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The Impact of Low Intensity Focused Ultrasound Sonication (LIFUS) of the Nucleus Accumbens on the Hedonic Experience of Music

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Abstract

Untersuchungen zur Rolle des Nucleus Accumbens (NAc) in der Verarbeitung von Glück (Berridge & Robinson, 2016; Smith et al., 2011) erlauben bislang nur selten Rückschlüsse auf Kausalzusammenhänge (Bergmann & Hartwigsen, 2021; Silvanto & Pascual-Leone, 2012). Dieser Mangel an kausalen Evidenzen schränkt das Verständnis der zugrunde liegenden Mechanismen erheblich ein. Low Intensity Focused Ultrasound Stimulation (LIFUS) gewinnt derzeit als vielversprechende Methode der tiefen Hirnstimulation an Aufmerksamkeit (Min et al., 2011; Yaakub et al., 2023). Durch die Möglichkeit, tiefliegende Hirnstrukturen wie den NAc zu stimulieren, überwindet sie räumliche Limitationen bestehender Verfahren wie der transkraniellen Magnetstimulation (Regenold, Deng & Lisanby, 2021; Crone, 2023). In Humanstudien ist die Methode bislang jedoch noch nicht etabliert.

Ziel dieser Studie war es zu untersuchen, ob LIFUS beobachtbare Effekte auf messbare behaviorale Daten erzeugen kann und damit sowohl zur Validierung von LIFUS als Methode als auch zu einem besseren Verständnis der Rolle des NAc in der Verarbeitung von Glücksgefühlen beiträgt. Als behaviorale Maße wurden emotionale Bewegtheit und wohlige Schauer gewählt (de Fleurian & Pearce, 2021), da Musik eine besondere Stellung in der Glücksforschung einnimmt und sowohl als Stimulus als auch als potenzielle Belohnung fungiert (Zatorre & Salimpoor, 2013).

Vierunddreißig Versuchspersonen bewerteten selbst ausgewählte Musikstücke in zwei Zehn-Punkt-Likert-Skalen hinsichtlich emotionaler Bewegtheit und wohligen Schauern unter zwei Bedingungen (aktive Beschallung und Sham-Beschallung) in einem Within-Subject-Design. Die Analyse zeigte einen signifikanten Unterschied in der Bewegtheit ($p < 0{,}01$) mit höherer Bewegtheit in der aktiven Bedingung im Vergleich zur Sham-Bedingung ($\beta = -0{,}07$). Wohlige Schauer wurden hinsichtlich Häufigkeit und Intensität analysiert; in beiden Fällen ergab sich ein signifikanter Vorteil der aktiven Bedingung, der jedoch einer Bonferroni-Korrektur für multiple Vergleiche nicht standhielt.

Auch wenn die vorliegenden Daten keine abschließenden Schlussfolgerungen zulassen, weisen sie auf LIFUS als vielversprechendes Instrument für zukünftige Studien hin und unterstreichen die Bedeutung des NAc als Schlüsselstruktur der Glücksverarbeitung.

Abstract

When investigating the role of the Nucleus Accumbens (NAc) in hedonic processing (Berridge & Robinson, 2016; Smith et al., 2011), only a few studies provide the possibility for establishing a causal connection (Bergmann & Hartwigsen, 2021; Silvanto & Pascual-Leone, 2012). This lack of causal evidence largely limits the ability to draw conclusive interpretations of the underlying neural mechanisms. Low-intensity focused ultrasound stimulation (LIFUS) has recently emerged as a promising non-invasive method to modulate deep brain structures such as the NAc (Min et al., 2011; Yaakub et al., 2023), overcoming the spatial limitations of existing techniques like transcranial magnetic stimulation (Regenold, Deng, & Lisanby, 2021; Crone, 2023). However, LIFUS has not yet been established as a feasible or reliable method in human research.

This study aimed to examine whether LIFUS produces observable effects on measurable behavioral outcomes, thereby contributing both to the validation of LIFUS as a method and to a deeper understanding of the NAc's role in hedonic processing. Hedonic ratings of music and musically evoked chills (MECs) (de Fleurian & Pearce, 2021) were chosen as behavioral measures. Music occupies a unique position in reward processing research, serving both as a stimulus and as a potential reward depending on individual preferences (Zatorre & Salimpoor, 2013).

Thirty-four participants rated self-selected musical pieces on two 10-point Likert scales, one assessing hedonic experience (rating) and one assessing chills, across two conditions (active and sham sonication) in a within-subjects design. The results revealed a significant difference in hedonic ratings ($p < 0.01$), with higher ratings for songs in the active condition compared to the sham condition ($\beta = -0.07$, coded from Active to Sham). Chills were analyzed for both occurrence and intensity; both measures initially showed higher values in the active condition, but did not remain significant after correction for multiple comparisons.

Although the findings are not conclusive due to methodological limitations, they support the potential of LIFUS as a promising tool for future research and reinforce the role of the NAc as a key structure in human reward processing.

Introduction

Anhedonia is commonly characterized as a reduced ability to derive pleasure from typically rewarding stimuli, or as a diminished recollection of previously experienced enjoyment (American Psychological Association, 2013). It often occurs as a symptom of neuropsychiatric disorders like major depressive disorder (MDD), schizophrenia, bipolar disorder, obsessive-compulsive disorder (OCD), and Parkinson's disease (Ward et al., 2019), as well as a side effect of substance abuse disorders (Kuhlmann, Walter & Schläpfer, 2013).

The disorder most commonly associated with anhedonia is depression, where it constitutes one of the three essential features required for the diagnosis of depression, along with a depressive mood (World Health Organization, 2022). Anhedonia has been identified as a negative prognostic indicator for the effectiveness of selective serotonin reuptake inhibitors (SSRIs) (McMakin et al., 2012), which represent the most commonly prescribed pharmacological treatment for depression (Khanassov, Hu, Reeves, & van Marwijk, 2018).

There are other instances in which anhedonia holds prognostic relevance. Research indicates that individuals with high levels of anhedonia are disproportionately more likely to develop psychotic-like experiences and schizophrenia spectrum disorders (Pelizza & Ferrari, 2009). Loas et al. (2012) state anhedonia as a possible risk factor for Parkinson's disease. Anhedonia has shown to have a strong negative impact on the severity of borderline symptoms in borderline personality disorders regardless of other factors (Marissen, M. A. E., Arnold, N., & Franken, I. H. A., 2012) and it mediates the relationship between childhood trauma and symptom severity in patients suffering from post-traumatic stress disorder (PTSD) (Haim-Nachum et al., 2024).

Although anhedonia is a prominent feature across multiple neuropsychiatric disorders and has garnered increasing scientific attention, the underlying neurobiological and psychological mechanisms responsible for its manifestation remain insufficiently characterized. This persistent knowledge gap limits the development of targeted interventions and impedes a comprehensive understanding of how anhedonia contributes to the pathophysiology of diverse psychiatric and neurological conditions.

