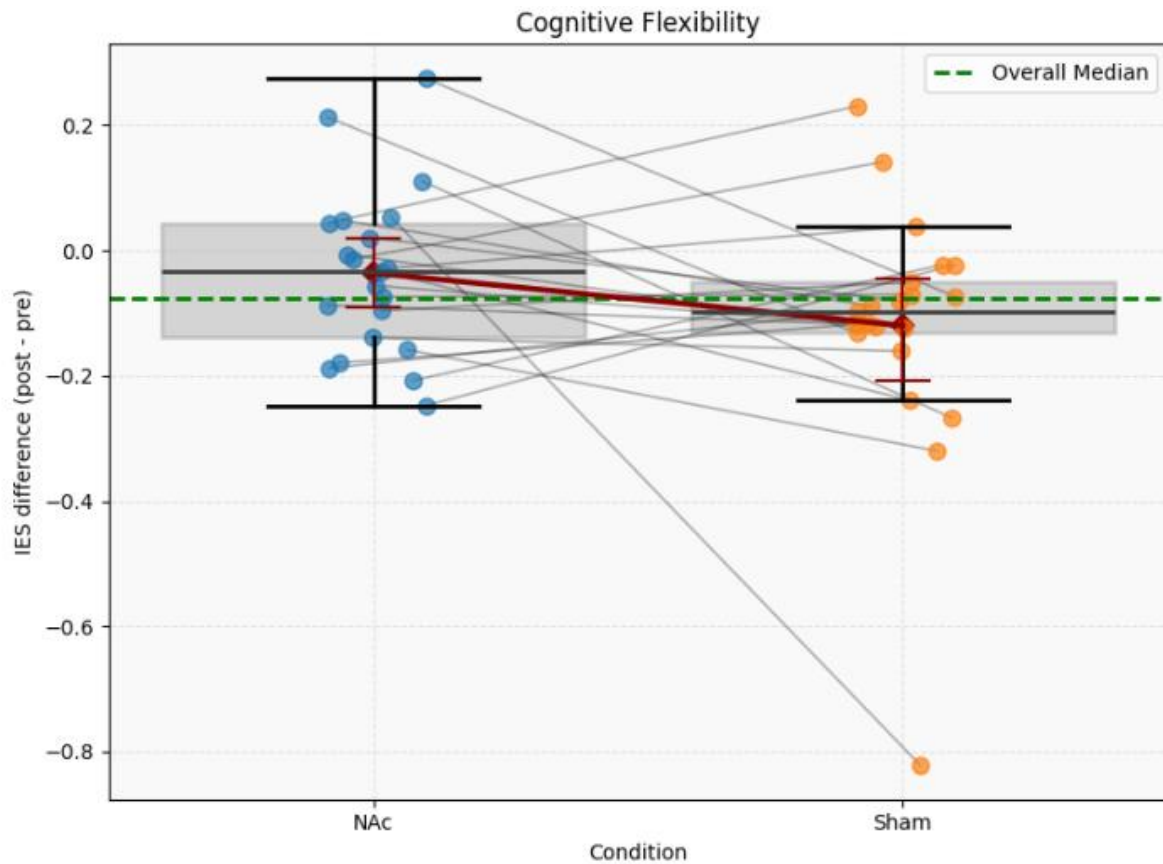
6.1 H1: LIFUS sonication of the NAc leads to a change in CF

The analysis of the data, after preprocessing, started with viewing data distribution and calculating Shapiro-Wilks to test if residuals are normally distributed ($W(21) = 0.87$; $p = .000268$). To check if the data itself was normally distributed, the Shapiro-Wilks test of the IES scores in each condition was implemented ($W(21) = 0.86$, $p = .000143$; [Appendix F: Stroop task – Supplementary Material](#)). Since neither data nor residuals were normally distributed (Fig.1), the correct method of analysis was a Wilcoxon signed-rank test ($= 83.0$, $p\text{-value} = .272$). Outliers were not excluded, even though one data point especially seems to be off (IES difference = $-.812$). However, since there is no effect and visually (figure1), it is apparent that without the outlier the effect would be even smaller. The hypothesis must be discarded (without excluding any outliers).

The data distribution visually (Fig.2) shows that the boxplots of the differences of the IES scores for each participant revolve around 0, indicating no effect in either condition. The individual differences between the conditions seem to be random, since all the negatives and positives equal each other out (data distribution of reaction times, accuracy and IES over both conditions pre *and* post are visualized in [Appendix F - Data visualization of IES scores, mean reaction times and mean accuracy over time and condition](#)). There is one outlier (sham condition at -0.8), but visually it is evident that the effect would have been even smaller and since there is no significance anyway, the outlier was included, keeping the sample size of $N = 21$. The hypothesis is rejected.

Fig. 3

Pairwise Comparison of IES differences in both conditions



Note: The figure demonstrates data distribution (blue dots in the NAc, orange dots in the sham condition) as well as the pairwise relationship, describing how the performance of each participant behaved in the two conditions (grey lines between blue and orange dots). The black lines and the grey box represent boxplots for each condition (middle line = median; grey area = 25th - 75th percentile (IQR); black “whiskers” = minimum – maximum; all points outside whiskers = outliers) The red line shows the mean value (95% confidence interval). The green line represents the median over both conditions (reference for Wilcoxon signed-Rank Test). The values on the Y-axis represent the post – pre difference of the IES score. Boxplots revolve around 0, indicating no effect.

6.2 H2: LIFUS sonication of the NAc leads to a change in mood

Mood was assessed using the VAMS. 21 Participants had completed the VAMS in all both conditions ($N = 21$), missing item values were viewed. Although the analysis plan avoided imputation, two isolated missing VAMS items were replaced with session means because they represented single-item omissions rather than missing sessions. These values were imputed with the mean of these sessions' values, which caught the trend of the session (if there was a trend). The internal consistency was at Cronbach's $\alpha = .757$, which was very similar over the different sessions. Then, an overall mood score and the values of the four subscores were

calculated. Only one pair (Tranquilization and Physical Sedation) was significantly correlated. Since correlations were low according to Cohen's benchmarks (Cohen, 1988), analysis was continued with four separate tests (each for one subscale).

Shapiro-Wilks was only significant in the Mental Sedation condition (Fig. 4) which is why a Wilcoxon signed-rank analysis was conducted in this subscale (p -value = .4733); however, residuals were not normally distributed (Shapiro wilks <.05 in most conditions; Q-Q plots showed non-normality over residuals). This led to paired t-tests in the three remaining conditions: Physical sedation (p = .561), Tranquilization (p = .55) and Other Feelings (p = .236). Outliers were not excluded, since most had an outlier only in one condition and in one dimension, which was attributed to an actual mood-related effect. Additionally, the non-parametrical analyses are designed to be robust towards outliers. Thus, to keep the statistical robustness, outliers were kept in. However, since no evidence was found to support this hypothesis, the null hypothesis could not be rejected.

