

Full-Length Article

Music Treatment for Anhedonia in Major Depressive Disorder: *Implications for Therapeutic Interventions*

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Abstract

This is a literature review examining the prospect of music as a treatment for anhedonia in major depressive disorder. It delves into the neural circuitry and neurological basis for pleasure, music, and anhedonia. Using the literature, it then explores the relationship among the three and the implications that these connections could have.

Keywords: *Major Depressive Disorder (MDD), anhedonia, music, pleasure, nucleus accumbens* multilingual abstract | mmd.iamonline.com

Introduction

Pleasure

No matter how technologically advanced our species continues to become, our species' brains remain physiologically unchanged and constrained by animalistic desires. These desires are hardwired into our DNA, and most of them exist for our survival and fitness. Desires, such as eating, sex, or socializing satiate our cravings and employ the use of our reward circuitry in the brain. Reward involves a composite of several psychological components: liking (core reactions to hedonic impact), wanting (motivation process of incentive salience), and learning (Pavlovian or instrumental associations and cognitive representations) [1]. Pleasure, or liking, is the key first step of the first component and, therefore, into the reward circuit. Pleasure serves as

motivation for an individual to pursue rewards necessary for fitness, but can allow ill-advised pursuits such as addictions.

Pleasure is inherently both objective and subjective because of our evolutionary past. It seems to be the evolutionary link between perceiving what is rewarding to us and whether we like it or not. Darwin suggested that affective reactions were selected by evolution for their useful functions and were adapted into emotional expressions. Mammalian brains dedicated millions of developing neurons to the mesocorticolimbic patterns of reward circuitry and probably persisted with this pattern because objective affective reactions conveyed substantial consequences to survival [1]. Evolution, down the road, was then able to translate objective pleasurable reactions to conscious feelings of pleasure. It is apparent that pleasure or displeasure is directly tied with emotion, as displeasure can cause pain, disgust, anxiety, fear or depression, and pleasure can cause happiness. Regarding how much of these feelings one would feel is absolutely subjective and contextual, but the universality of these emotions exists.

The study of affect, the hedonic quality of pleasure or displeasure, is indispensable in our developed society, as more and more people are diagnosed with affective or mood disorders, such as depression, bipolar disorder, and anxiety.

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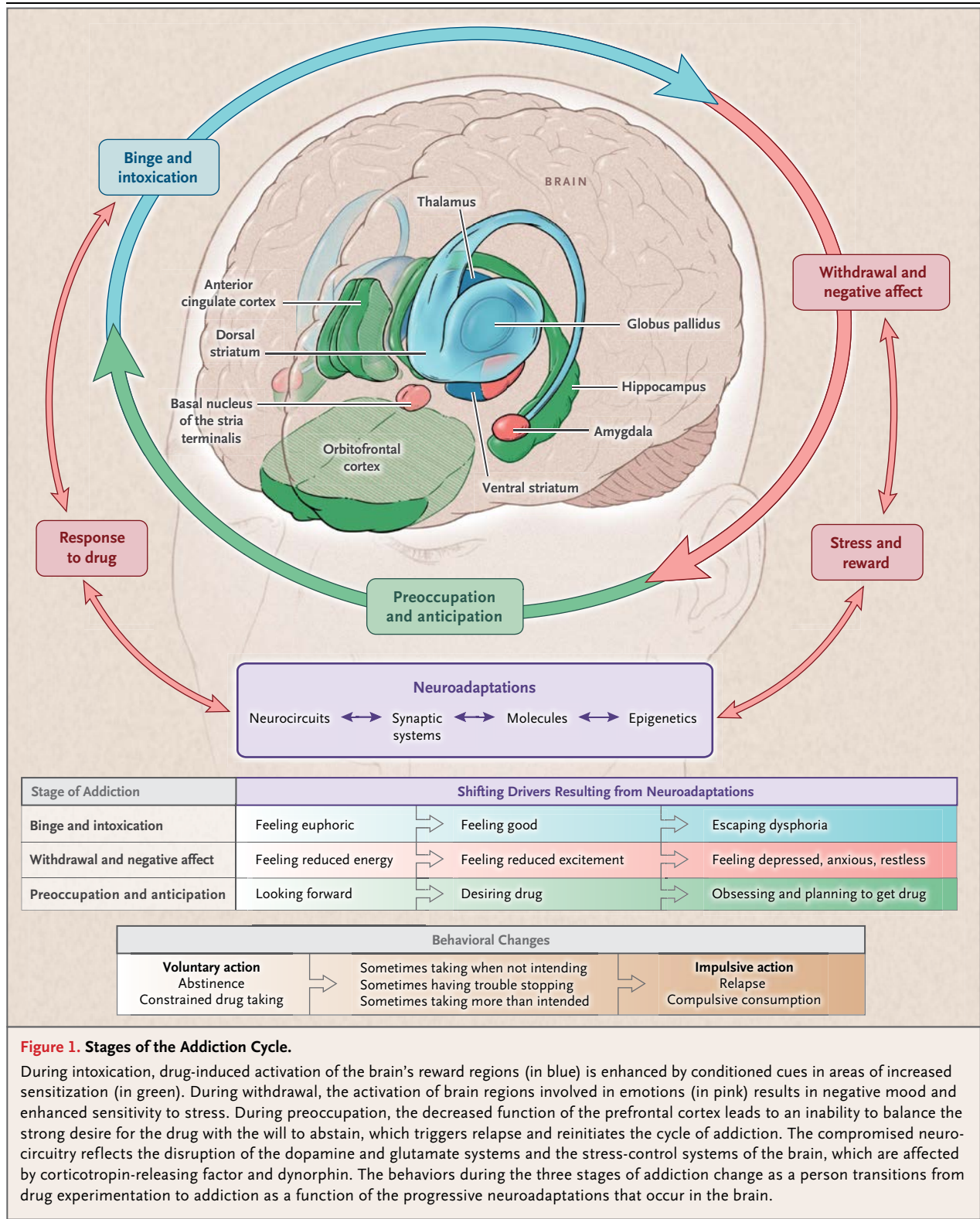


Figure 1. Stages of the Addiction Cycle.