The frequent occurrence of anhedonia across diverse psychiatric disorders has prompted a marked increase in scientific investigation of this phenomenon. This trend is evident in a substantial rise in scholarly publications: a PubMed search for the term “anhedonia” reveals that annual publication counts increased from fewer than 100 in the early 2000s to over 500 per year in the 2020s. This escalation in research activity underscores the growing recognition of anhedonia’s relevance for understanding both the etiology and prognosis of various neuropsychiatric conditions, signalling its emergence as a focal topic within psychiatric and neuroscientific research.

For instance, Keedwell, Andrew, Williams, Brammer, and Phillips (2005) have used functional magnetic resonance imaging (fMRI) to locate neural correlates of anhedonia in MDD. They found that dysfunction in the mesolimbic system correlates with anhedonia and a lack of motivation in patients with MDD.

The mesolimbic pathway is a dopaminergic circuit composed of neurons responsible for synthesizing and transmitting dopamine. It also carries the name “Reward system” (Keedwell et al., 2005). This system consists of projections of neurons from the ventral tegmental area in the midbrain to the structures of the limbic system, such as the amygdala, hippocampus, striatum, prefrontal cortex, and many others (Lewis et al., 2021). Within the mesolimbic system, one region in particular has piqued some interest. The nucleus accumbens (NAc) has established itself as one of the key regions, integrating excitatory and inhibitory signals to signal the salience of rewarding stimuli (Smith et al., 2011), and size, activity, and responsiveness correlate negatively with anhedonia (Knutson et al., 2001; Wacker, Dillon, and Pizzagalli, 2009).

Berridge and Robinson (2016) also refer to the NAc as a hotspot for liking. Liking is relevant in this context as Kuhlmann et al. (2013) propose it as the direct opposite of a subtype of anhedonia called consummatory anhedonia. Kuhlmann et al. (2013) distinguish two kinds of anhedonia, consummatory and anticipatory anhedonia. These two kinds are linked to the motivational concepts of liking and wanting, with each being the direct opposite to one of the anhedonia subtypes. Liking is being described as the hedonic effect when experiencing something joyful with consummatory anhedonia describing the absence of this hedonic effect when experiencing something that usually would be considered joyful. Wanting, on the other hand, is the joy experienced when looking forward to something joyful, with anticipatory anhedonia describing the absence of this anticipation and lack of motivation to pursue a pleasant stimulus. Smith and Berridge (2007) also found the NAc as the relevant region of interest (ROI) for liking when stimulating rats and observing their behavior. With the NAc being a hotspot for liking this means, following Kuhlmann et al. (2013), that it also is a hotspot for consummatory anhedonia.

When investigating the neural correlates of anhedonia, studies like Ward et al. (2019) primarily focus on trait anhedonia, which refers to a persistent alteration in the experience of otherwise joyful stimuli. This type of anhedonia offers valuable insights into neural differences in individuals who generally suffer from trait anhedonia, but it does not address the momentary fluctuations seen in state anhedonia—the temporary lack of pleasure during specific joyful experiences. To properly assess state anhedonia, one must measure neural activity during the immediate experience of the joyful stimulus, comparing it to individuals who do not experience state anhedonia at that moment. This requires a high spatial and temporal resolution for tracking neural activation in addition to a stimulus or activity reliably eliciting joyful emotions. According to Treadway and Zald (2011), capturing these differences necessitates precise and real-time neuroimaging techniques, such as fMRI or EEG, to discern how state-based disruptions in reward processing manifest during pleasurable events.

For instance, Keedwell, Andrew, Williams, Brammer, and Phillips (2005) have used functional magnetic resonance imaging (fMRI) to locate neural correlates of anhedonia in Patients with Major Depressive Disorder (MDD). This study found a strong correlation between dysfunction of the mesolimbic system and cases of anhedonia and a lack of motivation in patients with MDD.

Among the studies previously mentioned, varying approaches have been chosen to elicit the hedonic experience. Keedwell, Andrew, Williams, Brammer, and Phillips (2005) have chosen to use emotional stimuli, like images of facial expressions portraying happy and sad faces or autobiographical prompts instructing subjects to think of a moment that has caused a specific emotion to induce happiness and sadness. A common stimulus used in research related to anhedonia is a monetary reward. Studies like Wacker, Dillon, and Pizzagalli (2009) and Knutson et al. (2001) measured the responsiveness to a monetary reward in the nucleus accumbens. However, as noted by Rizvi et al. (2016), primary stimuli like food, sex, and other instinctual stimuli may be represented differently than secondary stimuli like money. A distinctive pattern in varying stimuli has also been reported by Lawhead et al. (2025) when using EEG to monitor neuronal activity during a monetary and a social task, further solidifying the arguments made by Rizvi et al. (2016). When discussing the differences between primary and secondary stimuli, Rivzi et al. (2016) also use the terms instinctual and non-instinctual and make the point that primary or instinctual rewards are inherent, whereas secondary rewards must be established as a reward of value first. This distinction leaves a grey area for rewards that are neither learned nor inherent as necessary for survival. One of the rewards falling into this category is music. Whilst by no means being vital for the survival of the human species, studies like Trainor & Cirelli (2015) have shown that a positive response to music does not require any significant history of exposure. Zatorre & Salimpoor (2013) argue that music might be a "pseudo-primary" reward, not strictly essential for survival but deeply rooted in evolutionary mechanisms for social cohesion, communication, and emotional processing. Music is also one of the most common answers when asked what induces emotional pleasure (Dubé and Lebel, 2003).

Another interesting aspect of music is that it is also capable of inducing a peak response in the NAc (Salimpoor et al., 2011), the same region that has been pointed out by studies using primary rewards like Keedwell, Andrew, Williams, Brammer, and Phillips (2005) as well as secondary rewards like Wacker, Dillon, and Pizzagalli (2009) and Knutson et al. (2001).

Building on this, Gold et al. (2009) investigated how the NAc processes different types of rewards and found that its response to music closely resembles its response to monetary rewards. This suggests that music, despite not being a tangible reinforcer like food or money, can still activate the brain’s reward circuitry comparably.

Beyond neuroimaging findings, direct stimulation studies further reinforce this connection. Mantione, Figee, and Denys (2014) demonstrated that deep brain stimulation of the NAc while listening to music induced intense musical pleasure, providing causal evidence for the role of this region in processing musical reward.

Music as a stimulus presents a particularly intriguing case in the context of anhedonia research due to a specific subtype known as “musical anhedonia”. In these conditions, participants show regular responses in behaviour and NAc activity to stimuli like money but not when presented with music (Belfi & Loui, 2019).

