



The Neuroscientific Basis for Aesthetic Preference as an Intervention for Drug Craving Associated with Addiction

Walter S Mathis*

University of Arkansas for Medical Sciences, Arkansas, United States

*Corresponding author: Walter Mathis, Resident Psychiatrist, University of Arkansas for Medical Sciences, 4301 W. Markham St. Slot #589, Little Rock, AR 72205, USA, Tel: 501 526 8200; Fax: 501 526-8198; E-mail: WSMathis@UAMS.edu

Received date: Feb 10, 2015; Accepted date: Mar 20, 2015; Published date: Mar 25, 2015

Copyright: © 2015 Walter Mathis. This is an open-access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.

Abstract

Substance Use Disorders remain a costly and dangerous illness despite decades of focused research and a sophisticated understanding of the mechanisms of acute and chronic use in the brain. It is clear that available therapies have only partial efficacy and effort should be made to translate a growing neuroscience understanding to improved therapeutic interventions. Compelling evidence suggests that the acute reinforcing effects of drugs of abuse are due to increased dopamine release in the nucleus accumbens, a brain mechanism associated with the processing of reward and saliency. But, with chronic drug use, select elements of striatal dopaminergic neurotransmission (receptors, transports, enzymes) are down-regulated, rendering a hypodopaminergic state when not augmented by drug use. This state contributes to drug craving, seeking, and ultimately relapse. Hence it is a target for relapse prevention. Recently it has been confirmed that listening to highly pleasurable music can induce not only a strong psychophysiologic response, but also dopamine release in the same neurocircuits as drugs of abuse. Hypothetically this effect of music could have therapeutic potential as an inducer of dopamine release that might ameliorate the hypodopaminergic state of the abstinent addict as a form of agonist substitution. However, a thorough review of the literature found no clinical trials assessing this potential therapeutic effect. Obstacles for consideration in such a trial are also discussed.

Keywords: Mesolimbic; Prefrontal; Glutamate; Nonpharmacological; Neuroaesthetics; Chills

Substance Use Disorder

Conceptualized broadly, Substance Use Disorder (SUD) is an acquired disorder in which chronic exposure to a drug of abuse yields neuroadaptive changes that lead to the loss of control over use [2]. Substance use disorders often follow a relapsing and remitting course associated with pain and suffering for the patient, the patient's family, and the treatment team. The loss of control and this course are both a consequence of the neuroadaptive changes brought about by chronic drug use.

Drug craving, though difficult to define, generally refers to an intense desire to use drugs. This subjective sensation and drive state is often distressing for addicted individuals and contributes to loss of control over their drug use. Research has demonstrated that episodes of craving are a principal factor in relapse to drug seeking and taking behaviors [3,4]. The mechanisms of craving are heterogeneous, multifaceted, and not fully understood. While psychological and social components contribute prominently, we will focus our review on determinants of craving that correlate with biological changes in the brain after acute and then chronic drug use.

Converging evidence from animal and human studies provides a well-developed characterization of the addiction process including the brain mechanisms of acute drug intoxication, the neuroadaptive changes that occur with chronic administration, and the sequelae of these changes during subsequent abstinence. While there is growing evidence of the multiple mechanisms involved, the role of the brain mesolimbic reward system is the best characterized and most relevant to the focus of this paper. It consists of an interacting network of dopaminergic, GABA-ergic, and glutamatergic neuronal systems in the midbrain, basal ganglia, limbic system, and cerebral cortex.

Introduction

"At night, I would take two strips of Bensedrine and go out to a bar where I sat right by the jukebox. When you're sick [from opiate withdrawal], music is a great help. Once, in Texas, I kicked a habit on weed, a pint of paregoric and a few Louis Armstrong records" [1].

Addiction medicine is in desperate need of additional effective therapies. The purpose of this article is to propose the use of moving music, an example of individual aesthetic preference, as an intervention for drug craving. We will attempt to demonstrate that this proposal, while unconventional, is based on rational inference about the mechanisms of drug addiction and aesthetic experience. To do so we will first review the state of understanding of the mechanisms of drug addiction as it involves the brain mesolimbic reward system. This will be paralleled with an exploration of the brain anatomy, neurocircuitry, and neurochemistry involved in listening to aesthetically moving music. Via this parallel, an implication is made for the therapeutic use of music in addiction. The result of a comprehensive literature search is outlined to highlight the lack of existing clinical evidence for this idea. Hence, the theoretical intervention needs experimental confirmation. But, if confirmed, it could serve as the basis for the expanded search for other methods of non-pharmacological endogenous neurotransmitter modulation as interventions for addiction.