In an explorative analysis, all 16 dimensions (see [Table G1](#)) were analyzed separately. This led to no significant results. However, some dimensions showed clear tendencies: Especially, the "alert – sleepy" (p = .104; d = .51) and "curious – bored" (p = .111; d = .42) dimensions exhibited non-significant results with medium-sized effect (Cohen, 1988).

Table 3

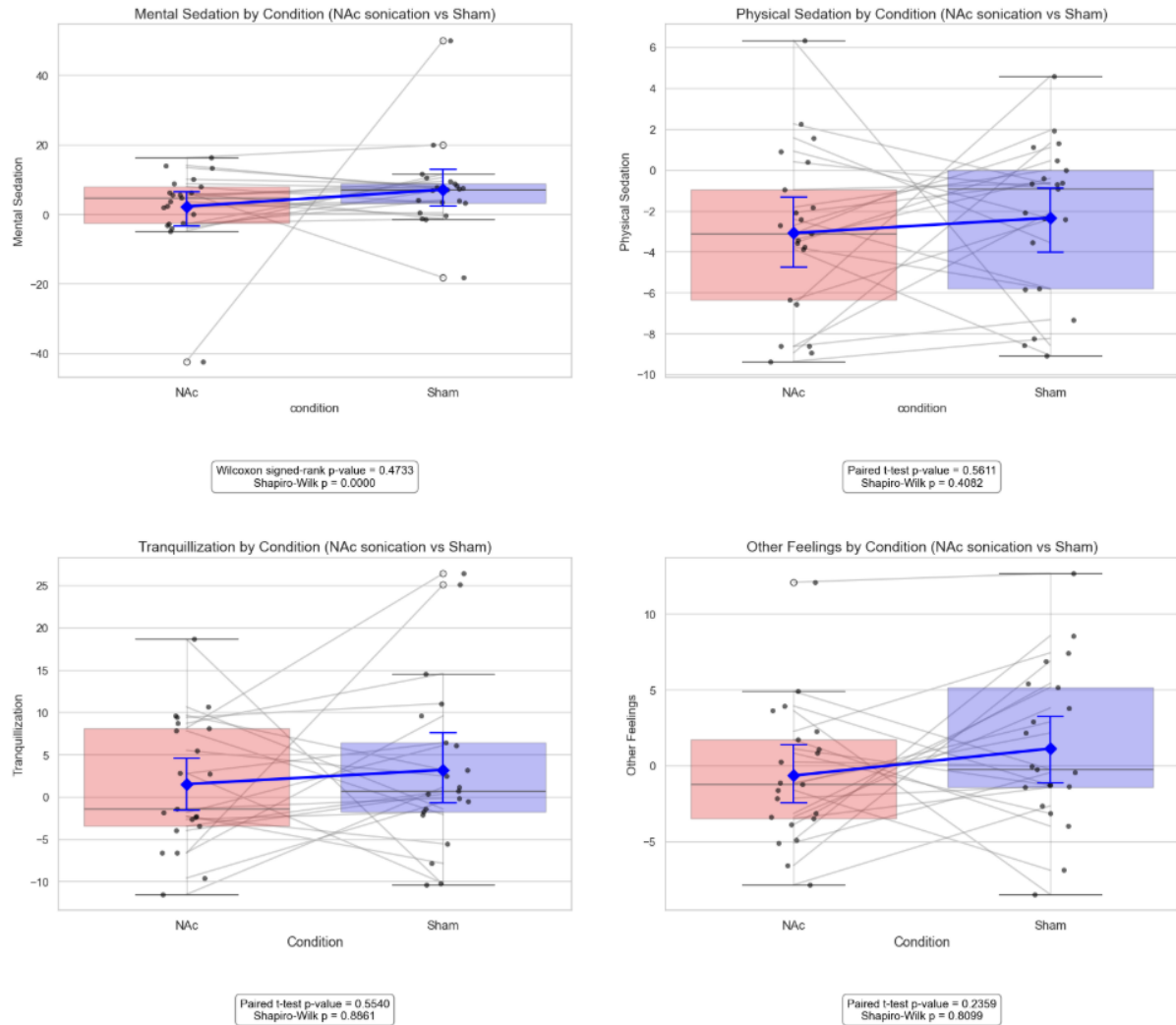
Correlations of the mood subscales

<i>Variable</i>	<i>1</i>	<i>2</i>	<i>3</i>	<i>4</i>
<i>1. Mental Sedation</i>	—	-.058	-.008	-.111
<i>2. Physical Sedation</i>	-.058	—	-.322*	.255
<i>3. Tranquillization</i>	-.008	-.322*	—	.136
<i>4. Other Feelings</i>	-.111	.255	.136	—

*Note. Values represent Spearman's rho (ρ) coefficients, except for the correlation between Physical Sedation and Other Feelings (Pearson's r). p values: Mental Sedation vs Physical Sedation, p = .714; Mental Sedation vs Tranquillization, p = .962; Mental Sedation vs Other Feelings, p = .484; Physical Sedation vs Tranquillization, p = .038; Physical Sedation vs Other Feelings, p = .103; Tranquillization vs Other Feelings, p = .390. *Statistically significant at p < .05.*

Fig. 4

Plots of the four subscales including p- values



Note: The grey lines show how each participant (darker grey dots) performed over both conditions. The blue line shows the mean-comparison (95% CI) over both conditions. Boxplots (blue and red are included); black whiskers are the IQR. White circles are an extension of the points on the X-axis to show where the grey lines would hit if data points were not distributed over the X-axis (No datapoints).