One factor considered to be a significant indicator for the pleasurable or hedonic experience of music is chills. Music-evoked chills (MECs) are often associated with positive emotional and aesthetic responses, serving as reliable markers of pleasurable experiences (de Fleurian & Pearce, 2021). MECs are intense physiological and psychological responses elicited by music. They are characterized by phenomena such as shivers down the spine, piloerection (goosebumps), and a sensation of being moved or touched emotionally. MECs are often but not always accompanied by subjective feelings of pleasure, awe, or transcendence. They are relatively common, experienced by up to 90% of people at least once, but are generally rare or occur infrequently for any individual. In the context of music, they can be an indicator of peak pleasure moments, making them a good measurement for hedonic experiences. Also, chills in general are associated with dopaminergic activity in the brain, particularly involving the release of dopamine in reward and salience regions such as the nucleus accumbens. The surge of dopamine during chills is thought to represent a peak in the consummatory phase of reward processing (Jain et al., 2024). MECs have also been reported with peak NAc activation by Salimpoor et al. (2011).

As pointed out by de Fleurian & Pearce (2021), however, MECs should not stand alone as a measurement since physiological reactions like piloerection can also be caused by confounding variables, like emotional or sensory stimuli, like a low room temperature. When relying on self–report alone, a reported chill can be misleading since the presence of chills can also happen as a reaction to unpleasant stimuli. Self-report and observation of physiological reactions also might not encompass the phenomenological richness of hedonic experiences, which involve subjective feelings that might not always be accompanied by physical reactions. This suggests that MECs alone are not sufficient to draw conclusions about the hedonic experience of music.

When investigating the relationship between music and its hedonic experience, as well as examining the role of the NAc in anhedonia, most studies rely on correlational measures such as functional Magnetic Resonance Imaging (fMRI) to infer a connection between the recorded activity and the measured results. This approach is the current gold standard of neuroscientific research as a non-invasive method to investigate the neurological counterparts of human behavior, emotions, and cognitions. However, this method is incapable of establishing direct causal relationships, as it relies on indirect recordings that serve as proxies for neural activity.

In the case of fMRI, the indirect measure that is recorded is the blood oxygenation level-dependent (BOLD) signal, which reflects changes in cerebral blood flow, which are then interpreted as neuronal activity (Soares et al., 2016).

Studies like Mantione, M., M. Figee & D. Denys (2014), which aim to uncover a causal connection, rely on invasive methods, like deep brain stimulation. Unfortunately, deep brain stimulation can only be used in case studies, which prevents them from being able to run their experiments on a sufficient number of participants to apply their findings to the wider population. Also, such invasive measures are usually only used in patients with pre-existing conditions that could alter the impact of the experimental manipulation compared to a healthy brain. A general trend in cognitive neuroscience to tackle this problem is to make use of non-invasive neurostimulation (NIBS) to infer causal brain mechanisms (Bergmann & Hartwigsen, 2021; Silvanto & Pascual-Leone, 2012). One such technique, low-intensity focused ultrasound stimulation (LIFUS), has garnered interest due to its numerous advantages over other methods, including the ability to target deeper brain structures with greater spatial precision (Crone, 2023). LIFUS has been shown to effectively modulate blood oxygen level-dependent (BOLD) signal dynamics in subcortical regions, such as the globus pallidus (Cain et al., 2021), and influence neurotransmitter levels, including dopamine, serotonin, and GABA, in both animal models and humans (Min et al., 2011; Yaakub et al., 2023), all without the need for invasive procedures. Other non-invasive methods are severely limited because of the range of the technology. Transcranial magnetic stimulation (TMS) is typically capped at a depth of 3cm, and deep TMS at a depth of 4cm, according to Regenold, Deng & Lisanby (2021). This depth is insufficient to influence deep brain structures, such as the ventral striatum, of which the NAc is a part. The same problem surfaces when talking about transcranial direct current stimulation, as the potential target area is limited to the cortical surface (Thair et al., 2017)

Although LIFUS has demonstrated reliable effects on subcortical activity and neurotransmitter dynamics, the specific biophysical mechanisms by which it produces excitatory or inhibitory modulation, as well as its impact on large-scale functional networks, are not yet fully understood (Yaakub et al., 2023)

Low-intensity focused ultrasound stimulation (LIFUS) presents a novel opportunity to modulate deep brain structures noninvasively, offering a means to move beyond correlational findings in affective neuroscience. While previous studies have consistently associated nucleus accumbens (NAc) activity with hedonic responses, especially in music-evoked pleasure, they have largely relied on observational neuroimaging techniques. With LIFUS, we can now begin to assess the causal role of the NAc in generating pleasurable experiences.

Research Questions and Hypotheses

Given the current lack of empirical literature predicting the directional effects of LIFUS on affective processing, the present study focuses on whether stimulation of the NAc alters musical pleasure, without presuming the direction of this modulation. Music, as a pseudo-primary reward, provides a uniquely accessible and emotionally potent stimulus, while musical anhedonia offers a compelling model for investigating hedonic processing. The current study aims to experimentally induce transient states of anhedonia through NAc sonication, with chills and self-reported pleasure serving as key behavioural markers. Given the potential confounding sources of chills, their measurement will be correlated against the hedonic ratings to ensure they are musically evoked.

This led to the following hypotheses:

H1: LIFUS stimulation of the NAc leads to a difference in the subjective rating of hedonic experience in music compared to the sham condition.

H2: LIFUS stimulation of the NAc leads to a difference in the occurrence and intensity of music-evoked chills compared to the sham condition.

H3: There is a correlation between subjective music ratings and the presence/intensity of chills in both stimulation and sham conditions.

Methods

Study Design & Blinding

This study was approved by the Ethics Committee of the University of Vienna (Reference No. 00639).

The study employed an offline, within-subject, repeated-measures design with a single factor and two intervention levels: active and sham LIFUS targeting the right NAc. Each participant completed three sessions.

The first session involved the acquisition of high-resolution anatomical MRI (Magnetic Resonance Imaging) scans for use in neuronavigation and LIFUS targeting. After this session, participants received an online questionnaire related to the music task, which was to be completed prior to the intervention sessions.

In sessions two and three, participants received either active or sham sonication of the right NAc in a counterbalanced order. The two conditions were identical in all procedures except for the gel pad used. Both pads (BrainSonix Corporation, Sherman Oaks, CA) had the same size and shape and differed only in color. The gel pad was applied after participants were seated and outside their field of view. Even if a participant saw the pad, they could not distinguish the sham from the active pad. The color differences were minimal and could not be interpreted without prior knowledge. The sham pad was also acoustically indistinguishable from the active pad. This prevented any auditory cues from affecting participant blinding.