Activation of the system leads to excitation of midbrain ventral tegmental area (VTA) neurons with resultant release of dopamine in VTA projection fields including the nucleus accumbens (NAc) as well as amygdala, hippocampus, and medial prefrontal cortex (mPFC) [5]. Inhibitory feedback is largely GABA-ergic while glutamate innervation from the prefrontal cortex is the primary excitatory input [6].

In both rats and humans, the mesolimbic system is activated by naturalistic, evolutionarily adaptive reward stimuli such as food and sex [7-9]. That such a response system is conserved in animal and man alike is not surprising for this phylogenetically ancient brain circuitry and evolutionarily adaptive stimuli. But, in humans there is evidence that less directly adaptive stimuli such as love, money, beauty, and even music activate these same circuits, suggesting a more evolved role in detecting stimulus salience and in coding aesthetic preference [10-12].

The dopamine pathway of the mesolimbic system, especially the efferents from the VTA to the NAc, is also a final common pathway for the reinforcing effects of all drugs of abuse [13]. There are various molecular mechanisms by which drugs of abuse accomplish this [14], and sometimes profound differences in respective addiction syndromes. Beyond the differences in withdrawal symptoms, other behavioral disparities arise secondary to the respective neuroplastic changes. For example, in heroin addicts, conditioned drug cues can produce a drug-opposite or withdrawal-like response [15] while drug cues in cocaine addicts produce craving, limbic activation [16] and dopamine release. In the end however, all drugs of abuse lead to increases of extracellular dopamine in the NAc [13]. Most of them (such as ethanol, morphine, nicotine, and cannabinoids) ultimately do so by increasing spontaneous activity of the VTA dopamine neurons via their respective pharmacodynamic pathways [17-19].

Acutely, extracellular dopamine increases in the striatum caused by drugs of abuse are associated with subjective feelings of "high" or euphoria [20]. The euphoric effects of most drugs correlate with the magnitude of dopamine increase they induce in the striatum [21-23]. This sensation is associated only with temporally fast dopamine increases, not slow [24]. It is thought that the fast dopamine increase secondary to drug exposure likely mimics the phasic dopamine firing that normally signals stimulus saliency [25].

The functional attributes of dopamine neurotransmission in the NAc are various and debated. Some theorists cite evidence that the role of midbrain dopamine cell firing is primarily for learning and prediction feedback [26]. Others cite evidence for incentive salience as the primary role [27,28]. And, at least one study suggests that subtypes of dopamine neurons might correspond to each function respectively, thus supporting both theories [29].

What is more generally agreed upon is that drugs of abuse act on the dopamine reward system for durations and in intensities beyond endogenous norms, causing long term changes in dopaminergic neurons and the circuitry in which they are involved, contributing to pathological incentive motivation for drug use and a loss of control over use [30]. When drug exposure is chronic, homeostatic setpoints are altered [31]. That is, chronic drug use leads to maladaptive, long-lasting changes to the dopaminergic reward system in response to its supraphysiological activation.

For 30 years, theorists have postulated that neuroadaptive changes that occur during chronic drug use render a hypodopaminergic state in the absence of exogenous stimulation [32]. Subsequent human PET imaging studies have extensively documented the hypo dopaminergic

state in the striatum of detoxified drug users. There is reduced dopamine release after a drug stimulus in detoxified cocaine [33] and alcohol addicts [34], reduced D2 receptors in detoxified cocaine [35] and alcohol addicts [36], reduced dopamine and vesicular monoamine transporters in detoxified methamphetamine addicts [37], and decreased dopamine synthesis via DOPA decarboxylase in detoxified cocaine addicts [38]. For a thorough review of these human molecular imaging findings see Volkow et al. [39].

With these changes to mesostriatal dopamine systems come subjective and behavioral sequelae that are strongly linked with drug craving and return to use. Abstinence after chronic drug use is associated with a negative emotional state characterized by dysphoria, anxiety, and irritability that persists beyond withdrawal [2,40]. It is hypothesized that the dopamine-deficient state contributes to this phenomenon [32-34]. Return to drug use relieves the dysphoric state, a mechanism of negative reinforcement that serves as a powerful behavioral component of craving and relapse.

Paradoxically, in the hypodopaminergic state resulting from chronic drug use, continued use no longer brings the feeling of euphoria it did to the naïve user. Detoxified cocaine addicts reported less euphoria following psychostimulant dosing than did non-drug-using controls [33]. Yet, it is hypothesized that this hypodopaminergic state leads to increased incentive motivation for the abused drug, but decreased motivation for nondrug-related stimuli [41]. When cocaine and nicotine addicted subjects are exposed to conditioned drug cue stimuli, there was a robust increase in dopamine in the dorsal striatum compared to neutral cues, and this increase correlated with craving [42,43]. But, animals in amphetamine withdrawal showed decreased hedonic responses to a sweet-tasting stimulus [44]. It is postulated that in the addicted subject, for whom the dopamine response to a drug cue is more robust but the dopamine response from the actual drug is diminished, further drug use is promoted in spite of its diminished reward effect [45].