6.3 H3: LIFUS Sonication of the NAc Alters Subjective Experience of Hedonia

Due to an error in presenting the auditory stimuli to the first participants, there was some missing data that was excluded from the analysis. The participants that only completed the task in one of the two conditions were excluded as well. The sample size was at N = 16 for this hypothesis. The data in both dimensions was normally distributed (Shapiro – Wilks (moved) p

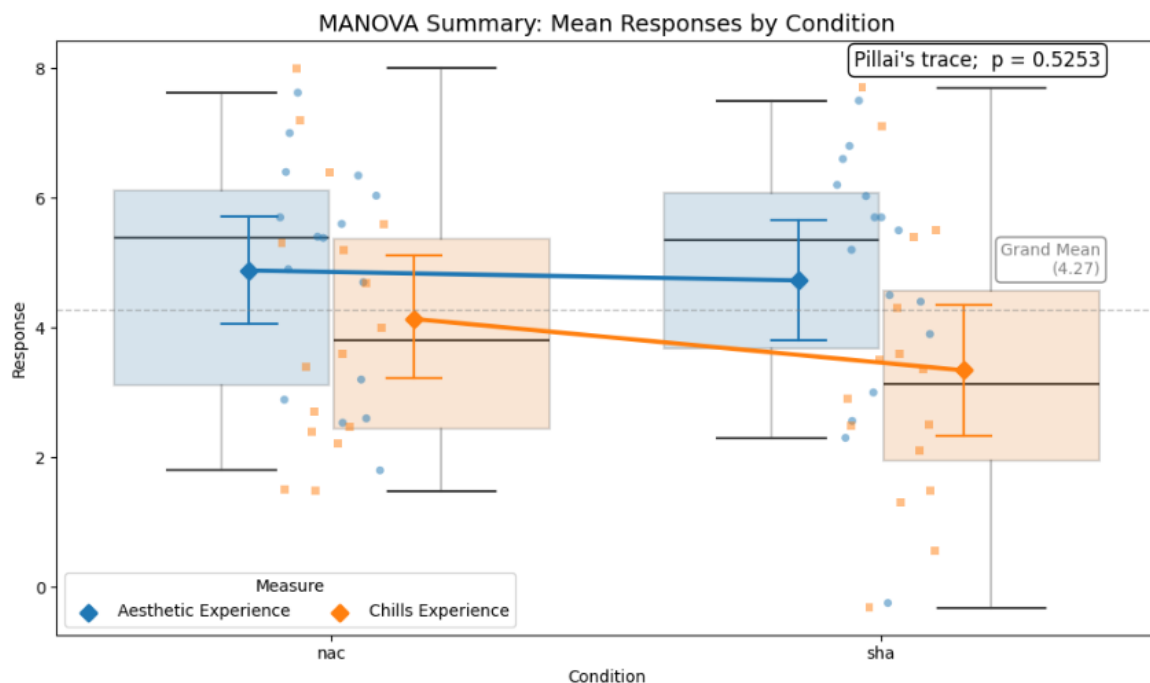
= .081; Shapiro – Wilks (Chills) $p = .454$). The dimension of being moved did not change significantly over both conditions ($p = .82$).

To include the chills rating into the model, both dimensions were correlated. Pearson's r was significant at $r(16) = .427$; $p < .001$. Thus, a MANOVA was the statistical measure of choice. For this, the *MANOVA* function out of the Python library *statsmodels.multivariate.manova* (view [Appendix H: Hedonia – Supplementary Material](#)) was imported and utilized. The results of the MANOVA were not significant (Pillai's trace (16) = 0.434; F -Value = 0.653; $p = .5253$, Fig. 5). Thus, the null hypothesis cannot be rejected.

Since the chills condition is showing a clear tendency to be increased after active sonication, a separate linear mixed model was conducted exploratorily. This model showed no significance (p -value = .300) in the *condition* (active sonication vs. sham) parameter. Opposed to the moved response, the smaller p -value underscores a certain tendency in the chills dimension. However, the result indicates that statistically, no significant effect can be measured.

Fig. 5

MANOVA Results and Data Structure of the Hedonia Music-task



Note: Orange data points = Chills data; blue data points = moved data. Black whiskers = IQR. Blue and orange line = connection between the means (95% CI) of the respective data between each condition. “Aesthetic Experience” is interpreted as “Hedonic experience”. nac = NAc sonication; sha = Sham sonication.

6.4 H4: A bootstrap-based simulation of the study's data will show that LIFUS of the NAc can explain an explorative model of mood and cognitive flexibility

Because the preceding analyses revealed no detectable effects and statistical power was low, conducting a bootstrap-based simulation was deemed unlikely to yield interpretable results. Analyzing a larger model with mainly synthetic data potentially leads to false positives. Thus, the fourth hypothesis was not tested. Also, all broader statistical tests (i.e., robust linear mixed model (rlmm) or a multivariate multilevel model) were not tested, due to their lower effect size. This hypothesis stays in this thesis to inform future studies that such larger models with data-driven simulations might be important to model the complex interactions between affective and cognitive processes.

6.5 Test Power

The results indicate that the LIFUS protocol applied to the NAc did not produce the hypothesized effects in humans. Statistical power, calculated using G*Power 3.1 (Faul et al., 2007), was generally low across all analyses. The following values summarize the estimated power for each analysis.

For these calculations, an effect size must be specified. Since effect sizes cannot be reliably derived from the collected data, power estimates were calculated using both small and medium effect sizes according to Cohen's benchmarks (Cohen, 1988). For the first two hypotheses concerning cognitive flexibility (CF) and mood, the estimated power ranged from $1 - \beta = .13$ (small effect) to $.56$ (medium effect). For the hedonia hypothesis, power ranged from $1 - \beta = .09$ (small effect) to $.263$ (medium effect). All effect sizes were evaluated based on Cohen's criteria. Medium effect sizes are presented for reference, while small effect sizes were adjusted to reflect the non-significant results.

7 Discussion

This study set out to test whether LIFUS of the NAc could modulate CF, mood, and hedonia. Although the findings were non-significant, the study nonetheless provides important insights: it establishes feasibility, it highlights methodological challenges, and it refines our understanding of which constructs are most promising targets for future work. In a young field like LIFUS research, null results should not be viewed as absence of knowledge, but as carefully drawn boundaries that guide subsequent investigations.

The absence of robust changes in CF and mood reflects the network-level nature of these constructs and the difficulty of influencing them via a single subcortical target. CF and mood involve widespread cortical-subcortical systems (Ding et al., 2014), which interact on multiple timescales (Dajani & Uddin, 2015; Kragel, Hariri, & LaBar, 2022). Similarly, CF is embedded in the executive control network and linked to distributed circuits (Miller & Cuttler, 2003). Modulating such large-scale processes through stimulating a single node (the NAc), particularly with an incompletely understood tool (LIFUS) may therefore produce effects that are subtle or highly context-dependent. In this sense, the null results are less surprising than they might first appear.

Hedonia, by contrast, emerged as the most promising construct. Even if statistical thresholds were not reached, the descriptive trend in chills suggests that hedonic responses may be sensitive to subtle neuromodulation of the NAc. This aligns with a long tradition of research situating the NAc at the heart of reward and pleasure (i.e., Kringelbach & Berridge, 2015). DBS studies have shown that direct stimulation of the NAc can alter hedonic tone, even if mood outcomes remain variable (Bewernick et al., 2010). The present findings echo this pattern, reinforcing the idea that hedonia is a narrower, more circumscribed entry point for probing NAc function than mood.