Due to safety regulations, the LIFUS device could only be operated by a licensed individual. This person was responsible for preparing the device for both active and sham conditions, as well as applying the gel pad to participants. Because these tasks could not be delegated, a fully double-blind design was not feasible under the given safety constraints. Prioritizing participant safety and compliance with regulatory requirements took precedence, and participant blinding was maintained to ensure the integrity of the experimental design.

Participants

Recruitment for the study was conducted primarily through flyers distributed within and around the University of Vienna. A total of 45 individuals initially expressed interest and were screened according to predefined inclusion and exclusion criteria. The first screening was carried out via an online questionnaire created with SoSci Survey (SoSci Survey GmbH, Munich, Germany) and was followed by an in-person assessment during the participant's first appointment.

Sample size estimation was performed using G*Power based on pilot data obtained from four participants. Power was set to 0.8, assuming a multiple regression model including the predictors of interest and planned covariates, consistent with the analytical approach used in related experiments by Schmid and Crone (2025). This analysis yielded a required minimum sample size of 30 participants. To account for an anticipated dropout rate of approximately 20%, the recruitment target was increased to 36 participants. Inclusion criteria required participants to be between 18 and 40 years of age, right-handed (as determined by self-report, to avoid confounding effects related to hemispheric lateralization), proficient in German at a C1 level or higher, and eligible for both MRI and low-intensity focused ultrasound (LIFUS) procedures. Exclusion criteria included a history of psychiatric or neurological disorders, current use of medication affecting the dopaminergic system, significant auditory impairments, and any physiological factors that could interfere with accurate ultrasound targeting of the nucleus accumbens (NAc).

Of the 45 individuals initially screened, 35 met the criteria and completed all three sessions of the study. One participant was excluded from the music task due to the inability to provide musical material, resulting in a final sample of 34 participants for the music-related analyses. The sample consisted of 22 female and 12 male participants, with a mean age of 24.24 years (SD = 4.7) at the time of participation. Total sampling numbers come out to 1.360, with 34 participants with 40 samples (20 songs in two conditions) each. Missing answers within the datasets caused the exclusion of a total of 40 samples. Therefore, the final sample included 1.320 samples across 34 participants.

All participants received a compensation of €50 upon completing the final session as an acknowledgment of their time and effort.

During the early stages of data collection, an irregularity occurred in the playback speed of the music files. The audio files for the first ten participants were played at approximately 110% of their intended speed. The playback was corrected, starting with participant eleven. Only one participant reported noticing a difference in music during the experiment; therefore, the data from these sessions were not excluded from analysis but will be considered as a possible confounding factor. To evaluate its potential impact, an additional analysis will be performed in which the affected subset (AS), the unaffected subset (US), and the total sample (TS) are compared to determine whether the playback speed had a measurable influence on the results.

Music

Following the first session, participants were provided with access to an online questionnaire hosted on SoSci Survey (SoSci Survey GmbH, Munich, Germany). Within this questionnaire, they were instructed to submit a total of twenty songs. Specifically, ten of these songs were to be tracks that the participant identified as reliably evoking a strong hedonic response, while the other ten were to be rated as emotionally “neutral.” The selection of songs by the participants themselves ensured ecological validity and accounted for large inter-individual differences in musical preference. The categorization further allowed us to exclude the possibility of presenting songs that participants might find unpleasant or aversive, while also preventing the unintended inclusion of songs that would otherwise fall into the hedonic category. An additional benefit of this procedure was that participants were introduced to the concepts of hedonic responses and music-evoked chills prior to sessions two and three, in which the neuromodulation took place. This familiarization step helped reduce misunderstandings during the actual experimental task.

Once the individual song lists were collected, audio processing was conducted on each track. Song lists were provided by the participants in the form of YouTube links, which were subsequently downloaded using 4k Video Downloader + (InterPromo GmbH, Baden-Baden) as MP3 files. Those MP3 files were converted to WAV-files using CloudConvert (LunaWeb GmbH, Munich) to make processing easier.

For processing itself, Ubuntu (Canonical Ltd., London, UK) was used in combination with modified scripts originally developed by Kathofer et al. (2025). The scripts were designed to generate 70-second snippets from the original full-length tracks, with separate versions for hedonic and neutral conditions. In the hedonic condition, participants were asked to indicate the precise moment within each song at which they experienced the strongest emotional response. The script then extracted a 70-second segment in which this peak was temporally centered, such that it occurred at the 35-second mark of the snippet. For the neutral condition, a different procedure was applied: here, the script determined a random centre point located between 35 seconds after the beginning of the track and 35 seconds before the end. This centre point was then treated analogously to the hedonic peak, producing a 70-second segment surrounding it.

The decision to reduce all songs to 70-second excerpts was motivated by practical considerations. Given that the main experimental protocol already exceeded two hours in duration, shorter excerpts were necessary to minimize participant fatigue and task-related burden. Importantly, previous findings suggest that preference ratings remain stable for excerpts longer than five seconds (Wallisch et al., 2023), meaning that this reduction in duration was not expected to negatively impact the validity of the hedonic ratings.

All audio stimuli were presented in randomized order using PsychoPy (Peirce et al., 2019) in three blocks of three to four songs in two trials of ten songs each. Playback was delivered via over-ear headphones at a standardized listening volume to ensure consistent sound quality and to minimize interference from environmental noise. Participants were instructed to remain seated comfortably, to keep their eyes open, and to focus their attention on their emotional reactions to the music during each trial.

Following the presentation of each snippet, participants were asked to provide two ratings: (1) how emotionally moved they felt by the music and (2) whether the music evoked chills. These ratings were collected using visual analog sliders displayed as continuous horizontal bars with a movable circular marker. Importantly, no numerical values were displayed to participants, thereby encouraging intuitive, subjective judgments rather than numerical anchoring. For the “moved” rating, a standard 1–10 scale was employed, with the slider’s starting position set to the midpoint value of 5.

For the chills rating, a modified 0–9 scale was implemented, with the slider initialized at 0. Participants were explicitly instructed to alter the chills slider only if they experienced chills during the excerpt. The chills scale was initialized at zero to reflect the natural baseline of “no chills,” while the moved scale was centered at the midpoint to account for the absence of a natural baseline for emotional responses.

Procedure

This experiment was part of a study conducted by Franz Roman Schmid and Julia Sophia Crone, investigating the dopamine system's causal role in flexible and creative thinking (Schmid & Crone, 2025).

Once recruited, three appointments were scheduled over the span of three weeks. Sessions were scheduled at the same time of day and day of the week one week apart for each participant to control for circadian and environmental influences and minimize carry-over effects (Bergmann & Hartwigsen, 2021).