In the dopamine deficient state, administration of a dopaminergic agonist can cause craving, but in a rate-dependent fashion. If induced dopamine increase is slow, for example with oral administration of methylphenidate, drug craving is not induced. But, if intravenous methylphenidate is administered, with subsequent fast dopamine increase, intense craving is induced [46]. This could theoretically underlie prevalent binge type drug use behaviors where dopamine surges in compromised dopaminergic reward systems cause further craving, reinforcing drug use behaviors. But it also introduces the treatment-congruent possibility of a slow-acting dopaminergic mechanism that relieves the hypodopaminergic state without inducing further drug craving.

The prefrontal cortex, a source of glutamatergic efferents to the NAc, seems to play an important role in drug craving via local changes in neural activity as well as the efferent modulation of midbrain dopaminergic circuitry. Intravenous methylphenidate activates the orbital and medial prefrontal cortices, associated with salience attribution, motivation, and cocaine craving [47]. In abstinent smokers, orbitofrontal and cingulate cortex activity are triggered by conditioned smoking cues that predict reward and trigger craving [43]; these prefrontal areas also regulate striatal dopamine cell firing and release [48]. Hence drug use-associated and drug cue-associated dopamine increases are likely the result of prefrontal glutamatergic activation of striatal cells.

There is growing evidence that longitudinally the addiction process usurps the learning mechanism of the brain, and the phases of addiction parallel the stages of learning, with each stage having specific brain circuitry and neurotransmitter involvement [6]. Though a complete review is beyond the scope of this paper, a brief overview is warranted. As already noted, the acutely rewarding aspects of drugs are largely mediated by mesocorticolimbic dopamine. This same mechanism is integral to new learning, presumably by attributing salience to the event, and studies have demonstrated decreased learning when dopamine transmission is limited [6].

But as drug use continues and addiction progresses, neuroplastic changes occur that down-regulate the role of mesolimbic dopamine (discussed above) and shift the focus to facilitate execution of a behavioral response [49]. Glutamate transmission from the cortex into the striatum, including the NAc, is critical for executing learned behavior [50] and the integration of declarative memories [6].

With even more chronic use, drug-seeking behavior progresses from declarative to compulsive – from a verbal, conscious decision to a more habitual, automatic one [51]. Neurofunctionally this transition is thought to parallel a decreased importance of the glutamatergic projections from the cortex to the NAc and an increased importance of glutamatergic projections from the sensory cortical areas to the dorsal striatum, generator of motor patterns and procedural memories of unconscious behaviors [52].

In non-addicted learning, the prefrontal, executive circuitry can intrude on a behavior by regulating the value of a reward if the importance of the stimulus or context changes such that the behavior is no longer adaptive. But, in addiction, impairment of prefrontal function makes intercession of executive function on drug-seeking much more difficult [34,50].

While chronic drug users show less dopamine system reactivity to drug use than drug-naïve individuals, they demonstrate an enhanced sensitivity to conditioned drug cues [43]. This phenomenon has been attributed to the long term potentiation (LTP) of excitatory glutamatergic circuits, as a molecular mechanism of addiction learning and memory. It has been shown that even a single exposure to psychostimulants induces LTP of excitatory neurotransmission of dopamine neurons [53] and, in another study, LTP persisted after 3 months of abstinence in rats that self-administered cocaine [54]. There is evidence that this LTP elicited in addiction is mediated by brain-derived neurotrophic factor (BDNF) [55]. Chronic exposure to drugs of abuse correlates with both LTP of excitatory synapses (both glutamate- and AMPA-mediated) and reduced concentration of glutamate in the prefrontal cortex [6]. This combination results in a state of heightened reactivity to drug cue-induced glutamate release which may play a role in promoting drug seeking behaviors [56].

Given this understanding of the central role of altered dopamine neurotransmission, particularly within the mesolimbic dopamine system, in the acute and chronic effects of drugs of abuse, it would follow that modulation of this neurotransmitter system might be useful in the treatment of SUD. To this end there have been several studies of pharmacological dopaminergic modulation via agonists, antagonists, and partial agonists.