Another interpretive layer concerns the temporal dynamics of LIFUS. While the present design focused on acute, immediate effects, several studies (i.e., Beisteiner et al., 2020; Popescu et al., 2021, Darmani et al., 2022) have documented delayed or cumulative changes in connectivity and metabolism after sonication. These delayed effects may reflect gradual changes in neural excitability, connectivity, or metabolic activity induced by ultrasound stimulation. If LIFUS effects emerge gradually, they may elude detection in designs limited to short-term measurements. Thus, the absence of immediate CF or mood effects here does not necessarily indicate ineffectiveness; rather, it suggests that longitudinal designs may be essential for capturing the full temporal profile of LIFUS-induced changes.

Finally, the feasibility demonstrated here is itself an important finding. Until recently, causal manipulations of the NAc were almost exclusively the domain of invasive techniques such as DBS (Peng et al., 2024). By showing that LIFUS can safely and non-invasively target the NAc, even with modest psychological outcomes, this study extends the methodological landscape. In doing so, it opens possibilities for bridging basic neuroscience with clinical applications, while also underscoring the caution required in interpreting early-stage results.

7.1 Limitations

Several limitations must be considered. The most obvious is the small and homogeneous sample, which limited statistical power and generalizability. As noted in Chapter 5, the chosen statistical tests were underpowered to detect small-to-medium effects. Only very large effects could realistically have emerged, which likely contributed to the absence of significance. This is consistent with broader challenges in brain stimulation research, where underpowered pilot studies often produce null results or inconsistent findings (Button et al., 2013). Future studies should therefore prioritize larger, more representative samples to strengthen inferential validity.

A second limitation relates to task design and participant fatigue. The combination of multiple tasks, administered across sessions, was intended to maximize data richness. Yet, it may have inadvertently obscured subtle effects by taxing attentional and motivational resources. Fatigue is not trivial in this context: as [Chapter 3.1](#) noted, CF is particularly sensitive to cognitive load (Dajani & Uddin, 2015), and hedonic responses may also be blunted under strain. Thus, what may look like absence of modulation could in fact reflect ceiling or floor effects induced by fatigue. Future studies could address this by adopting shorter, more targeted task batteries designed specifically to detect the hypothesized constructs.

Third, the ambiguous mechanism of LIFUS itself is a fundamental limitation. As highlighted in [Chapter 2.1](#), LIFUS can exert both excitatory and inhibitory effects (Also see [Appendix A](#)), depending on factors such as intensity, frequency, and anatomical context (Legon et al., 2018; Fomenko et al., 2020). This unpredictability complicates both hypothesis generation and interpretation. Was the NAc inhibited when stimulation parameters were set as in this study? Or was it excited, but insufficiently to overcome network-level dynamics? Without direct neurophysiological markers, behavioral null effects remain difficult to interpret. This challenge points to the need for multimodal designs combining LIFUS with fMRI or EEG, to trace how stimulation alters network activity in real time.

Fourth, the measurement of constructs warrants caution. Mood, as discussed in [Chapter 3](#), is diffuse (Clark, 2005) and consequently, not easily captured by brief self-report scales. Similarly, hedonia was operationalized through music-induced chills and moving experiences - a rich but variable paradigm influenced by individual differences in musical sensitivity, familiarity, and cultural background. The null effects on “moving experiences” but trend in chills highlight how operationalization matters: even within hedonia, some measures may be more sensitive than others. This echoes the literature showing that “peak emotional” experience of music are particularly tied to dopaminergic reward circuits (Salimpoor et al., 2011), whereas broader affective responses are distributed across wider networks.

Another consideration is inter-individual variability in neuroanatomy and functional organization. Differences in NAc morphology, dopaminergic signaling, or baseline reward sensitivity could influence responsiveness to neuromodulation (Castro & Bruchas, 2019; see also [Appendix C](#)). Such variability may contribute to heterogeneous behavioral outcomes and may partially obscure stimulation effects in small samples. Future studies could address this by incorporating individual-level neural markers or stratified sampling strategies.

Finally, the proof-of-concept nature of this study imposes interpretive limits. The design was necessarily exploratory, with no confirmatory model available. As a result, the study cannot draw strong conclusions about causality, but instead maps out a space of possibilities. In doing so, however, it fulfills a critical role: it identifies both the opportunities (hedonia as a promising construct, feasibility of NAc targeting) and the blind spots (uncertain mechanisms, fatigue, small samples) that future confirmatory studies must address.

7.2 Outlook and Conclusion

Despite its limitations, this thesis provides valuable groundwork for future research on LIFUS of the NAc. The results suggest that hedonic responses may be more directly modulated than CF or mood, aligning with existing literature that positions the NAc as a hub of reward and pleasure. At the same time, the null findings in CF and mood highlight the need to refine methodological approaches, especially regarding task design, timing of measurements, and stimulation parameters.

Future studies should expand sample sizes, employ multimodal imaging to trace causal pathways, and consider longitudinal designs to capture delayed effects. Such refinements would not only clarify whether the descriptive trends in hedonia can be confirmed but also illuminate the broader potential of LIFUS as a tool for probing complex psychological constructs.

In conclusion, this thesis demonstrates the feasibility and the challenge of applying LIFUS to a subcortical target long implicated in reward and affective processing. Even null results are informative, as they help delineate the boundaries of what LIFUS can achieve in its current form. By situating these findings within the literature on NAc function, mood, and hedonia, the study contributes a small but significant step toward the larger goal of developing non-invasive tools for causal brain–behavior research.

Supplementary Material

All relevant datasets (as *.csv*-files) and code-files (saved as *.ipynb* notebooks-files) are available at <https://ucloud.univie.ac.at/index.php/s/Yc9TBKAMRtpRRX3>.

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Appendix

Appendix A

LIFUS – exciting or not?

The focus of explaining and predicting this phenomenon is to analyze how differences in intensity, duty cycle, or frequency of the ultrasound waves induced affect the direction and intensity of effect (Wang et al., 2020a provided a thorough review on this topic). However, there is no consistent explanatory theory yet. The so-called neuronal intramembrane cavitation excitation (NICE) model (Plaksin et al., 2014) is one of the more accepted since it seems to at least predict excitatory effects of LIFUS to a certain degree (duty cycle above 50% induce significantly more often excitatory effects). However, if certain duty cycle settings significantly influence inhibitory effects – which interestingly, seem to be more likely to be induced – remains unclear for the most part (thorough review: Dell'Italia, et al., 2022).

Consequently, studies (and potential applications) implementing LIFUS are somewhat hard to predict, and as of now, hypotheses should not be directed. More research will be needed to develop a sufficient model that explains under which circumstances excitatory and inhibitory effects are exhibited. Though, it is possible that effects are modulated by situational factors (i.e., mood or fatigue intra-individually etc.), which is a clear research gap, since this has not yet been addressed in LIFUS research.