The first session took place at the Universitätszahnklinik Wien (Sensengasse 2a, 1090 Vienna). At the beginning of the session, participants were informed about all relevant aspects of the study, including its purpose, expected duration, possible risks of MRI and LIFUS, the overall procedure, compensation, confidentiality, and data handling, as well as their right to withdraw from participation at any point without consequences. After this, participants were provided with a written consent form, which they read and signed before proceeding.

Following these preparations, an anatomical MRI scan of each participant’s brain was acquired, together with a Pointwise Encoding Time Reduction with Radial Acquisition (PETRA) scan. The PETRA sequence was included to obtain high-contrast images of the skull and surrounding tissue, which are necessary for precise neuronavigation and accurate targeting during LIFUS. Both scans were performed using a Siemens MAGNETOM Skyra 3 Tesla MRI scanner equipped with a 32-channel head coil.

At the end of the first session, participants were given access to an online questionnaire via SoSci Survey. They also received written instructions for preparing their music selections for the later sessions, along with the researcher’s contact information in case of follow-up questions.

Sessions two and three took place at the laboratory for LIFUS and TMS, in the basement of the faculty of psychology of the University of Vienna (Liebiggasse 5, 1010 Vienna). The room was fitted with a seat for the participant, the necessary equipment behind the chair, and a shelf without any decorations to minimize distractions. Prior to participant arrival, the necessary data and tasks were uploaded to the test-computer as well as the participant's anatomical data. LIFUS equipment was laid out out of the participant's field of view, ready to use with the corresponding gel pad for the session already applied to the LIFUS coil. Upon arrival, all participants were greeted, placed in their seats, and given a short rundown of the procedure as well as reminded of their right of withdrawal. In accordance with the experiment designed by Schmid & Crone (2025), participants first completed the Visual Analog Mood Scale (VAMS) and the Short Scale of Creative Self (SSCS), followed by the cognitive tasks for the pre-sonication condition, before being prepared for the LIFUS. These tasks were a Stroop Task, Random Number Generation Task (RNG), Controlled Oral Word Association Test (COWAT), and a Cued Drawing Paradigm in that order. The music task was only applied in the post-sonication protocol to limit the impact of listener fatigue.

During the setup, a previously calculated neuronavigation was used to align the transducer with a predefined cranial landmark corresponding to the individualized trajectory for optimal targeting of the right nucleus accumbens. Any hair obstructing the path was separated and fixated in the realm of possibility. A degassed LIFUS conduction gel (GIMA S.p.A., Gessate, Italy; degassing is done with a Mxmoonant 80-1 Laboratory Centrifuge, Mxmoonant, Zhengzhou, China) was applied to the area. Degassing was necessary to ensure that no air bubbles would occupy space between the transducer and the participant’s head, possibly altering the sonication process. The degassed gel was applied until no hair in the specified region was uncovered in the degassed gel, and no air bubbles remained. The previously mentioned gel pad was applied to the transducer in a small water bowl to prevent air from getting trapped between the transducer and the gel pad. Afterwards, the participant was fixated on a head and chin rest, and the transducer was applied to the ideal trajectory. The trajectory of sonication, as well as distance and angle compared to the simulation, were actively monitored and recorded during the sonication process. Post sonication, a 12-minute pause was held. A time window of 10-15 minutes between the end of sonication and the beginning of the post-sonication testing is advised (Dallpiazza et al., 2017; Yaakub et al., 2023).

During the sonication session and the post sonication pause, no conversation was held in the experiment room, during the sonication to keep the distracting factors as minimal as possible, and during the break to minimize the impact of the researcher on the participant.

After the break, the post-sonication condition for the cognitive tasks was conducted.

Afterwards, we conducted the music task. At the beginning of the task, participants were reminded of the definitions of “Ästhetisch Bewegt” (Aesthetically Moved) and “Wohliger Schauer” (Chills) and instructed to move the slider according to their sensations during the presented song. For the aesthetically moved condition, the indicator on the slider was placed in the middle of an unnumbered horizontal axis; for the chills condition, it was moved on the left end of the slider, with the instruction to only move it if chills were present. Participants were able to move the slider to the left with the number 4 and to the right with the number 6 on the keypad of the test computer. After 30 seconds, their answer would be locked in, but they were able to lock their answer in earlier if they were satisfied with the position of the slider on the axis using the spacebar. After 20 of the 40 songs, the program closed, and they were offered a short break before the second half of the task started. For the second half, no instructions were given, but participants were reminded that the second task worked identically to the first one.

Following the music tasks, participants were asked whether something out of the ordinary appeared and were sent home.

After the last session, a quick debriefing was held, and the participants received their compensation of 50€ and were given the opportunity to ask questions about the study.

LIFUS - Sonication Protocol

Sonication was administered in a block design consisting of alternating five-minute periods of active sonication and rest, with each sonication phase subdivided into 50-second stimulation blocks. The total stimulation duration per session amounted to ten minutes. The specific acoustic and temporal parameters are summarized in the table below. For a comprehensive description of the LIFUS setup, calibration, and targeting procedure, please refer to Schmid & Crone (2025).

Table 1 - LIFUS Sonication Parameters

Parameter	**Transducer 65mm**	**Transducer 80mm**
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%
ISPTA	720 mW/cm²	661.12 mW/cm²
Pressure Amplitude	0.725 MPa	0.71 MPa

Analysis

All analyses were performed in RStudio (RStudio Team, Bell Laboratories) using the packages: performance, effectsize, DHARMa, dplyr, lmerTest, lme4, emmeans, ggplot2, effects, lattice, sjPlot, tidyverse and writexl.

Statistical analysis was conducted using a linear mixed effects model (LMER) to evaluate linear ratings of pleasurable music and chills across conditions. The LMER was chosen as it is well-suited for linear data derived from Likert-type rating scales.

Potential models based on different combinations of random effects (participant and the participant specific song ID), and regressors (active or sham, positive or neutral, and affiliation to the affected group) were evaluated as recommended by Bürkner & Vuorre (2019). The winning model consisted of a regressor for active or sham and one for positive or neutral, with random effects for the participant and their respective song IDs. The winning model was chosen based on the Bayesian Information Criteria (BIC) calculated with the performance package77. Notably, no interaction was included in the winning model. Membership of the group affected by the playback error was assessed by including it in the possible model combinations, but was deemed nonessential to the analysis due to its exclusion from the winning model. An exploratory analysis of the best fitting model, including the group affiliation, was made, and no difference in the results was observable, leading to the conclusion that the playback error had no significant impact on the effect of the sonication.

The winning model was evaluated separately for each hypothesis using the corresponding dataset, and it remained consistent across all datasets.
For the first hypothesis, no adjustments to the winning model were necessary.
For the second hypothesis, two analyses were conducted: one examining whether sonication influenced the occurrence of chills, and another assessing whether sonication affected the intensity of chills.
For the analysis of chill intensity, no modifications to the winning model were required.
To assess the impact on the occurrence of chills, the dataset was modified into a dichotomous structure including the options “chills” and “no chills”. The same model as before was used, but to account for the dichotomous nature of the data, a generalized linear mixed model (glmer) was used instead of lmer.