In hopes of blocking the dopaminergic reward related to alcohol ingestion, several studies have examined the effect of dopamine receptor antagonists on acute alcohol craving and consumption behaviors in active alcoholics. Pretreatment with haloperidol significantly reduced alcohol craving and the amount ingested [57],

and olanzapine pretreatment reduced the urge for and consumption of alcohol after conditioned alcohol use cues or following a priming dose, but did not affect the subjective feeling of euphoria [58].

The same rationale of blockade of dopamine-mediated drug reinforcement has also been studied in attempts to promote drug abstinence. Tiapride, an atypical D2 receptor antagonist, reduced alcohol consumption and improved abstinence in detoxed alcohol-dependent participants [59]. Quetiapine improved alcohol abstinence over a 2-7 month period in alcohol-dependent participants with comorbid affective disorder [60], as did clozapine at 6 months or longer with comorbid schizophrenia [61]. Aripiprazole, a dopamine receptor partial agonist, was shown to attenuate the ventral striatal response to alcohol cues [62], but had mixed results in a pair of clinical studies of the promotion of abstinence from alcohol [63,64]. These collective findings provide empirical support for the possible therapeutic use of dopamine system modulation in preventing relapse in drug-dependent individuals.

With the demonstration of brain dopaminergic deficit associated with chronic drug abuse, it would follow that dopamine agonism might be effective therapy [65]. Early preliminary studies found promising results with bromocriptine, a dopamine receptor agonist, in the ability to significantly reduce drug craving in detoxed cocaine addicts [66] and alcoholics [67]. But, a confirmatory study with a long-acting formulation of bromocriptine found no difference in relapse rates between treatment and placebo groups, though it did not collect information on craving [68]. A Cochrane review published in 2010 assessed the data from 23 studies on seven different dopamine agonists for the treatment of cocaine addiction concluded that while one of the agents, amantadine, did show some promise, none of the agonists had clear statistically significant advantage over placebo [69]. A limiting aspect of all dopamine agonist and antagonist therapies discussed were the side effects secondary to systemic administration. Also, such medication approaches lack selectivity for those dopamine systems affected by the addiction process as well as state-dependency.

To the extent that addiction is related to a brain hypodopaminergic state secondary to chronic, intermittent drug use, disproportionately affecting the mesolimbic system, a compelling argument could be made for interventions that activate this system as a form of agonist substitution therapy. This would include the very successful opioid agonist therapies [70] and nicotine replacement therapies [71] among such dopamine-targeted approaches. The following makes the case for aesthetically-preferred stimuli as a form of individualized reinforcer substitution that acts by activating mesolimbic dopamine neurotransmission to reduce relapse in drug-addicted persons.

Music as an Aesthetic Preference

As mentioned above, the mesolimbic dopamine system is activated by naturalistic, adaptive stimuli such as food and sex [8,9], and in humans more abstract stimuli such as love [10], money [11], and, as we will see, beauty. Pleasing or moving aesthetic stimuli such as music, which serve even less directly adaptive function, nonetheless engender strong subjective hedonic experience suggestive of increased incentive salience and approach behavior.

To aid in discussion of this topic, it would first be helpful to outline some general concepts related to the phenomenon of aesthetic experience, of which moving music is but one example. Borrowing from Kant, one can derive a working definition of an aesthetic experience as an emotionally impactful experience induced by external

sensory stimulation that is not predicated on an evolutionarily adaptive gain [72]. Leder proposed a psychological model of aesthetic experience where the art stimulus, preclassified by context and the affective state of the viewer, is processed both automatically via formal elements and deliberately via cognitive aspects, and the output of this processing is two-part: an aesthetic judgment of the piece and an aesthetic emotion [73].

Neuroimaging studies have largely substantiated this model while delineating the neural processing correlates of human aesthetic experience. Aesthetic preference processing involves the cerebral cortex, especially prefrontal cortex [74-76]. Imaging studies have repeatedly shown orbitofrontal cortex activation during aesthetic preference formation tasks for both visual and musical stimuli [75,77]. Preference choice and perception of pleasantness are formed, revised, and represented in the medial orbitofrontal cortex (mOFC) an area of neural integration for diverse sensory stimuli [78]. It is theorized that the human brain's phylogenetically expanded prefrontal cortex and cortical projections to the mesolimbic dopamine system allow for such abstract conceptualizations to be rewarding.

The emotional impact of the aesthetic experience correlates with activation of the limbic structures and cingulate gyrus when experiencing highly pleasing aesthetic stimuli. Further, there is a strong correlation between the intensity of musical pleasure and sympathetic arousal while listening [79]. But, perhaps even more striking is the revelation that aesthetic stimuli can activate the mesolimbic reward circuits of the brain, first demonstrated as ventral striatal activation while listening to highly pleasurable music [12].