Appendix B

Sensory and Motor Effects of LIFUS

. The findings indicate that this kind of sonification can lead to an increase in motor inhibitory control (Zhang et al., 2021), improved reaction times in stimulus – response tasks (Legon et al., 2018b), and Fomenko et al. (2020) showed that LIFUS sonification of M1 could lead to quicker, though not more accurate movement of a cursor towards a visual target on a screen. Sonication of the hippocampus and substantia nigra has been associated with improved motor function, with most participants demonstrating stable or enhanced performance in fine and gross motor tasks (Nicodemus et al., 2019).

In somatosensory studies evidence was gathered towards the belief that LIFUS might be suitable to reduce pain: Sonication of the left anterior Thalamus could increase thermal pain

thresholds (Badran et al., 2022). Sonicating the Anterior, posterior Insular (Legon et al., 2023), and the posterior frontoparietal cortex (Hameroff et al., 2013) each lead to a decrease in perceived pain. Other somatosensory findings indicate the increase in sensory discrimination after sonicating the primary somatosensory Cortex (S1) (Legon et al., 2018b, Liu et al., 2021) and sonicating the secondary somatosensory cortex (S2) could lead to feeling a tactile sensation (Lee et al., 2016).

Appendix C

Comparison of Nucleus Accumbens Core and Shell

Anatomical differences within the NAc seem to play a large role in how inputs are processed and outputs projected. It must be noted that the discussed inputs and outputs are organized topographically across the NAc's anatomically distinct core and shell regions (sometimes subdivided into core, *lateral* and *medial* shell; Castro & Bruchas, 2019 , see Appendix 1: Comparative Table of Nucleus Accumbens Core and Shell) and often converge on the same neuronal populations, facilitating the integration of complex cognitive and emotional information (Floresco, 2015). LIFUS (even though the most precise NIBS method) does not seem to be precise enough to account for this anatomical complexity.

To illustrate the relevance of anatomical differences: The medial shell's dopamine receptors are mainly D3 receptors (which are D2-like, but still modulate targeted cells differently, and seem to be not prevalent in the rest of the NAc), indicating complex differences in functionality of the NAc's anatomical parts (Castro & Bruchas, 2019). Since there is no scientific consensus on how these anatomical differences might influence behavioral outcomes, this is a potential limitation of targeting the small, but complex NAc.

The following table summarizes the key anatomical and functional distinctions between the NAc core and shell, as synthesized from primary anatomical literature and recent findings in cognitive and affective neuroscience. The distinctions include differences in morphology, neurochemical profile, connectivity, and functional specialization.

Table C1

Differences in Functionality between NAc Core and Shell

Feature	NAc Core	NAc Shell
---------	----------	-----------

Location	Encircles the anterior commissure, ventrolateral position (Záborszky et al., 1985).	Extends medially and ventrally, surrounding the core (Záborszky et al., 1985).
Histology	Higher acetylcholinesterase, calbindin-rich, matrix-dominant (Jongen-Rêlo et al., 1994).	Lower acetylcholinesterase, calbindin-poor, patch-dominant (Jongen-Rêlo et al., 1994).
Neuronal Morphology	MSNs ~12 μ m, homogenous distribution (Meredith et al., 1992).	MSNs ~10 μ m, ~20% less spine density, more excitable (Meredith et al., 1992).
Receptor Expression	D1 or D2 receptor predominant; less co-expression (Kupchik et al., 2015).	Frequent D1/D2 co-expression; D3 receptors present (Landwehrmeyer et al., 1993).
Afferent Inputs	PFC (prelimbic), hippocampus, BLA, insula, VTA (Ikemoto, 2007; Wright & Groenewegen, 1996).	Infralimbic cortex, lateral hypothalamus, NTS, BLA, VTA (Castro & Bruchas, 2019; Wang et al., 2015).
Efferent Outputs	Ventral pallidum, VTA, substantia nigra (Ikemoto, 2007).	Ventral pallidum, hypothalamus, brainstem regions (Mansour et al., 1994).
Interneurons	PV-expressing interneurons prevalent (Fino et al., 2018).	Few PV cells; increased SOM and CIN populations (Meredith et al., 1989).
Functional Specialization	Instrumental behavior, motor planning, fear extinction (Rodríguez-Romaguera et al., 2012).	Affective regulation, homeostatic integration (Marinescu & Labouesse, 2024).
Patch-Matrix Pattern	Matrix-dominant (calbindin-rich) (Jongen-Rêlo et al., 1994).	Patch-dominant (calbindin-poor) (Jongen-Rêlo et al., 1994).
Behavioral Modulation	Fear extinction (dorsal); fear potentiation (ventral) (Rodríguez-Romaguera et al., 2012; Martínez-Rivera et al., 2016).	Aversive and appetitive state encoding; motivational drive (Castro & Bruchas, 2019).

Note: this is only in the Appendix because there is no direct link to the study. However, these anatomical differences might prove to be important when thinking about targeting such small nuclei with clear anatomical distinction.

Appendix D

Table D1

Overview of studies about NAc involving circuits and functionality

Function	Input Sources	Output Targets	Key Roles	Source
Reward processing	VTA (DA), PFC, Amygdala, Hippocampus	Ventral Pallidum (VP) -> Thalamus	Encoding reward salience, hedonic valuation, reinforcement learning	Bayassi-Jakowicka, M., et al. (2021).
Motivation	VTA, Insula, OFC	VP, Hypothalamus	Drives effortful behavior and goal pursuit	Salamone, J., Correa, M., Mingote, S., & Weber, S. (2005)
Addiction	VTA, Amygdala, PFC	Thalamus, VP, PFC (Loop)	Mediates craving, reinforcement loops, drug-cue reactivity	Kalivas, P. W., & Volkow, N. D. (2005a).
Depression / Anhedonia	mPFC, Amygdala, Hippocampus	VP -> Thalamus	Reduced reward sensitivity; linked to anergia, psychomotor slowing	Zhou, B., et al. (2022).
Effort-based decision-making	ACC, dPFC, VTA	VP, Motor Cortex	Computes cost–benefit of physical/mental effort	Salamone, J. D., Correa, M., Farrar, A., & Mingote, S. M. (2007)
Aversion & negative prediction errors	Amygdala, PFC	Habenula, Lateral Hypothalamus	Balances reward/aversion learning	Verharen, J. P. H., & Adan, R. A. H. (2020)

Decision-making	OFC, dACC, PFC, VTA	Thalamus, PFC	Evaluates reward magnitude, delay, probability	Diekhof, E. K., Falkai, P., & Gruber, O. (2008)
Pain modulation	Amyg., Raphé., PFC, Hipp., **(Image-links in Appendix)	Hypothalamus, VP, Habenula (-> PAG)	Gating of chronic pain and affective pain responses	Harris, H., & Peng, Y. (2020).
Goal-directed behavior	Hippocampus, OFC	Ventral Pallidum	Links spatial/contextual cues to motivational states	Xu, Y., Lin, Y., Yu, M., & Zhou, K. (2024).
Risk-taking & learning under uncertainty	mPFC, VTA, agranular insular cortex	dACC, Orbitofrontal Cortex	Encodes subjective value & guides exploration	Haber, S. N. (2011).