During intoxication, drug-induced activation of the brain’s reward regions (in blue) is enhanced by conditioned cues in areas of increased sensitization (in green). During withdrawal, the activation of brain regions involved in emotions (in pink) results in negative mood and enhanced sensitivity to stress. During preoccupation, the decreased function of the prefrontal cortex leads to an inability to balance the strong desire for the drug with the will to abstain, which triggers relapse and reinitiates the cycle of addiction. The compromised neurocircuitry reflects the disruption of the dopamine and glutamate systems and the stress-control systems of the brain, which are affected by corticotropin-releasing factor and dynorphin. The behaviors during the three stages of addiction change as a person transitions from drug experimentation to addiction as a function of the progressive neuroadaptations that occur in the brain.

Figure 1 shows the mesolimbic reward system, which will be mentioned frequently. It’s important to mention the ventral striatum contains the nucleus accumbens. The ventromedial prefrontal cortex is dorsal to the orbitofrontal cortex and has overlap with it. (Used with permission from Volkow et al., 2016).

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Neuroscience of Pleasure

There is widespread overlap and activation in the brain among many pleasurable rewards, such as food, sex, addictive drugs, friends and loved ones, music, and art [1]. The hotspots for pleasure in the brain are proposed to be in the nucleus accumbens, ventral pallidum, amygdala, parabrachial nucleus of the pons, and scattered areas of the frontal cortex, such as areas of the orbitofrontal cortex, cingulate cortex, medial prefrontal cortex, and insular cortex [1]. Specifically, the midanterior part of the orbitofrontal cortex is a locus for conscious perception of pleasure, and the nucleus accumbens presents itself as the most crucial reward evaluator with a spectrum of positive-negative valence and high-low intensity regions. These different regions are activated at varying intensities and in response to different situations, however this entire network of regions across the brain suggests a hedonic neural circuit. Rising levels of neurochemicals, such as dopamine, opioids, endocannabinoids, glutamate, and GABA are suggested substrates for these receptive brain regions. Though dopamine was an extremely popular candidate for the pleasure molecule, it likely mediates the second component of reward, wanting.

In humans, encephalization may result in a greater cortical involvement in affect and emotion, expressed as top-down regulation, but mesocorticolimbic circuits still primarily mediate core affective reactions [2]. This means the nucleus accumbens most likely controls the actual pleasure felt during an experience and relays it to the ventral pallidum, whereas the orbitofrontal cortex, the region most faithfully representing pleasure in experiments, is more so concerned with consciously monitoring and predicting reward value [2]. Case studies involving patients with significant damage to their prefrontal cortices show retaining of affect, which suggest subcortical causation of affect.

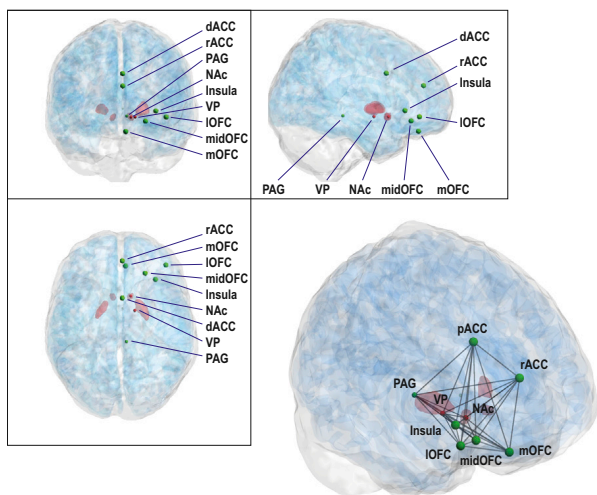


Figure 2 shows connectivity of the reward circuit regions, including the orbitofrontal cortex (OFC), anterior cingulate cortex (ACC), ventral pallidum (VP), and nucleus accumbens (NAc).

Music

Music is one of the rewards that give us pleasure. Music has been around for tens of thousands of years and has withstood evolutionary pressures and changes. It is no secret that either playing or listening to music is extremely pleasurable and can become a very emotional experience. Historically and culturally, music has been developed separately and differently yet commonly existed as a cornerstone for each culture. There is an extraordinary range of musical sounds, genres, and tastes, yet music is pleasurable for its respective audiences. Each culture and genre manipulates the sounds that music makes and can enhance or detract complexity, sound quality, artistry, lyricism, depth, rhythm, cohesiveness, or originality to name only a few qualities of music. Music seems to be contextually based like other learning experiences in our lives; for example, a 12-pitch chromatic scale may sound exceedingly minor and unpleasant to those in Western cultures, yet provides familiarity and pleasure to those in non-Western cultures.

However, how can an activity such as music, something that seems so ineffectual and lasts for successive generations, be imperative for our survival? Humans listen to or play music, not for mating rituals (exclusively), not for a demanding satiety like hunger or thirst, but for leisure and pleasure. It's understandable that a non-imperative or secondary activity, like using drugs, which makes us feel good, would last and persist, so perhaps music or art can be seen in a similar light when discussing the endurance of its history. In fact, for the caveman, music was most likely the drug of choice, an activity to pass time and escape boredom. But research on the neuroscience of music has implicated that it is much more than just a leisure activity.

Listening to or playing music is an extremely engaging experience for the brain. Music is very closely related to language, which is unsurprising since both speech and music are grounded in listening; humans use sound to communicate cognitive representations and internal states, including emotion [3]. Therefore, music is inherently social (language exists to communicate to others) and compound. There is hierarchical organization in the way sounds and rhythms are processed, which generate representations of structural regularities of music. These representations are essential for creating expectancies of events as they unfold, a phenomenon described in linguistic experiences as well [3]. The auditory cortices have dorsal and ventral streams, which interact with premotor cortex, dorsolateral frontal cortex, limbic structures, and subcortical basal ganglia; when passively listening to music, even our motor cortex shows activation. This interconnectedness suggests the link between temporal structure in music and movement, so you're technically exercising whether you're playing, dancing to, or listening to

music. Finally, music at its core is an emotional experience; we wouldn't be human without emotion, and music serves as a fluid liaison between our feelings and our expression of them. Sympathetic nervous system activity can be used as a reliable measure of emotional arousal; there is a positive correlation between arousal and subjective feelings of pleasure.