Music is the most studied of all aesthetic stimuli, and there is good reason for it. Every known culture, current or historical, has music [80]. It seems that as long as there has been man, there has been music – a claim supported by the discovery of a vulture bone flute crafted along the Danube 42,000 years ago [81]. Appreciation of its therapeutic potential is also ancient. The oldest extant medical text, the *Kahun Papyrus* of Egypt dating from 1825 BCE, makes reference to the use of song in healing [82]. Some cite Pythagoras, 6th century BCE, as the father of “musical medicine” for his belief that specific tones and harmonies had healing powers [83]. Western philosophers from Aristotle to Nietzsche have examined man's experience of music and its impact on health [84]. Plato, for instance, observed that some rhythms and harmonies induced in man idleness and relaxation while others engendered courage and violence [85]. During the last century, the healing uses of music became formalized as Music Therapy.

Modern brain imaging techniques have elucidated the functional neuroanatomy of the musical experience. Many studies have focused on how music is processed acoustically and cognitively [86]. Others have attempted to understand how music, the most abstract art form, is able to modulate emotion and create such pleasing experiences [87].

Integral to these explorations has been the phenomenon familiar to most music listeners called a “frisson” or “chill”: the sensation of goose bumps or hairs rising on the neck when listening to a particularly moving piece of music. This feeling, pleasant while listening to music but unpleasant in fearful situations, is more generally an indicator of profound autonomic nervous system activation [12] and correlates with psychophysiological findings. There are roughly linear correlations between progressive pleasure level as reported by participants and their respective skin conductance, blood volume pulse, heart rate, temperature, and respiratory rate while listening [79]. The chills reaction is not universal; one study found that between

10-38% of participants had not experienced any chills reaction in the previous five years [88]. But, it lends itself to study because it is an objective physical sign of a subjective personal experience.

The chills reaction most strongly correlates with perceived pleasantness of the music piece [89]. Certain musical and acoustical characteristics are most strongly correlated to chills, chief among them the entry of a new instrument or voice, a change in volume, a contrast in voice, or a new harmony [89]. Different listeners might react to different parts of a piece, but the same person tends to react to the same sections on repeated exposures. While there is no evidence for the extinction of the phenomenon in general, there is evidence of reduced chills response upon repeated exposures to the same music stimulus [89]. Personality and personal experience strongly correlates with chills – most strongly correlated with non-sensation-seeking and non-thrill-seeking on the SSS-V [89], openness to experience on Five-Factor personality analysis, self-reports of importance of music, time spent listening to music, and ability to play an instrument [90].

A watershed study used PET imaging to measure cerebral blood flow of musicians listening to musical pieces that consistently produced chills upon listening. This study confirmed that listening to these highly pleasurable pieces was associated with activation of the ventral striatum, amygdala, orbitofrontal cortex, and ventromedial prefrontal cortex, for the first time definitively linking the experience of highly pleasurable music to the same reward circuits of the brain activated by food, sex, and drugs of abuse [12]. Subsequent studies also confirmed this response to unfamiliar but highly pleasurable music [91]. With the increased spatial and temporal resolution of fMRI, further studies confirmed not only specific activation of NAc, VTA, hypothalamus, and insula, but also used effective connectivity analysis to infer strong causal correlation between NAc and VTA activation, highly suggestive of activation of the mesolimbic dopamine system in response to aesthetically pleasing music [92]. The effect seems to be dose-dependent in that the more pleasurable the music, the more striatal activation was observed [93]. A PET study using a radiolabelled D2 receptor antagonist ([11C] raclopride) that indirectly maps brain regional dopamine release via radioligand binding competition found that indeed dopamine is released in the ventral striatum during peak emotional arousal associated with the aesthetic experience of music [93]. Hence, through neuroanatomic inference, and then direct confirmation by *in vivo* molecular neuroimaging, it is shown that the experience of highly pleasurable music directly modulates the mesolimbic dopamine reward system.

Clinical Evidence Supporting Music-based Therapies

Clinical studies have demonstrated the efficacy of music interventions in ameliorating pain [94] and stress [95]. Mental health disorders such as dementia, depression, psychosis, and autism have also shown positive response to music interventions [96-99]. Given the strong parallels between the brain mechanisms of SUD and aesthetic musical experience, one wonders what interaction the two would have on each other. A literature review was undertaken to collect the extant clinical data.