Disclaimer: NAc involved in complex circuits – this is a simplification and might even differ, depending on which study you are reading

Appendix E: Re-thinking Dopaminergic Mechanisms

Recent findings refine the mechanistic understanding of dopamine transmission in the NAc. Rather than being diffuse, dopamine release occurs at sparse, “active zone–like” sites with high release probability, followed by a pronounced, seconds-long depression that constrains transmission during repeated firing (Liu et al., 2021). Such dynamics suggest that dopaminergic signaling is highly structured and temporally limited, influencing how motivationally relevant signals are integrated.

The domain-overlap framework further proposes that asynchronous tonic firing generates small, local dopamine domains, while synchronized phasic firing causes these domains to overlap, enabling dopamine to reach more distant receptors (Liu et al., 2021). This organization indicates that the mode of neuronal activity, tonic vs. phasic, directly shapes the spatial extent of dopamine’s influence in the NAc. Functionally, this region, sometimes termed the “motivational striatum,” appears to assign value to effort and regulate the allocation of limited resources such as time and energy (Berke, 2018). Within this system, the NAc core encodes the perceived value of work, whereas the NAc shell is more strongly involved in probabilistic learning (Berke, 2018).

Dopamine release in the NAc is further modulated by local control mechanisms at presynaptic terminals. For instance, inputs from the amygdala can alter release independently of VTA firing, suggesting a regulatory interplay between emotional salience and motivational drive (Liu et al., 2021).

Disruptions in this finely tuned signaling are consistently linked to addiction-related behaviors, where impaired NAc function contributes to a loss of behavioral control in substance use disorders. This is supported by the role of dopamine in modulating striatal synaptic plasticity, which helps explain the persistent behavioral changes induced by addictive drugs (Berke, 2018). Beyond addiction, alterations in NAc function are increasingly associated with a wider spectrum of neuropsychiatric and neurodegenerative disorders, including depression, schizophrenia, and Alzheimer's disease, highlighting its central role in both affective and cognitive processes.

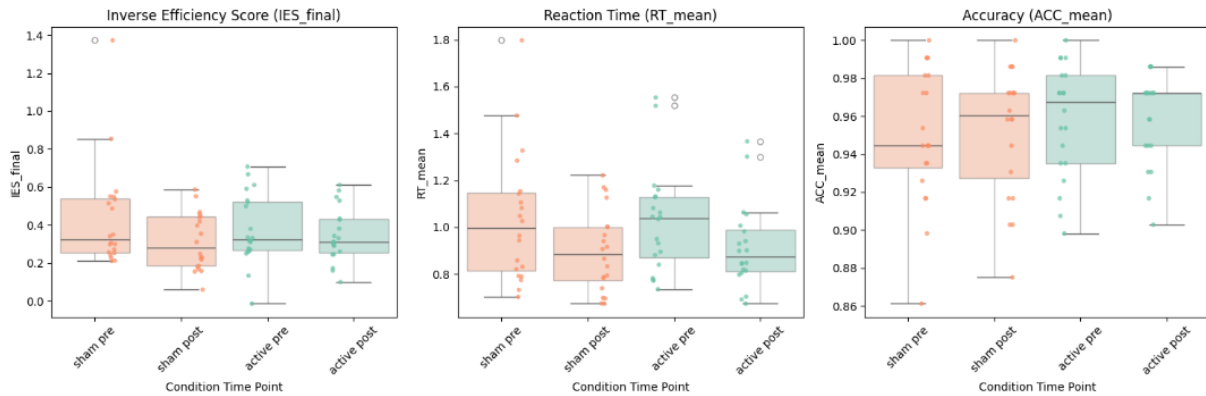
One emerging mechanism involves the regulation of belief updating. Blocking D2/D3 receptor, a common pharmacological target in antipsychotic treatment, has been shown to increase volatility in social learning, suggesting that these receptors play a critical role in tuning the precision of beliefs. Dysregulation of this process may lead to overly rigid belief formation, a hallmark feature of psychotic disorders (Mikus et al., 2023).

The framework proposed by Liu et al. (2021) provides a mechanistic basis for how external modulation, such as LIFUS, could enhance neuronal synchrony and thereby strengthen dopaminergic signaling in the NAc, making a behavioral effect of such an intervention plausible. Berke's (2018) characterization of the NAc as the "motivational striatum" supports the choice of this region as a target, since its role in evaluating effort and reward aligns closely with the study's focus on cognitive flexibility and hedonic processing. Finally, Mikus et al. (2023) demonstrate that direct manipulation of dopamine receptors can alter adaptive cognition, offering empirical support that modulating dopaminergic function in the NAc can yield measurable changes in behavior, the core assumption of this thesis.

Appendix F: Stroop Task Supplementary Material

Fig. F1

Data Visualization of IES Scores, Mean Reaction Times and Mean Accuracy over Time and Condition



Code Cognitive Flexibility Modelling

```
import scipy.stats as stats

# Calculate descriptives for both conditions
nac_ies = final_df[final_df['condition'] == 'nac']['delta_IES']
sha_ies = final_df[final_df['condition'] == 'sha']['delta_IES']

# Descriptive statistics for both conditions
nac_descriptives = nac_ies.describe()
sha_descriptives = sha_ies.describe()

print("Descriptive Statistics for NAC condition:")
print(nac_descriptives)
print("\nDescriptive Statistics for SHA condition:")
print(sha_descriptives)

# Perform the Wilcoxon Signed-Rank Test between the two conditions (nac vs sha)
wilcoxon_test = stats.wilcoxon(nac_ies, sha_ies)

print(f"\nWilcoxon Signed-Rank Test: Statistic = {wilcoxon_test.statistic}, p-value = {wilcoxon_test.pvalue}")
```

Descriptive Statistics for NAC condition:

Statistic	Value
count	21.000000
mean	-0.035871
std	0.133657
min	-0.247669
25%	-0.138949
50%	-0.033770
75%	0.044107
max	0.274289
Name	delta_IES, dtype: float64