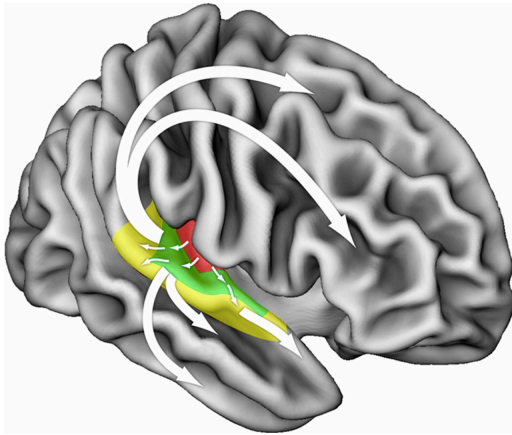


Figure 3 shows a schematic of the functional pathways for auditory information processing in the brain. Pathways originating in core auditory areas project outward and travel ventrally toward targets in superior and inferior temporal sulcus and gyrus, eventually terminating in the inferior frontal cortex, and dorsally toward distinct targets in parietal, premotor, and dorsolateral frontal cortices. Taken from Zatorre and Salimpoor, 2013.

Whether pleasurable music is objective or subjective is debatable and probably a mixture between the two. There's practical evidence that support each, such as the distinction between good and bad music. There is general consensus over what sonically sounds pleasing versus a cacophonous, arrhythmic blob of notes. While this may sound restraining, humans have found thousands and thousands of ways to express their emotions through sounds that are objectively pleasant. Subjective feelings about music are apparent as well, yet seems to exist as a smaller element. Listeners can be more experienced or amateur, nitpicky or stubborn, or critical or light. Whether one of Mozart's pieces is one's favorite piece ever or Mozart's best piece is very subjective, but asking if Mozart made pleasurable music is a universally objective question. This is because music elicits emotions, which are universal.

The mechanics of music perception in the brain are quite complex, and this paper will briefly gloss over significant details but mainly focus on music and pleasure. Primate auditory cortex is organized in a hierarchical manner with feed forward and feedback projections, as seen in Figure 3. This architecture allows integration of auditory information with other modalities, such as memory, planning, and motor systems [3]. Humans have an excellent ability to maintain auditory information, using a phonological loop in working memory mechanism, which allows us to process tonal

information for extended periods of time. Primary auditory cortex is also topographic for pitch frequency. These variations in pitch make up the melodies in music. The perception of a melody involves a subjective, active component, since expectancies and anticipations are based upon a listener's implicit knowledge about musical rules that have been acquired by previous exposure to music of that culture [3]. This can be compared to the exposure of different foreign languages in various cultures, as speech and music learning appears early in life yet depends on context. Melodies also contain a temporal or metrical aspect, which seems to test the predictive power of the listener more than pitch, since determining the rhythm or when the pitch occurs can be simpler than determining what the pitch will be. Finally, the integration of auditory information to memory can be thought to accumulate over time as a template, containing information about sound patterns that recur in musical structures [3]. Therefore, each individual can develop his or her own template for distinct musical imagery. There is functional interaction between frontal and temporal cortices during musical imagery that is predictive of individual differences in subjective vividness of imagery, suggesting a direct link between engagement of this frontotemporal system, the ability to imagine music and to subjectively enjoy it [3]. It is this storage system that allows humans to categorize and understand incoming sounds; this process leads to a series of predictions that can be confirmed or denied, and ultimately determines the reward value to the individual.

How can music cause pleasure?

Music has been used therapeutically since antiquity, but study of the psychological and physiological effects underlying the putative health benefits of music is more recent. As stated above, the sympathetic nervous system will be activated while listening to music, indicating emotional arousal. In preliminary studies examining peak emotional arousal (chills) and listening to music, they showed the ventral striatum and other brain regions associated with emotion (mesolimbic reward system) recruited as a function of increasing intensity of the chills response [4]. More studies were conducted using raclopride-based, a ligand that binds with dopamine receptors, positron emission tomography (PET) to show large dopamine release in the mesolimbic striatum, which can help explain why music is considered rewarding [5]. Researchers then examined the neural activity during rewarding responses to novel music and revealed that the nucleus accumbens was most associated with the reward value of the musical stimuli [6].

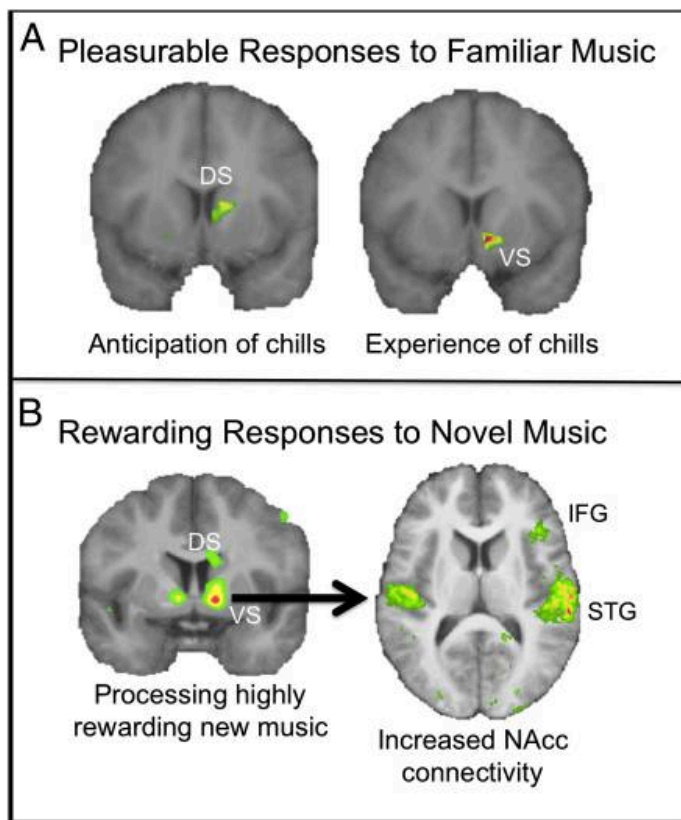


Figure 4 shows the neural correlates of processing highly rewarding music. (A) increased hemodynamic activity in the ventral striatum (VS) during peak emotional moments (marked by “chills”), and the dorsal striatum (DS) preceding chills, in the same regions that showed dopamine release. (B) fMRI scanning showing that the best predictor of reward value of new music was activity in the striatum, particularly the NAcc; the NAcc also showed increased functional connectivity with the superior temporal gyri (STG) and the right inferior frontal gyrus (IFG) as musical stimuli gained reward value.