The online databases MEDLINE and PsychINFO were searched from 1967 to September 1, 2014 for the terms “music” or “music therapy” and all the expanded subheadings of “substance-related disorders” in the title, subject headings, or abstracts. This query was limited to those written in English and involving human subjects. Of the results, only four involved listening to music and measured an

outcome related to substance use treatment. To augment these results, the bibliographies of these articles were reviewed for relevant studies, finding five additional articles. Of these nine studies, six assessed the efficacy of music as an augmenting agent for existing behavioral therapy modalities for substance use disorder, measured through change in the client's enjoyment and perceived efficacy [100], attendance of group sessions [101], participation in group therapy [102], motivation in program [103], facilitation of emotional expression during therapy [104], and reported readiness to change [105]. Two studies examined the effect of music on secondary psychiatric signs and symptoms such as depression, anxiety, and relationship problems [106] and depression, stress, anxiety, and anger [107] in the SUD population. Strikingly, all eight of these studies found that music yielded a positive effect on the studied outcome.

Two studies considered music and drug craving. The first used music to induce a negative emotion in participants, finding that it exacerbated craving for nicotine among those in early abstinence, most profoundly so in women [108]. The second used drug-associated rock music paired with a film documentary discussing the band members' successful recoveries from their addiction. This intervention was found to have a significant positive impact on readiness to change (as noted above) but no statistically significant effect on drug craving [105]. To date, no clinical study found in this literature search has directly examined the effect of listening to personally-selected moving music on the frequency or intensity of experiences of drug craving associated with addiction.

Discussion

The goal of this review and synthesis was to make the theoretical case for the use of aesthetic experience as an intervention for drug craving in drug-addicted individuals based on our understanding of their shared brain functional and molecular mechanisms. The discussion of these mechanisms was largely limited to their common features to help make a focused argument, and was not an exhaustive review. As confirmed via literature review, the proposal is theoretical at this point with minimal to no empirical support of clinical efficacy. Also, there are several points of discussion that may serve as theoretical challenges to such an intervention.

First, and perhaps most daunting, is that craving is a complicated and heterogeneous phenomenon with at least three different etiologies (drug-induced, cue-induced, stress-induced) each with their respective neurofunctional correlates [2]. Though it is unknown how an aesthetic experience affects each of these types of induced craving, it is hypothesized that it would work best for drug-induced craving as it is the most directly dopamine-dependent [2]. Conversely, there is a danger that aesthetic experiences such as music might worsen cue-induced craving as music itself is sometimes a central component of conditioned associations to patterns of drug use, either in content or mnemonic association. Alternatively, it is conceivable that music's ability to modulate stress (i.e. relax) could soothe stress-induced craving. But, listening to emotionally moving versus merely relaxing music is a subjectively different phenomenon with opposite physiological responses [79].

Another theoretical hurdle to efficacy is the negative effect chronic use and the subsequent hypodopaminergic state has on reinforcer saliency and hedonic responding. Drug addicts are highly motivated to seek their drug of abuse – the drug has high incentive saliency – but can be otherwise apathetic to non-drug rewards or activities [45].

Prefrontal activation in response to a sexual stimulus was significantly impaired in cocaine addicts compared to controls [109]. These effects of addiction on drug and non-drug reinforcers could potentially limit the efficacy of a non-drug stimulus such as music.

There are also a number of concrete practical obstacles facing a clinical trial evaluation of this proposed intervention. First and foremost would be inducing and then confirming an aesthetic musical experience has occurred. Though music is culturally universal, not everyone enjoys or is moved by it. And, as noted above, a significant percentage of people do not experience chills reactions to music [88]. An ecologically valid study cohort would need to be selected independent of music enjoyment factors, though information about participant's musical experience, preference, and historical chills responses would be crucial for control comparison. Since the rewarding effect of music is causally linked with the listener's pleasure, and not to any abstract quality of the music itself, emphasis must necessarily be placed on maximizing the pleasurable of the samples. Given the extreme subjectivity of personal preference, participant-selected music, known to be pleasurable to the participant and ideally having induced chills in the past, is imperative to maximize the likelihood of being personally moving and eliciting the desired phenomenon. This unfortunately introduces variability of music tempo, emotional valence, etc., that might have influence on the outcome of the study, but seems a necessary concession in order to maximize participant pleasure.

Confirming pleasurable and that a chills response has occurred is another practical hurdle. Participant report of a subjective phenomenon is problematic in that it lacks an absolute scale, is difficult to verify, and is difficult to confirm inter- and intra-reporter reliability. Functional neuroimaging of all study participants is logistically unwieldy. Luckily, existing studies have already established that the subjective sensation of chills in the setting of music listening correlates with activation of the mesolimbic dopamine system [92] and that patient report could serve as a reliable confirmation of an aesthetic musical experience. Further, there seems to be a dose-dependent aspect to this effect in as much as the higher the reported level of pleasure (reported as intensity of chill), the more change in dopamine binding in the NAc [93]. Alternatively, as noted above, there are reliable psychophysiological markers of emotional arousal during pleasurable music listening, and such physiological metrics – skin conductance, blood volume pulse, heart rate, temperature, and respiratory rate – could be used to confirm patient report of pleasure [79].