Descriptive Statistics for SHA condition:

Statistic	Value
count	21.000000
mean	-0.119830
std	0.202081
min	-0.821122
25%	-0.132037
50%	-0.098313
75%	-0.050342
max	0.230492
Name	delta_IES, dtype: float64

Wilcoxon Signed-Rank Test: Statistic = 83.0, p-value = 0.27221012115478516

Appendix G: VAMS – Supplementary Material

16 Mood Dimensions

1. **wach** (alert) **schläfrig** (sleepy)
2. **ruhig** (calm) **aufgeregt** (agitated)
3. **stark** (strong) **schwach** (weak)
4. **wirre Gedanken** (confused thoughts) **klare Gedanken** (clear thoughts)
5. **geschickt** (skillful) **ungeschickt** (clumsy)
6. **schlapp** (exhausted) **energiegeladen** (energetic)
7. **zufrieden** (content) **unzufrieden** (discontent)
8. **besorgt** (worried) **unbesorgt/sorglos** (carefree)
9. **glücklich** (happy) **unglücklich** (unhappy)
10. **feindselig** (hostile) **freundlich** (friendly)
11. **langsame Auffassungsgabe** (slow comprehension) **schnelle Auffassungsgabe** (fast comprehension)
12. **angespannt** (tense) **entspannt** (relaxed)
13. **aufmerksam** (attentive) **unaufmerksam** (inattentive)
14. **interessiert** (interested) **gelangweilt** (bored)
15. **verschlossen** (reserved) **kontaktfreudig** (sociable)
16. **unfähig** (incapable) **fähig** (capable)

Mood Scoring

The items are divided into 4 categories (no assumption is made that feelings of sedation actually break down into these categories):

1. **Mental Sedation / Intellectual Impairment** (Items 1, 4, 11, 13)
2. **Physical Sedation / Bodily Impairments** (Items 3, 5, 6, 16)
3. **Tranquillization / Calming Effects** (Items 2, 7, 8, 12)
4. **Other Types of Feelings or Attitudes** (Items 9, 10, 14, 15)

Reversal of Items (incl. reasoning)

1. Mental Sedation / Intellectual Impairment (Items 1, 4, 11, 13)

- **Item 1:** "wach" (alert) is positive, "schläfrig" (sleepy) is negative.

- *Reverse scoring*: If higher scores should indicate *more impairment*, score "wach" low and "schläfrig" high.
- **Item 4**: "wirre Gedanken" (confused) is negative, "klare Gedanken" (clear) is positive.
 - *No reversal needed* if higher scores = more confusion.
- **Item 11**: "langsame Auffassungsgabe" (slow comprehension) is negative, "schnelle Auffassungsgabe" (fast) is positive.
 - *No reversal needed* if higher scores = slower comprehension.
- **Item 13**: "aufmerksam" (attentive) is positive, "unaufmerksam" (inattentive) is negative.
 - *Reverse scoring* if higher scores = more inattention.

2. Physical Sedation / Bodily Impairments (Items 3, 5, 6, 16)

- **Item 3**: "stark" (strong) is positive, "schwach" (weak) is negative.
 - *Reverse scoring* if higher scores = more weakness.
- **Item 5**: "geschickt" (skillful) is positive, "ungeschickt" (clumsy) is negative.
 - *Reverse scoring* if higher scores = more clumsiness.
- **Item 6**: "schlapp" (exhausted) is negative, "energiegeladen" (energetic) is positive.
 - *No reversal needed* if higher scores = more exhaustion.
- **Item 16**: "unfähig" (incapable) is negative, "fähig" (capable) is positive.
 - *No reversal needed* if higher scores = more incapability.

3. Tranquillization / Calming Effects (Items 2, 7, 8, 12)

- **Item 2**: "ruhig" (calm) is positive, "aufgeregt" (agitated) is negative.
 - *Reverse scoring* if higher scores = more agitation.
- **Item 7**: "zufrieden" (content) is positive, "unzufrieden" (discontent) is negative.
 - *Reverse scoring* if higher scores = more discontent.
- **Item 8**: "besorgt" (worried) is negative, "unbesorgt" (carefree) is positive.
 - *No reversal needed* if higher scores = more worry.
- **Item 12**: "angespannt" (tense) is negative, "entspannt" (relaxed) is positive.
 - *No reversal needed* if higher scores = more tension.

4. Other Feelings / Attitudes (Items 9, 10, 14, 15)

- **Item 9**: "glücklich" (happy) is positive, "unglücklich" (unhappy) is negative.
 - *Reverse scoring* if higher scores = more unhappiness.
- **Item 10**: "feindselig" (hostile) is negative, "freundlich" (friendly) is positive.
 - *No reversal needed* if higher scores = more hostility.
- **Item 14**: "interessiert" (interested) is positive, "gelangweilt" (bored) is negative.

- *Reverse scoring* if higher scores = more boredom.
- **Item 15:** "verschlossen" (reserved) is negative, "kontaktfreudig" (sociable) is positive.
 - *No reversal needed* if higher scores = more reservedness.

Table G1

VAMS-Items, checked for significance

Item	N	Sham Mean Diff	Active Mean Diff	Mean Difference	t-value	p-value	Cohen's d	p-value corrected
Alert - sleepy	20	-27.3169	-13.1328	14.1841	1.7104	<u>0.1035</u>	0.5100	0.7373
Calm - agitated	21	-6.9934	-6.6946	0.2989	0.0530	<u>0.9582</u>	0.0148	0.9582
Strong - weak	21	-3.5764	-0.2540	3.3224	0.9588	<u>0.3491</u>	0.3067	0.7373
Confused – clear thoughts	21	-2.5304	-1.8779	0.6525	0.1437	<u>0.8872</u>	0.0416	0.9464
Well-coordinated - clumsy	21	-1.6388	1.1158	2.7545	0.7848	<u>0.4418</u>	0.2412	0.7373
Exhausted - energetic	20	-9.0847	-6.3023	2.7824	0.7955	<u>0.4362</u>	0.1897	0.7373
Content - discontent	21	-1.8081	-0.8717	0.9364	0.2608	<u>0.7969</u>	0.0681	0.9464
Worried - carefree	20	9.4979	2.0188	-7.4791	-1.0930	<u>0.2880</u>	-0.3601	0.7373
Happy - unhappy	19	-2.2077	1.1892	3.3968	1.0518	<u>0.3068</u>	0.3647	0.7373
Hostile - friendly	19	-4.3548	-2.1526	2.2022	0.7240	<u>0.4784</u>	0.2937	0.7373
Slow - Fast comprehension	20	-3.3891	4.2416	7.6308	0.6764	<u>0.5069</u>	0.2865	0.7373
Tense - relaxed	19	-9.6675	-5.4283	4.2392	0.8003	<u>0.4340</u>	0.2337	0.7373
Attentive - inattentive	19	-3.2207	-1.0405	2.1801	0.3352	<u>0.7413</u>	0.1054	0.9464
Curious - bored	19	-7.0249	-2.8848	4.1401	1.6766	<u>0.1109</u>	0.4200	0.7373
Reserved - sociable	20	-1.0199	-1.4749	-0.4550	-0.1445	<u>0.8866</u>	-0.0374	0.9464
Incapable - capable	20	-6.9979	-2.3797	4.6182	0.9903	<u>0.3345</u>	0.2984	0.7373