This distinct dopamine release in the striatum during anticipation and outcome implicates links with the reward system and the mesolimbic system overall, which regulate motivation and pleasure. More importantly, the nucleus accumbens is implicated in making predictions, anticipations, and reward prediction errors, which is the calculated difference between what was expected and the actual outcome [7]. This is evidence that temporal predictions play an important role in the way individuals obtain pleasure from musical stimuli, as I’ve discussed above how the nucleus accumbens is the major hedonic hotspot. Also, the increased functional connectivity between the nucleus accumbens and the superior temporal gyri (STG), shown in Figure 4, suggests that predictions were linked with information contained in the STG, meaning it could be related to the templates of sound gathered from prior experience. This link from a subcortical reward circuit to a highly individualized region of the neocortex may explain why different people like different

music, as a function of their previous experiences with music [3]. As Zatorre and Salimpoor state, “these corticostriatal interactions exemplify the cognitive nature of rewarding responses to music and help to explain why the complexities of the highly evolved human brain allow for the experience of pleasure to an abstract sequence of sound patterns” [3]. It is most likely that the cerebral cortex and striatum work together not only to make predictions about potential rewards and to assess the outcome but also to process unexpected events in music processing [8]. These circuits are highly complex yet can explain basic observations in preliminary music studies on emotional arousal. For example, the nucleus accumbens is tightly connected to the amygdala and hippocampus (implicated in processing, detecting, and expressing emotions), hypothalamus, insula, and anterior cingulate cortex, areas of the brain that are implicated in controlling the autonomic nervous system, which could explain the psychophysiological phenomena associated with music and emotional arousal. Finally, the nucleus accumbens is tightly integrated with the orbital and ventromedial frontal lobes, areas largely implicated in assigning and rewarding reward value to stimuli, which will be discussed more later [9].

In addition, during duet performances, the brain shows higher release of oxytocin, a molecule that elicits trust and pleasure. One must take into account the subjective agreeability to different types of music, usually due to cultural and social backgrounds and differences; however, emotions elicited by music, such as joy, fear, and neutrality correlate with brain activity no matter the subjection.

In summary, perceiving music has much to do with our sense of time and anticipation. We anticipate what will happen next, and this predictive timing or coding is coupled to the release of dopamine or other neurochemicals, such as opioids. Also, hearing a rhythm will activate several brain areas, including the mesolimbic reward circuit, parts of the secondary motor areas of the cortex even if we are not moving at all, and prefrontal cortical areas.

Anhedonia

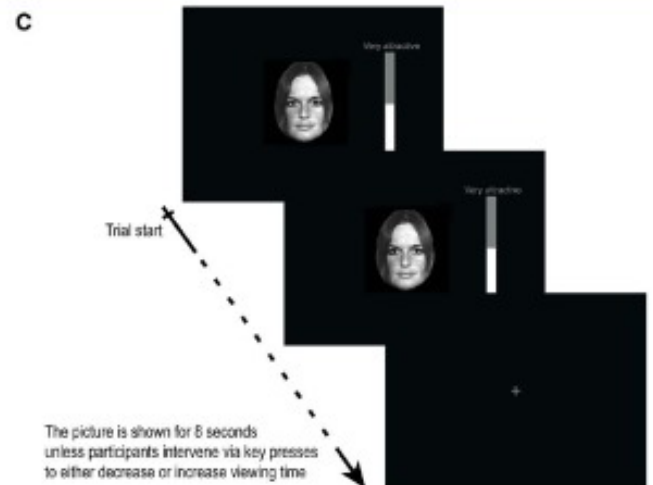
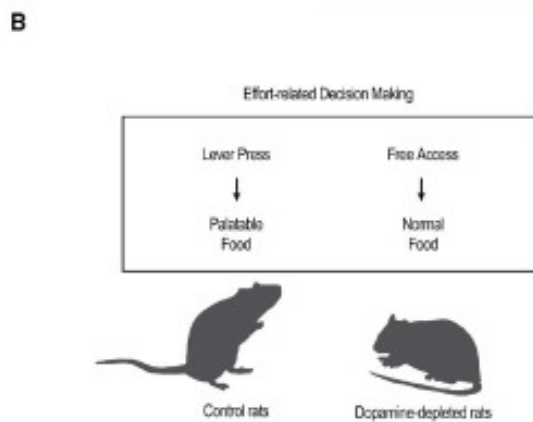
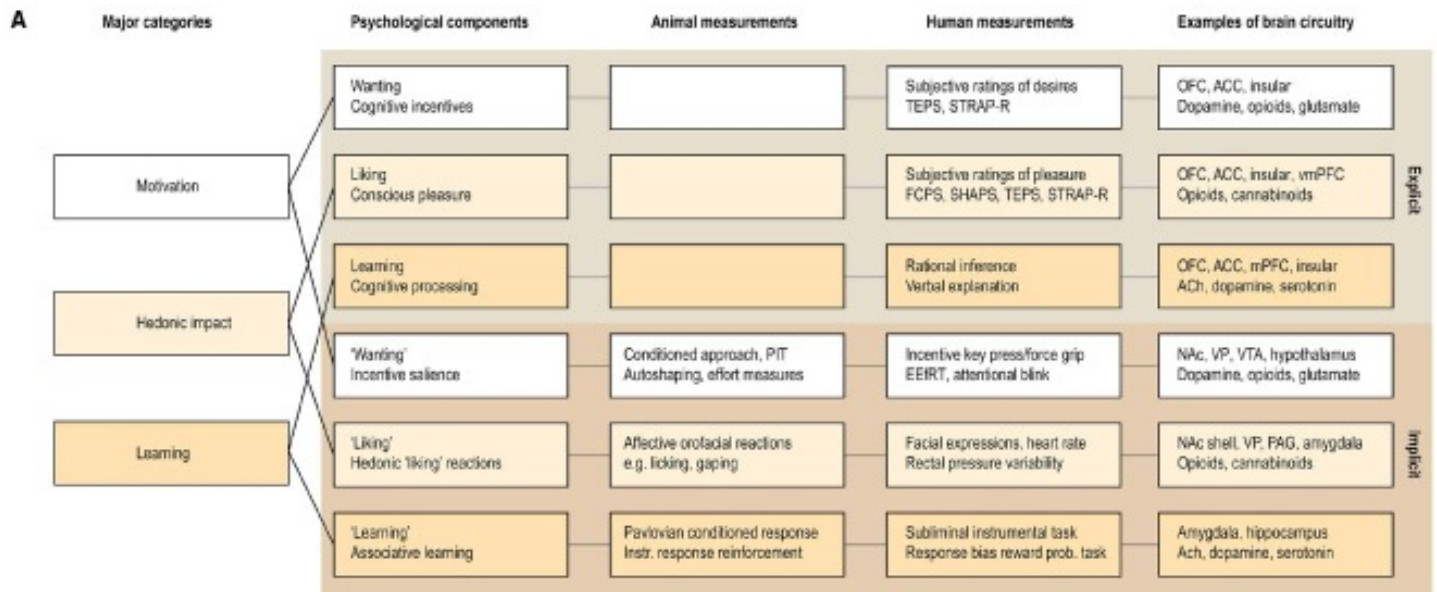
Anhedonia is historically defined as reduced response to pleasure in response to reward or normally pleasant stimuli and more recently has been defined as “impaired ability to pursue, experience and/or learn about pleasure, which is often, but not always accessible to conscious awareness” [10]. Though pleasure can be highly subjective and contextual, anhedonia remains to be a highlighting trait of major depressive disorder (MDD) and one of the two required traits (the other being depressed mood) to be diagnosed MDD. This paper will explore the correlates of anhedonia in MDD, music, and the use of music therapy to reverse anhedonia in MDD patients. Anhedonia presents itself in schizophrenia patients, MDD patients, Alzheimer’s, withdrawal states of addiction,