Given the proposed mechanism of this intervention – endogenous dopamine modulation to relieve a hypodopaminergic state – in order to control for the dopaminergic effects of music, one would want to minimize the influence of other dopaminergic agents, both pharmacological and illicit. It is unclear at this point what role aesthetic interventions might play in addiction treatment. If the intervention is proven effective clinically, then aesthetically moving music might be added to the gamut of treatments used against the complex disease of addiction, alongside pharmacological, therapy-based, and peer support interventions. It is not known how music interacts with these other options, with the exception of opioid antagonists. An early study reported that naloxone, an opioid antagonist, blocked chill induction from music [110]. It is not yet known how naltrexone, an oral opioid antagonist frequently used to help with cravings in alcohol use disorder, would interact with the aesthetic musical experience.

Addiction involves long-term neuroplastic changes to the brain and the current mechanistic understanding of the aesthetic experience does not yield clear hypotheses on what effect music might have on these long-term changes. But, if a music intervention can ameliorate craving in the short term, prolonging abstinence, it might contribute to longer-lasting recovery. Given the attenuated nature of addiction recovery, it would be important to monitor for long-term usage and effect in naturalistic settings.

A prominent omission from the current discussion is what effect genetic variation has on the mechanisms of both addiction and aesthetic experience. There is ongoing work in this area, with several prominent hypotheses mostly focused on variations in genes encoding opioid and dopamine receptors. But, there is not yet a clear, uniting model and a great deal of work is needed before we have a clear understanding of these relationships.

Still unresolved is how the disparate phenomena aesthetic experience and drugs of abuse, as reinforcers, are mechanistically connected at the neural network level. Broadly, the mechanisms of addiction start with dopaminergic activation of the ventral striatum with subsequent downstream effects. Evidence suggests a distinct pathway for the aesthetic experience, starting in the prefrontal areas where sensory integration, salience attribution, and preference representation turn a very abstract stimulus into a rewarding experience. A hypothetical mechanism connects these two: prefrontal activation from a preferred aesthetic stimulus causes VTA excitation via glutamate efferents, leading to dopamine release on the NAc and subsequent attribution of reward. This model requires further clarification.

As mentioned above, an interesting early study demonstrated that naloxone, an opioid receptor antagonist, seemed to block the induction of chills from music [110]. This study was not without its flaws, most notably a very small N of 3, but does support a role for endogenous opioids in aesthetic experiences. It has been demonstrated that opioids in the NAc, not dopamine, are most essential to the evolutionarily ancient hedonic response to sweet stimuli common to both rats and humans [111]. Moreover, music has been demonstrated to relieve pain in cancer patients and postoperative surgical patients [112,113]. However, the role of opioid mechanisms in the experience of music remains unknown.

Conclusion

In summary, we have reviewed the role of dopamine mechanisms in drug reinforcement, the subsequent hypodopaminergic state that comes from chronic drug use, and the experiential and behavioral sequelae of this state that contribute to discomfort, craving, and relapse during abstinence. A review of the dopaminergic pharmacological interventions for SUDs indicated promising but mixed support, owing in no small part to side effects and the non-selective influence of systemic, exogenous drug administration. A review of the neuroscience of the aesthetic experience of music revealed strong and conserved frontal cortex and ventral striatum activation and specific PET support of music-induced dopamine release in the NAc. However, a further literature review found no existing clinical evidence directly evaluating the effect of music on SUD generally or craving specifically.

While our understanding of the neuromechanics of addiction has grown in leaps and bounds, our available treatment approaches are wanting. New therapeutic interventions have focused on

pharmacotherapies, the efficacies of which are partial at best. It might be that pharmacotherapies administered systemically act too broadly and non-specifically. By rationally modulating the specific neurotransmitter systems involved in addiction, it might be that we can improve the efficacy of our therapies. Moving music is only one example of using external stimuli or interventions to modulate endogenous neurotransmission targeted by addiction. One could imagine a similar mechanism behind exercise, behavioral activation, cognitive therapies, mindfulness and meditation to name a few. Further, if this intervention were found useful, it would suggest potential use for other dopamine-driven addiction pathologies such as overeating, gaming addiction, and gambling addiction [114].

Acknowledgement

Thanks to Dr. Kilts who helped in his review of the paper.