Statistical significance was set at $\alpha = .05$, and all data were standardized to increase comparability across hypotheses and to account for the high individual variance.

To test the correlation between chills intensity and hedonic ratings (H3), Spearman’s rank correlations were calculated separately for each sonication condition.

Results

H1: LIFUS stimulation of the NAc leads to a difference in the subjective rating of hedonic experience in music compared to the sham condition.

A linear mixed-effects model was conducted to examine the effects of stimulation condition (AorS: Active or Sham) and music category (PorN: Positive or Neutral) on standardized hedonic ratings (rating_moved_cont_z). The model included random intercepts for participants nested within conditions, as well as song IDs nested within each participant, to account for repeated measures and item-specific variance.

Table 2

Results of Linear Mixed Model for Simulation Condition and Music Category

	Standardized Rating z			
Predictors	*Estimates*	*CI*	*t-value*	*p*
Intercept	-0.74	-0.87 – -0.61	-11.33	**<0.001**
Stimulation Condition (AorS)	-0.07	-0.11 – -0.03	-3.46	**0.001**
Music Category (PorN)	1.55	1.48 – 1.62	44.13	**<0.001**
Random Effects				
σ^2	0.14			
$\tau_{00\ condition:participant}$	0.13			
$\tau_{00\ participant}$	0.12			
ICC	0.64			
$N_{condition}$	20			
$N_{participant}$	34			
Observations	1320			
Marginal R^2 / Conditional R^2	0.602 / 0.855			

Among the tested models, the selected model demonstrated the best fit, as indicated by the lowest Bayesian Information Criterion (BIC = 2025.71).

Both fixed effects, sonication (AorS) and condition (PorN), showed statistically significant influences on the dependent variable (p < .001; see Table 2). The condition factor (PorN) was coded from Neutral to Positive (N → P), such that positive β coefficients indicate higher ratings for positive music, whereas the sonication factor (AorS) was coded from Active to Sham (A → S), such that negative β coefficients indicate lower ratings in the sham condition and thus higher ratings under active

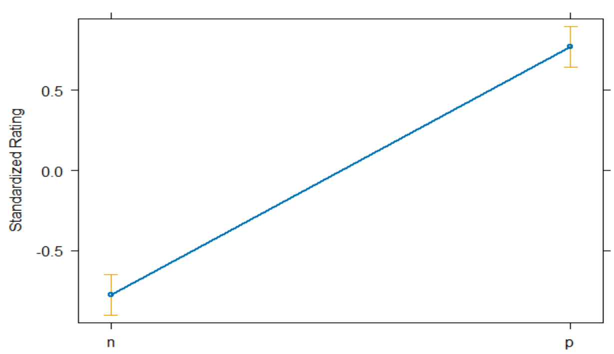

Figure 1
Effect of Music Category.

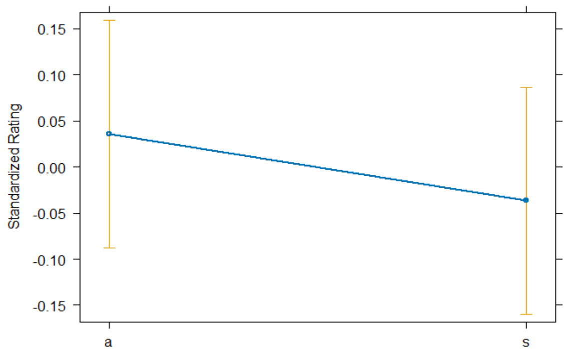

Figure 2
Effect of Sonication Condition.

LIFUS. The t-values were 44.13 for PorN and −3.46 for AorS, with corresponding standardized effect sizes (β coefficients) of 1.55 (see Figure 1) and −0.07 (see Figure 2), respectively, reflecting a small but reliable effect (Cohen, 1988).

The final model did not include an interaction term between the two predictors, as this addition did not improve model fit. Correlation between fixed effects was low ($r < .01$).

All model assumptions regarding normality, independence, and homoscedasticity were checked and met.

H2: LIFUS stimulation of the NAc leads to a difference in the presence and intensity of music-evoked chills compared to the sham condition.

A generalized linear mixed model (GLMM) was used to evaluate the effects of AorS and PorN on the occurrence of music-evoked chills. Significant effects were observed for both predictors (AorS: $p = 0.049$; PorN: $p < .001$; See Table 3), with z-values of −1.92 for AorS and 12.61 for PorN. Corresponding effect sizes (β coefficients) were −0.38 (See Figure 4) and 5.46 (See Figure 3), respectively. Correlation between predictors remained low ($r = -0.16$).

Table 3

Results of Generalized Linear Mixed Model for Stimulation Condition and Music Category

	Chills Occurance			
Predictors	*Odds Ratios*	*CI*	*z-value*	*p*
Intercept	0.12	0.05 – 0.31	-4.43	**<0.001**
Stimulation Condition (AorS)	0.68	0.47 – 1.00	-1.97	**0.049**
Music Category (PorN)	234.27	100.34 – 546.94	12.61	**<0.001**
Random Effects				
σ^2	3.29			
$\tau_{00\ condition:participant}$	0.38			
$\tau_{00\ participant}$	5.88			
ICC	0.66			
$N_{condition}$	20			
$N_{participant}$	34			
Observations	1330			
Marginal R^2 / Conditional R^2	0.439 / 0.807			

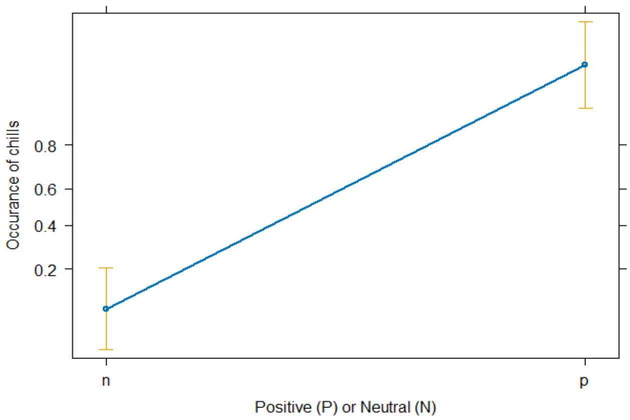

Figure 3
Effect of Music Category.