and chronic stress patients. The interest in anhedonia and MDD stems from MDD's relatively low remission rate with various antidepressants and adjunctive treatments and high treatment-resistant population; therefore, studies into possible biomarkers or specificities of anhedonia can compartmentalize MDD into a more clinically understandable, treatable disorder. There is also a need for alternative, effective therapies for anhedonia and MDD. Finally, anhedonia seems to receive less attention than depression's other symptoms yet is a negative predictor for SSRI effectiveness and the number of depression-free days [11].

Research suggests depression is characterized by deficits in motivational processing and dysregulation of the brain's reward system [12]. Behavioral studies reveal that individuals with depression have deficits in establishing reward bias and reward-related decision-making; patients with higher levels of clinical depressive symptoms showed blunted reward sensitivity or bias, meaning they were less likely to modulate responses to reward [13]. Currently, the behavioral tasks used to assess reward processing and learning include probing anticipating and consumption of delay discounting, reward response bias, prediction error, reversal learning, and effort to acquire rewards [11]. These different tasks are used to measure the subcomponents of anhedonia, which measure impairment in the ability to pursue reward, learn about reward, and experience pleasure. The division of tasks for different subcomponents acknowledges the fact that anhedonia is comprehensive of all reward components, and treatment of anhedonia may require more than just targeting the pleasure aspect of reward. For example, the last described behavioral task, Effort Expenditure for Rewards Task (EEfRT), has been used to show that MDD patients are less willing to expend effort for reward than controls and less able to effectively use reward information about magnitude and

probability of rewards, showing that decision-making or motivational deficits, which is more tied to the "wanting" reward component, are to be considered along with the "liking" or consummatory component [14].

Currently, anhedonia or hedonic experience in MDD is assessed using the Snaith-Hamilton Pleasure Scale (SHAPS), as a 14-item questionnaire with disagree responses receiving a score of 1 and with higher scores indicating a higher level of anhedonia [15]. There's also use of the Physical Anhedonia Scale (PAS) and Social Anhedonia Scale (SAS) [16]. These are usually used in tandem with depression rating scales, such as Hamilton Depression Rating Scale to compare the difference and overall condition of the patient. Patients with higher depression ratings will also have higher PAS ratings. In the use of the Fawcett-Clark Pleasure Capacity Scale, depressive patients were more sensitive to displeasure than normal control patients, and physical anhedonia may be independent of low emotional reactivity [17]. There is also the Dimensional Anhedonia Rating Scale (DARS), which is a dynamic scale that includes facets of desire, motivation, effort, and consummatory pleasure and demonstrates very high internal consistency reliability and validity [18]. Due to the wide differences in each scale, some scales are more focused in a certain area, such as consummatory pleasure, and most scales are used in conjunction with others to cover inconsistencies and increase generalizability. It would be important to state that the results of this paper were not drawn from the sole use of anhedonia questionnaires but rather from fMRI and neuroimaging studies, as a combination of behavioral tasks and neuroimaging are paramount for the advancement and accuracy of this topic.



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Pharmacological treatment for anhedonia is experimental. Currently, agomelatine, an agonist of melatoninergic receptors MT1 and MT2, has been studied to be effective in the treatment of anhedonia [19]. A study on Deep Brain Stimulation (DBS) showed that 100-150 Hz (above the gamma frequencies associated with consciousness) stimulation to the nucleus accumbens was an effective frequency to activate hedonic hotspots and saw substantial positive changes in clinical symptoms and social life [20]. This experiment produced a “multiplier effect for the perception of pleasurable experiences” and is extremely promising for future treatment of anhedonia; it also shows the importance of the nucleus accumbens in anhedonia. An open-label study on ketamine’s effects on depression showed alleviation of overall depression symptoms; in this study, reduced anhedonia was correlated with increased glucose metabolism in the hippocampus and dorsal anterior cingulate cortex and decreased metabolism in the orbitofrontal cortex [21]. A dopamine agonist named pramipexole is prescribed to

Parkinson’s Disease patients and is a D2 receptor agonist with higher selectivity for D3 receptors, whose prominence in the limbic system show theoretical promise for anhedonia [22]. Typical antidepressants, such as escitalopram have been studied in specificity for anhedonia treatment, yet fail to be very effective for it [23, 24].