Note: This table shows that now item is significant (paired t-tests). However, a few items show tendencies. Especially, the “alert – sleepy” and “curious – bored” dimensions exhibited non-significant but medium effect sizes (.51; .42), indicating a possible effect with a larger sample. p-value corrected = Corrected via Bonferroni-correction to control for type-I-errors; in this explorative analysis, this correction is not necessary, since no hypothesis is confirmed and no item is significant. It is only included for completeness.

Code: Mood Modelling

```
df_sub['condition'] = df_sub['condition'].astype('category')
df_sub['session'] = df_sub['session'].astype('category')
df_sub['participant'] = df_sub['participant'].astype('category')

# List of dependent variables (last 5 columns)
dv_list = [
    'Overall_Mood_Score',
    'Mental Sedation',
    'Physical Sedation',
    'Tranquillization',
    'Other Feelings'
]

for dv in dv_list:
    print(f"\nModel for {dv}:")
    formula = f"{dv} ~ condition * session"
    model = smf.mixedlm(formula, df_sub, groups=df_sub["participant"])
    result = model.fit()
    print(result.summary())
```

Appendix H: Hedonia - Supplementary Material

Code: Hedonia Modelling

```
from scipy.stats import shapiro, friedmanchisquare
from statsmodels.multivariate.manova import MANOVA

# 1. Normality check for both DVs
aes_p = shapiro(positive_vs_neutral['aes_diff'].dropna()).pvalue
chills_p = shapiro(positive_vs_neutral['chills_diff'].dropna()).pvalue
print(aes_p)
print(chills_p)
if aes_p > 0.05 and chills_p > 0.05:
    # 2. MANOVA (parametric)
    manova = MANOVA.from_formula(
        'aes_diff + chills_diff ~ condition',
        data=positive_vs_neutral
    )
    print("✅ MANOVA Results:\n")
    print(manova.mv_test())
else:
    print("⚠️ Data not normally distributed, running Friedman test per DV")

# 3. Prepare data in wide format for Friedman
df_aes = positive_vs_neutral.pivot(index='participant', columns='condition', values='aes_diff')
df_chills = positive_vs_neutral.pivot(index='participant', columns='condition', values='chills_diff')

# Keep only complete cases for both DVs
df_aes = df_aes.dropna()
df_chills = df_chills.dropna()

aes_friedman = friedmanchisquare(*[df_aes[col] for col in df_aes.columns])
chills_friedman = friedmanchisquare(*[df_chills[col] for col in df_chills.columns])

print("\n📊 Friedman Test Results:")
print(f"Aesthetic response:  $\chi^2 = \{aes\_friedman.statistic:.3f\}$ ,  $p = \{aes\_friedman.pvalue:.4f\}$ ")
print(f"Chills response:  $\chi^2 = \{chills\_friedman.statistic:.3f\}$ ,  $p = \{chills\_friedman.pvalue:.4f\}$ ")
```

0.08162624091343702
0.4543268441349555
✓ MANOVA Results:

```

Multivariate linear model
=====

-----
Intercept      Value  Num DF  Den DF  F Value  Pr > F
-----
Wilks' lambda  0.2139  2.0000  29.0000  53.2884  0.0000
Pillai's trace  0.7861  2.0000  29.0000  53.2884  0.0000
Hotelling-Lawley trace  3.6751  2.0000  29.0000  53.2884  0.0000
Roy's greatest root  3.6751  2.0000  29.0000  53.2884  0.0000
-----

-----
condition      Value  Num DF  Den DF  F Value  Pr > F
-----
Wilks' lambda  0.9566  2.0000  29.0000  0.6583  0.5253
Pillai's trace  0.0434  2.0000  29.0000  0.6583  0.5253
Hotelling-Lawley trace  0.0454  2.0000  29.0000  0.6583  0.5253
Roy's greatest root  0.0454  2.0000  29.0000  0.6583  0.5253
=====

```

Erklärung zur Verwendung von Künstlicher Intelligenz (KI)

Hiermit erkläre ich, dass ich die folgenden KI-Hilfsmittel zur Erstellung meiner Masterarbeit mit dem Titel „Exploring the Potential of Low-Intensity Focused Ultrasound Stimulation (LIFUS) Targeting the Nucleus Accumbens: A Causal Study of Cognitive and Affective Outcomes, and a Methodological Proof-of-Concept“ verwendet habe. Ich versichere, dass die Kennzeichnung der verwendeten KI-Hilfsmittel vollständig ist, inkl. Verwendungszweck, Produktname, als auch ggfs. Prompts und Outputs des KI-Hilfsmittels. Ich verantworte die Auswahl und die Übernahme sämtlicher Ergebnisse der von mir verwendeten KI-Hilfsmittel vollumfänglich selbst.

Verwendungszweck	Produktname des KI-Hilfsmittels	Ggf. Prompt (Input) und Output des KI Hilfsmittels
Fehlercodes der genannten Python Version kontrollieren und „Debugging“-Vorschläge generieren	ChatGPT (Modelle: GPT 4; GPT 5)	Beispiel-Input: „Bitte kontrolliere diesen Fehlercode: (Fehlercode eingefügt); er bezieht sich auf die folgende Codezeile: (Codezeile

		eingefügt). Wie kann ich diesen Fehler ausbessern?“
Unsaubere Formulierungen ausbessern	ChatGPT (Modelle: GPT 4; GPT 5)	Beispiel-Input: „(Einfügen des betreffenden Satzes). I think the phrasing here is off. Could you please help me to improve it? The audience consists of psychologists and neuroscientists. This is from an actual thesis.”
Hilfe bei dem Recherchieren. Insbesondere, wenn ich unsicher war bezüglich mancher Aussagen, die ich im Paper getroffen habe.	ChatGPT (Modelle: GPT 4; GPT 5) Consensus.ai (Modelle: GPT 4; GPT 5)	Beispiel-Input: “In my thesis I claim that transcranial electrical stimulation cannot be used to stimulate subcortical targets. Please find either papers that falsify this claim or a highly cited review on this topic.”