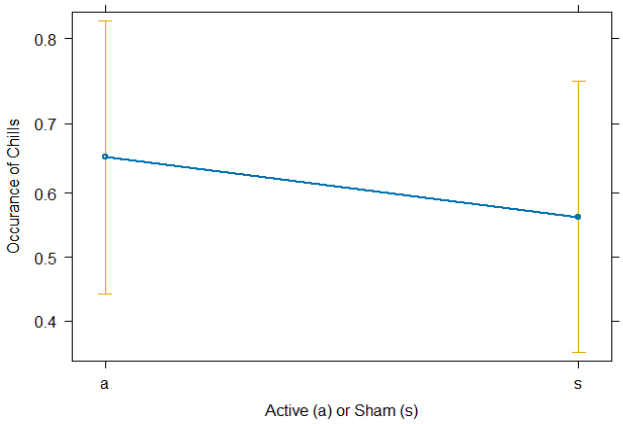

Figure 4
Effect of Stimulation Condition

A separate GLMM was computed to assess differences in chills intensity. Both fixed effects again reached significance (AorS: $p = 0.047$; PorN: $p < .001$; See Table 4), with t-values of −1.99 for AorS and 16.19 for PorN, and β coefficients of −0.08 (See Figure 6) and 1.06 (See Figure 5), respectively. Correlation between predictors was again low ($r = -0.03$).

To control for potential Type I error inflation due to multiple testing, a Bonferroni correction was applied, adjusting the threshold for significance from $p < .05$ to $p < .025$. After correction, the effect of AorS was no longer statistically significant, whereas the effect of PorN remained robust.

Table 4

Results of Linear Mixed Model for Simulation Condition and Music Category

	Chills Intensity			
Predictors	*Estimates*	*CI*	*t-value*	*p*
Intercept	-0.23	-0.49 – 0.03	-1.77	0.077
Stimulation Condition (AorS)	-0.08	-0.16 – -0.00	-1.99	**0.047**
Music Category (PorN)	1.06	0.93 – 1.19	16.19	**<0.001**
Random Effects				
σ^2	0.27			
$\tau_{00\ condition:participant}$	0.09			
$\tau_{00\ participant}$	0.44			
ICC	0.67			
$N_{condition}$	20			
$N_{participant}$	34			
Observations	707			
Marginal R^2 / Conditional R^2	0.185 / 0.730			

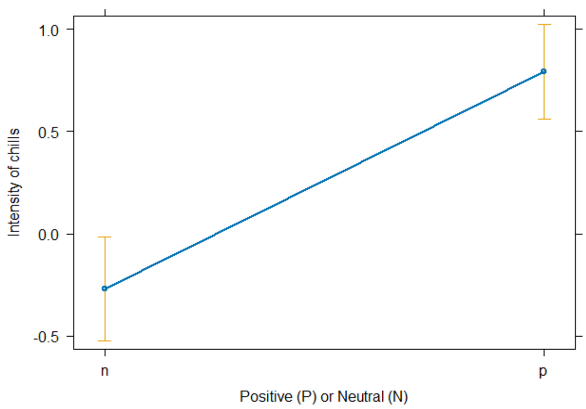

Figure 5
Effect of Music Category.

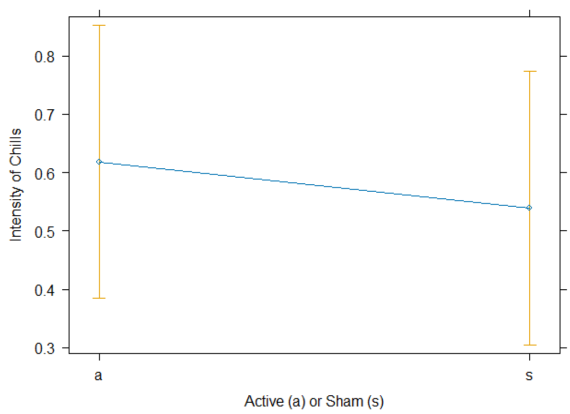

Figure 6
Effect of Stimulation Condition.

H3: There is a correlation between subjective music ratings and the presence/intensity of chills in both stimulation and sham conditions.

A linear mixed-effects model was used to evaluate the association between the standardized variables of music ratings and chills. The model returned a significant effect ($p < 0.001$; See Table 5) with a β coefficient of 0.63 (See Figure 7). Since both variables were z-standardized, the β coefficient represents a standardized effect size and can be interpreted analogously to a correlation coefficient, indicating a strong positive relationship between the two measures.

Table 5
Results of Linear Mixed Model for Chills and Rating

	Correlation Chills & Rating		
Predictors	*Estimates*	*CI*	*p*
(Intercept)	-1.23	-1.74 – -0.73	**<0.001**
rating moved cont	0.63	0.60 – 0.67	**<0.001**

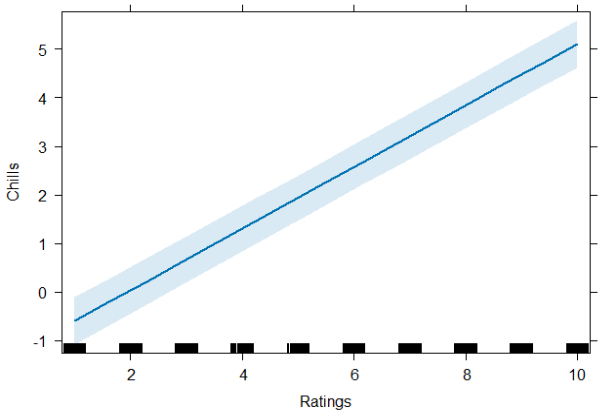

Figure 7
Correlation between Ratings and Chills.

Discussion

This study investigated whether low-intensity focused ultrasound (LIFUS) targeting the NAc modulates the hedonic experience of music and the occurrence and intensity of chills. Overall, the findings indicate a small but consistent trend toward enhanced hedonic responses following active sonication, suggesting a potential modulatory influence of the NAc on musical pleasure.

Higher hedonic ratings for positively reported songs compared to songs reported as neutral

Music category (PorN) is a significant predictor across all analyses, but the tested models show no interaction between the category and the sonication condition (AorS), suggesting that the effects of LIFUS are consistent across categories.

A higher hedonic rating, occurrence and intensity of chills in the positive category point towards the provided songs significantly differing in hedonic processing. Due to the lack of previous literature an exclusivity of the effect for either category could not be ruled out therefore a verification that both categories differ was necessary.

Low Intensity Focused Ultrasound Sonication Increases Hedonic Ratings of Music

The first hypothesis concerned itself with the question whether LIFUS of the NAc led to a difference in the reported rating of music. The analysis returned a small but significant effect showing significantly lower ratings in the sham condition compared to the active condition. With the sham condition having no intervention it is treated as the baseline, and therefore the effect will be interpreted from the sham to the active condition meaning as an increase in ratings in the active condition compared to the sham condition.