MDD and Music

There have been several brain areas implicated in music: from auditory cortex to striatum, nucleus accumbens, prefrontal cortex, orbitofrontal cortex, hippocampus, hypothalamus, insula, and amygdala. There is irrefutable overlap between the systems involved with music and anhedonia; although music might be considered noninvasive and nonpharmacological, this is not strictly true if one considers the neural processes involved in music perception and processing.

There’s a complex relationship between depression and immune system function as well, and research has shown

music can correlate with an increase in immunoglobulin A [25]. Music exposure reduces state and trait measures of anxiety, which is associated with decreased cortisol levels [25]. This shows some regulation of the hypothalamic-pituitary-adrenal axis, which has implications in mood, psychotic, and psychiatric disorders. In fact, antidepressants suppress pro-inflammatory cytokine production, suppress stress hormone release, and may stimulate anti-inflammatory cytokine release; endotoxins or pro-inflammatory cytokines can induce neuropsychological symptoms like anhedonia [26]. Relaxing music has been shown to decrease blood pressure, heart rate, and respiration rate.

Examining antidepressant drugs and comparing their effects to music's are a great way to examine any overlap between the two. Antidepressant drugs increase expression of brain-derived neurotrophic factor (BDNF), and music exposure increases BDNF brain concentrations in animals [25]. There have been studies that determined that mu-opioid receptor expression was increased in peripheral blood mononuclear cells in individuals listening to music; the opioid receptor antagonist drug naloxone attenuated the emotionally arousing chills elicited by music in a few individuals. This indicates that music's therapeutic effects on the brain can come from dopamine and opioid release in the mesolimbic circuit along with reinforced connectivity to prefrontal areas like the orbitofrontal and ventromedial prefrontal cortices to perceive pleasure, increased immune system function and dampening of cortisol levels, and increased BDNF levels.

Hypothesis

Current treatments for anhedonia are sparse and highly experimental, whereas, conventional treatments for depression include selective serotonin or norepinephrine reuptake inhibitors (SSRIs & SNRIs), monoamine oxidase inhibitors (MAOIs), and other medications. More unconventional, non-pharmacological therapies that may be more invasive include electroconvulsive therapy and transcranial magnetic stimulation. Finally, noninvasive, talk therapies, such as cognitive behavioral therapy and interpersonal therapy have shown very promising treatment effects in comparison to pharmacological treatments.

Anhedoniacs, as described from observed behavioral studies, show blunted affect towards anticipating or predicting rewards and show general dysregulation in motivational decision-making for reward-related activities. Music seems to activate areas that mediate reward prediction and is potentially related to these key anhedonic features. These behavioral tasks, however, do not uncover the underlying neurobiological processes related to these deficits. Therefore, the use of neuroimaging data is necessary to create tangible, comparable links between musical processing circuitry and anhedonic circuitry.

I have discussed music's therapeutic effects, but more importantly, I have discussed music's relationship with cortical and mesolimbic circuits that regulate our processing of pleasure, reward, and emotion. I hypothesize that music, if effectual on the same regions that anhedonia affects, can reverse or alleviate anhedonia in MDD patients in a natural, noninvasive manner. Music therapy could be used as a viable therapy in conjunction with other therapies for MDD patients.

Results

The goal of the studies linked in these results was to collect neuroimaging data about previous discussion on regions associated with pleasure in anhedonia and music. These regions included connections among the nucleus accumbens, orbitofrontal cortex, ventromedial prefrontal cortex, and others. There was also an attempt to collect any supportive data about music listening and therapy on anhedonia or depression in general.

First, studies that delved into the relationships between intrinsic functional connectivity (iFC) among relevant structures, measured by spontaneous bold-oxygenation-level-dependent (BOLD) in fMRI, and severity of MDD and anhedonia were observed. One study showed increased iFC between all striatal regions (dorsal caudate, ventral caudate, nucleus accumbens, dorsal-rostral putamen, dorsal-caudal putamen, ventral-rostral putamen) bilaterally and the dorsomedial prefrontal cortex (dmPFC), as well as between the right ventral caudate and the anterior cingulate cortex (ACC) [27]. Positive correlations between striatal iFC and the pregenual ACC, supplementary motor area, and supramarginal gyrus were associated with anhedonia severity; negative correlations were seen between the nucleus accumbens with the subgenual ACC and caudate [27]. Another study found that in response to happy stimuli, anhedonia, but not depression severity per se, was positively and negatively correlated with ventromedial prefrontal cortex and amygdala/ventral striatal activity, respectively [28].

Secondly, studies examining the brain regions activated during music listening were researched. This section is not as comprehensive, since I discussed such regions in the introduction; rather, I looked for any evidence that similar regions from anhedonia studies were activated in music studies. A study on subjectively pleasurable music's effects on regional cerebral blood flow (rCBF), which more or less suggests activation, showed increased rCBF in the left ventral striatum, dorsomedial midbrain, bilateral insula, right orbitofrontal cortex, thalamus, anterior cingulate cortex, supplementary motor area, and bilateral cerebellum. Decreases in rCBF were seen in the bilateral amygdala and ventromedial prefrontal cortex [4]. A study that focused only on the nucleus accumbens and its relationship to music delved into several papers that used animal, human, and fMRI studies

[29]. Significant findings include the following: opioid transmission in the nucleus accumbens is associated with dopamine release in the ventral tegmental area (VTA) [30], extracellular dopamine levels in the nucleus accumbens increases during a conditioned musical stimulus [31], there is significant connectivity between the VTA-mediated interaction of the nucleus accumbens with the hypothalamus, insula, and orbitofrontal cortex [32], depressed patients show less activation than controls in medial orbitofrontal cortex and nucleus accumbens when listening to their favorite music [33], and trait anhedonia is negatively correlated with pleasantness ratings of music stimuli and effective connectivity between the nucleus accumbens, VTA, and other paralimbic regions [34]. Zatorre in 2015 found that as the desirability of the music increased (as indexed by monetary amounts the listener was willing to pay) the nucleus accumbens showed increased functional connectivity with the auditory cortices, inferior frontal gyri, ventromedial prefrontal cortex, orbitofrontal cortex, and amygdala. These findings suggest that the reinforcement value of musical experiences arises as a result of interactions between regions involved in auditory perception, high-level temporal sequencing, and emotional processing and valuation [35].

Thirdly, studies that actually involved music listening and anhedoniacs (or MDD patients) were examined. A study that questioned anhedonia's association to posterior ventromedial prefrontal cortex (pVMPFC) functional connectivity in a resting-state versus a context-specific manner, using task-based fMRI involving pleasant music, found that pVMPFC connectivity was negatively correlated with anhedonia during music listening in key reward- and emotion-processing regions [36]. These regions include the nucleus accumbens, ventral tegmental area/substantia nigra, orbitofrontal cortex and insula, as well as fronto-temporal regions involved in tracking complex sound sequences, including middle temporal gyrus and inferior frontal gyrus. This study also showed that pVMPFC resting-state connectivity was not associated with anhedonia in MDD [36]. There are a myriad of studies that have examined music therapy's positive effects on MDD patients, and I will list several. Erkkila et al. [37] and Chen et al. [38] found that music therapy plus standard care is significantly more effective than just standard care for depression symptoms, anxiety symptoms, and general functioning after 3 months. Fachner et al. [39] did a similar study, but they also measured rest-EEG levels in the patients and observed modulations in the fronto-temporal activity after 3 months of music therapy. This presents actual physical measurements in correlation with depression and anxiety reduction. Jasemi et al. [40] found significant decreases in the levels of depression and anxiety in cancer patients only after 3 days of music therapy, which was 20 minutes of light music per day. Hsu and Lai found that the patients' listening to their choices of music for two weeks resulted in significantly better depressive scores compared with controls, indicating a

cumulative dose effect. Other studies by Chan et al. [41] have also supported this cumulative dose effect that music listening has on depressive patients.

Finally, I have included a few papers that I thought to be relevant to the question, but not directly to fMRI studies. An extremely interesting paper by Pauwels et al. [42] suggests music-generated emotions (Mozart in this experiment's example) are linked to higher-level cognitive abilities, such as reasoning skills by mere listening, and that music therapy benefits its patients by diverting their attention from unpleasant experiences and future interventions and by modifying stress through strengthening the immune system. In an attempt to understand how music therapy works in depressed patients, I came across a study by Maratos et al., 2011 [43]. They suggest actively playing music with a therapist assists depression through aesthetic, physical, and relationship dimensions. I will discuss this in more depth below. Another study I found interesting was by Mallik et al. [44] and found that naltrexone, a mu-opioid antagonist, induces reversible anhedonia and found that both positive and negative emotions whilst listening to music were attenuated. Lastly, a study by Lepping [45] found that MDD patients showed greater activation in the anterior cingulate cortex in response to negative sounds while control patients showed the greater activation in response to positive sounds.

Discussion

Key Findings:

- 1) There are large amounts of evidence supporting music therapy as treatment for depression.
- 2) Activation and connectivity of the nucleus accumbens with its associated prefrontal pleasure regions, the orbitofrontal cortex and ventromedial prefrontal cortex, are associated with anhedonia severity and reward value of music.

There is significant overlap between the regions affected by anhedonia and those activated while listening to music, and the evidence in support of music therapy for depressed patients is quite staggering. Patients who underwent music therapy plus standard care reported significantly lower depression scores than controls three months after they underwent music therapy. A measure of anhedonia is represented in depressive scores, so it would appear the effects of music therapy are apparent and long lasting. Earlier, I discussed why there is a need to take another look at existing treatments for MDD, which largely include medications and talk therapy, since up to 30% of MDD patients do not respond to two antidepressants and are diagnosed with treatment-resistant depression. From a psychological standpoint, I speculate that music therapy could work just as well as talk therapy, especially if the patient is engaged in listening to or

playing music with a therapist. Music activates the same pathways in interpretation of speech yet is more emotionally derived and salient. Listening to or playing music with a therapist could create a meaningful, social connection where an aesthetic experience can be shared between people. This shared connection can elicit oxytocin release along with opioid release; the relationship is quite harmonious (excuse the pun), and listening to novel music can be a springboard for both individuals to behave, discuss, and feel differently. Another aspect of music therapy is the inherent physicality of listening to or playing music. We have already discussed the activation the striatal and mesolimbic system concurrently has with the supplemental motor area, a mechanism that ties us to the meter of the music and helps us produce and predict movements and tones with the music. There is already surmounting evidence for physical exercise assisting depression patients, and music offers a unique physical experience, one that is also inherently musical and easily shared with others. Lastly, the final and most interesting aspect of music therapy would be the relational one. From before we had a conscious memory, our first experiences of relating (with our primary caregiver) are fundamentally musical [43]. It is these non-verbal sounds that can suggest a whole world of pleasure for the newborn baby and the parent; there is even evidence that when mothers of infants are depressed the musicality of conversational engagement is demonstrably affected with significant developmental implications for the child.

Music therapy, in a sense, can be taken in this neo-parental perspective, where music nurtures the patient in a process of discovery and self in relation to others, including the capacity for experiencing meaning and pleasure [43]. This engagement and interaction is two-fold: we not only relate with others through music but also relate with ourselves through unconscious mechanisms similar to meditation and mindfulness methods. In fact, musical intervention could possibly decrease addictive behavior along with depressed mood because of increased self-control and awareness. Other means of therapy are viable, such as art therapy. However, I speculate that music's biggest strength is the fact that it is an integrating means for unpleasant experiences and future experiences, especially for those suffering from MDD, other mood disorders, or neurological symptoms. On top of one's capacity to integrate and be re-directed from unpleasant experiences, it offers natural pleasurable emotion in the brain.