A significant effect of sonication across both music categories suggests an increase in hedonic processing following active stimulation of the NAc. This pattern aligns with the view that the NAc plays a central role in mediating hedonic experience.

An increase in ratings represents an increase in liking and therefore a reduction in consummatory anhedonia (Kuhlmann et al., 2013). Similar results have been reported before by Mantione et al. (2014), reporting an increase in the reported liking of several songs by an individual following deep brain stimulation of the NAc. This suggests an effect in the dopaminergic pathways of the reward system, likely increasing the activity of the NAc (Knutson et al., 2001).

LIFUS Stimulation Shows a Trend Toward Increased Music-Evoked Chills

The second hypothesis was divided into two sub-hypotheses assessing the influence of LIFUS on (a) the occurrence of chills and (b) their intensity. Both analyses initially yielded significant effects of sonication; however, these effects did not survive Bonferroni correction due to marginal p-values. Importantly, even after correction, both effects remained in the same direction as those observed for hedonic ratings, again suggesting a potential enhancement of hedonic experience under active LIFUS. For the occurrence of chills, the β coefficient corresponded to a medium effect size, whereas the effect size for intensity was small. As expected, the condition factor

(PorN) was highly significant, showing very large effects, with chills being more frequent and intense for positive compared to neutral music.

Although these results were not statistically significant, a clear trend was observable in the collected data, indicating an increase in music-evoked chills (MECs) under LIFUS, mirroring the pattern identified for the first hypothesis. This observation aligns with findings by Salimpoor et al. (2011), who linked MECs to peak activation of the NAc. Chills have further been associated with phasic dopamine release during the consummatory stage of reward processing (Jain et al., 2024), and the results of the first hypothesis demonstrated an increase in liking, also a consummatory component, under active sonication.

Assuming the observed trend reflects a genuine effect, these findings would reinforce two key points: (1) LIFUS targeting the NAc is capable of modulating hedonic processing, particularly its consummatory phase, and (2) the NAc plays a central role in consummatory hedonic processing, as sonication yielded measurable increases in subjective ratings as well as in the occurrence and intensity of chills, all of which index consummatory reward experience.

Hedonic Music Ratings Are Strongly Associated With Music-Evoked Chills

The third hypothesis examined the relationship between hedonic ratings and chills. This served to ensure that the reported chills were representative of MECs rather than attributable to alternative explanations such as low room temperature or emotionally evocative external stimuli, as noted by de Fleurian and Pearce (2021). They further emphasized that chills can also occur in response to unpleasant stimuli; therefore, within the context of hedonic processing and particularly in a study introducing a causal manipulation that could influence this processing the direction of the correlation is essential for interpreting the results.

A strong positive correlation with a large effect size was observed, indicating that the chills reported by participants were consequences of the musical stimulus rather than confounding factors. This robust positive association supports the position of de

Fleurian and Pearce (2021) that MECs constitute a valid indicator of hedonic experience.

Implications

Although not all results reached statistical significance, they consistently indicated an increase in hedonic experience following LIFUS. Although limited to behavioral measures, these findings suggest that LIFUS may influence the dopaminergic system and modulate neurotransmission pathways, as an increase in hedonic experience is plausibly explained by altered NAc activity, given its established role within the mesolimbic dopaminergic circuit (Keedwell et al., 2005; Lewis et al., 2021) and its well-documented involvement in liking responses and consummatory hedonic processing (Smith et al., 2007; Berridge & Robinson, 2016; Kuhlmann et al., 2013).

This interpretation aligns with previous evidence from Min et al. (2011) and Yaakub et al. (2023), who reported LIFUS-induced alterations in neurotransmitter systems such as GABA, serotonin, and dopamine in both animal and human studies. Furthermore, the findings support the claim by Crone (2023) that LIFUS of deeper brain structures, such as the nucleus accumbens (NAc), is feasible as a method of inducing non-invasive brain stimulation (NIBS).

In line with the interpretation that LIFUS is a suitable method for NIBS, the measurable increase in hedonic ratings observed following active sonication may be attributable to several neurophysiological mechanisms. One possibility is that LIFUS increased neuronal excitability in the right NAc, thereby enhancing hedonic responsiveness during music listening. An increase in responsiveness—and consequently neural activity—in the NAc has previously been linked to improved hedonic experiences (Knutson et al., 2001; Wacker, Dillon & Pizzagalli, 2009). The observed increase in MECs, although not statistically significant after correction for multiple comparisons, is consistent with this interpretation, as MECs are tightly associated with peak NAc activation (Salimpoor et al., 2011).

Another possibility is that LIFUS transiently inhibits inhibitory circuits within the NAc, thereby reducing suppression of downstream hedonic regions and amplifying affective responses. The NAc contains a dense population of GABAergic medium spiny neurons that exert inhibitory control over ventral pallidum and ventral tegmental area targets, both of which are critical for reward and affective processing (Salgado & Kaplitt, 2015). A temporary reduction in this inhibitory output would be expected to increase firing in these downstream regions, producing a net facilitation of hedonic processing.

While the precise processes remain speculative, the pattern of results makes it plausible that sonication of the NAc contributed to these effects.

The lack of a significant interaction between condition and sonication in the best-fitting model supports the interpretation that LIFUS influenced hedonic processing consistently across conditions, rather than selectively enhancing responses to already pleasurable stimuli.

Limitations and future directions

The applicability of the present findings is limited due to a playback error and the remaining possibility that this technical issue may have influenced participants' responses even though it was accounted for when investigating potential model fits. While the behavioral data revealed an observable effect, there has been no data acquired regarding the underlying neuronal mechanisms. Therefore, no claim can be made on how LIFUS impacts the NAc on a neuromechanical level and in turn how that impact leads to the observed differences.

Future studies employing complementary neuroimaging methods such as fMRI or EEG, combined with an analogous experimental design, are needed to clarify how LIFUS modulates hedonic processing as the additional data could clear up the neuromechanical differences following sonication.

Furthermore, individual differences such as musical expertise and background were not assessed in the current study. Given that these factors can meaningfully influence the hedonic experience of music, their inclusion in future research would allow for a more comprehensive understanding of how LIFUS interacts with personal and experiential variables.

Conclusion

The finding that stimulation of the NAc alters subjective experience further reinforces the theory that the NAc plays a central role in hedonic processing. However, the precise direction of the effect of sonication on the NAc requires further investigation to complete the picture. The observed differences in hedonic processing support the potential of LIFUS as an effective tool for both basic neuroscience and clinical applications, though further testing is required before definitive conclusions can be drawn.

This study contributes to the emerging evidence that targeted non-invasive stimulation of deep reward structures can causally influence affective experience, offering a valuable framework for future multimodal investigations combining LIFUS with neural and physiological measures.

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Artificial intelligence was used to correct grammar, language and help prevent repetitions in word usage.