From a neurobiological standpoint, I speculate that music is a strong, indirect D2 agonist by dopamine release and concurrent opioid release in the nucleus accumbens. The music originates from the auditory cortices and quickly relays to the mesolimbic reward circuit by a direct corticostriatal pathway. The striatum relays its dopaminergic (or glutamatergic and GABAergic) message to its most ventral region, the nucleus accumbens. The nucleus accumbens is the origin of pleasure or hedonic hotspot and stimulates the initial

feeling of chills from very pleasurable music, and if the music is emotionally salient or pleasurable, the nucleus accumbens will heighten its connections to associated pleasure regions around it. The physiological response from chills also comes from the nucleus accumbens's activity with the hypothalamus, insula, and anterior cingulate cortex, regions associated with autonomic nervous system function. Connections to the anterior cingulate cortex could also mediate what stimuli we are paying attention to and could make pleasure more emotionally salient. Connections between the nucleus accumbens and certain regions of the prefrontal cortex were most significant in the results' findings, however. These two primary regions are the orbitofrontal cortex and the ventromedial prefrontal cortex. The ventromedial prefrontal cortex (VMPFC) has connections to limbic structures that are central to emotion-processing and hypothalamic regions that modulate autonomic reactivity [46]. The more severe one's anhedonia is, the less effective connectivity exists between the nucleus accumbens and the VMPFC. Evidence suggests the VMPFC is implicated in encoding goal-values and correlated with the subjects' value for each category of good [9]. Moreover, the VMPFC has been seen to be correlated with the subjects' valuations for all categories of goods (primary or secondary), and the brain encodes a "common currency" that allows for a shared valuation for different categories of goods [9]. The orbitofrontal cortex shows a similar role as the locus for conscious pleasure perception. It is most likely these two higher-order regions that are able to allow us human beings to hear a series of consonant sounds and to label and perceive these sounds as memorably pleasurable in concordance with the hedonic hotspot, the nucleus accumbens. Because the fMRI studies found that connectivity between the nucleus accumbens and these areas were weakened in correlation to anhedonia severity, it would follow that anhedoniacs would perceive less pleasantness from a certain piece of music compared to controls, yet it is most likely this very pathway that music affects when used passively or for therapy.

From a physiological standpoint, music most likely alleviates levels of anhedonia through anti-inflammatory methods as blood flow increases to those regions that affect both anhedonia and rewarding musical listening. This mechanism, however, may only treat anhedonia for "right now" or the short term. Music is an immediate, smaller reward, which anhedoniacs do not prefer [47]. This is where the lasting overall effects of music therapy on MDD are relevant yet contradictory. It may be pertinent that music can be used as an effective conditioned stimulus, and prior experience with certain music coupled with pleasurable experiences may be needed before making a lasting impact. Perhaps it is because music is used in couple with standard treatments, such as medications, exercise, talk therapy, and other options. Perhaps music elicits long-term changes, such as long-term neural plasticity, which could alleviate depressive symptoms. Future studies should delve into the effective

functional connectivity between the VMPFC, orbitofrontal cortex, and the nucleus accumbens before and after music therapy.

Given these key findings, I speculate that music very well can alleviate the severity of anhedonia in MDD patients in a noninvasive, non-pharmacological manner, through the “master” pleasure region, nucleus accumbens. Though the neurological basis of how music therapy can assist MDD patients in general is not well known, I speculate the strengthening of intrinsic functional connectivity among the nucleus accumbens and key pleasure areas discussed above contributes to a visibly more psychologically healthy individual.

Because the effects of music are temporally transient, how does music therapy measure up against other antidepressant or anti-anhedonic methods? It may help to always couple activities with music to improve pleasure, but more studies need to be done to compare the effectiveness of music therapy compared to control methods. I speculate that music therapy could find a niche in depression therapy, because of the evidence that reward processing deficits are not restricted to diminished experience of pleasure but also reward wanting and reward learning. Music is a complex experience that associates wanting and learning experiences and is more perceptible, experiential, and intimate than taking a pill every day. However, to play devil’s advocate, music may be more apt to deal with reward deficiency syndrome and related behaviors, including substance use disorder instead of depression due to the heavy link to the nucleus accumbens. In the end, it may depend “on which subcomponents of reward processing are mainly affected, [so] different medical treatments may be afforded. For example, depressed patients characterized by impaired ability to pursue pleasurable activities may benefit from medical interventions that target neurotransmitter systems such as the mesolimbic dopamine system and the opioid system, which have been shown to play a crucial role in reward motivation” [10]. Music could be that viable intervention that affects the mesolimbic dopamine and opioid system.

This information can put into perspective why activities, events, or everyday duties are more memorable, enjoyable, and more possible when coupled with music. It’s not a secret that music can calm us, help us fall asleep, help us stay focused on work or a workout, be the cornerstone of festivals, concerts, and a night out, and bring together people in a socially peaceful fashion. Though it cannot be assumed that these mechanisms are tied with depressive disorder or that depressed patients consciously feel the same emotions a non-depressed patient would in these situations, the affect of music is apparent.

Limitations

It would be instrumental to list limitations and keep a critical mind about these papers. Authors may show a

tendency to cherry pick to find evidence that only supports their claim and share none that refute it. Also, we listen to music for different reasons, and as I’ve observed, different regions of the brain will activate for different actions, such as right orbitofrontal cortex activation when listening for musical consonance. So perhaps these brain regions lighting up are for both musical percepts with pleasure percept.

What type of music can you listen to? Is subjectively calm or pleasurable music the only option? It may depend on the music, and because there’s no ideal biomarker for anhedonia patients, music may affect the brain health in an overall way through other pathways rather than directly affecting reward pathways.

It is important to remember that neuroimaging studies are correlational in nature rather than causal, and that the physiological bases of underlying signals (such as the blood-oxygen-level- dependent [BOLD] signal measured with fMRI) are only partly understood [48]. Interpreting correlational signals is complicated, and some correlational neuroimaging activity may of course reflect causal mechanisms for pleasure, while other activity may be a consequence, rather than cause. That is because many brain regions that become active during a normal pleasure may not actually generate that pleasure per se, but rather activate as a step to causally generating their own different functions, such as cognitive appraisal, memory, attention, and decision making about the pleasant event.

Finally, it is possible that not everyone derives pleasure from music. Treating all depressed patients through music is complicated because of variances in personality, learning, and biases.

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