References

1. Burroughs WS (1953) *Junky*. Grove Press, New York City, NY.
2. Koob GF, Volkow ND (2010) Neurocircuitry of addiction. *Neuropsychopharmacology* 35: 217-238.
3. Heather N, Stallard A, Tebbutt J (1991) Importance of substance cues in relapse among heroin users: comparison of two methods of investigation. *Addict Behav* 16: 41-49.
4. Schneekloth TD, Biernacka JM, Hall-Flavin DK, Karpyak VM, Frye MA, et al. (2012) Alcohol craving as a predictor of relapse. *Am J Addict* 21 Suppl 1: S20-26.
5. Wise RA (2002) Brain reward circuitry: insights from unsensed incentives. *Neuron* 36: 229-240.
6. Kalivas PW, O'Brien C (2008) Drug addiction as a pathology of staged neuroplasticity. *Neuropsychopharmacology* 33: 166-180.
7. Di Chiara G, Imperato A (1988) Drugs abused by humans preferentially increase synaptic dopamine concentrations in the mesolimbic system of freely moving rats. *Proc Natl Acad Sci U S A* 85: 5274-5278.
8. Small DM, Jones-Gotman M, Dagher A (2003) Feeding-induced dopamine release in dorsal striatum correlates with meal pleasantness ratings in healthy human volunteers. *Neuroimage* 19: 1709-1715.
9. Komisaruk BR, Whipple B (2005) Functional MRI of the brain during orgasm in women. *Annu Rev Sex Res* 16: 62-86.
10. Aron A, Fisher H, Mashek DJ, Strong G, Li H, et al. (2005) Reward, motivation, and emotion systems associated with early-stage intense romantic love. *J Neurophysiol* 94: 327-337.
11. Knutson B, Fong GW, Adams CM, Varner JL, Hommer D (2001) Dissociation of reward anticipation and outcome with event-related fMRI. *Neuroreport* 12: 3683-3687.
12. Blood AJ, Zatorre RJ (2001) Intensely pleasurable responses to music correlate with activity in brain regions implicated in reward and emotion. *Proc Natl Acad Sci U S A* 98: 11818-11823.
13. Koob GF (1992) Neural mechanisms of drug reinforcement. *Ann N Y Acad Sci* 654: 171-191.
14. Nestler EJ (2005) Is there a common molecular pathway for addiction? *Nat Neurosci* 8: 1445-1449.
15. O'Brien CP, Testa T, O'Brien TJ, Brady JP, Wells B (1977) Conditioned narcotic withdrawal in humans. *Science* 195: 1000-1002.
16. Childress AR, Mozley PD, McElgin W, Fitzgerald J, Reivich M, et al. (1999) Limbic activation during cue-induced cocaine craving. *Am J Psychiatry* 156: 11-18.
17. Gessa GL, Muntoni F, Collu M, Vargiu L, Mereu G (1985) Low doses of ethanol activate dopaminergic neurons in the ventral tegmental area. *Brain Res* 348: 201-203.
18. Grenhoff J, Aston-Jones G, Svensson TH (1986) Nicotinic effects on the firing pattern of midbrain dopamine neurons. *Acta Physiol Scand* 128: 351-358.

19. Melis M, Gessa GL, Diana M (2000) Different mechanisms for dopaminergic excitation induced by opiates and cannabinoids in the rat midbrain. *Prog Neuropsychopharmacol Biol Psychiatry* 24: 993-1006.
20. Volkow ND, Wang GJ, Fowler JS, Gatley SJ, Ding YS, et al. (1996) Relationship between psychostimulant-induced "high" and dopamine transporter occupancy. *Proc Natl Acad Sci U S A* 93: 10388-10392.
21. Drevets WC, Gautier C, Price JC, Kupfer DJ, Kinahan PE, et al. (2001) Amphetamine-induced dopamine release in human ventral striatum correlates with euphoria. *Biol Psychiatry* 49: 81-96.
22. Sharma A, Brody AL (2009) In vivo brain imaging of human exposure to nicotine and tobacco. *Handb Exp Pharmacol*: 145-171.
23. Volkow ND, Wang GJ, Fischman MW, Foltin RW, Fowler JS, et al. (1997) Relationship between subjective effects of cocaine and dopamine transporter occupancy. *Nature* 386: 827-830.
24. Grace AA (2000) The tonic/phasic model of dopamine system regulation and its implications for understanding alcohol and psychostimulant craving. *Addiction* 95 Suppl 2: S119-128.
25. Volkow ND, Fowler JS, Wang GJ, Swanson JM (2004) Dopamine in drug abuse and addiction: results from imaging studies and treatment implications. *Mol Psychiatry* 9: 557-569.
26. Schultz W (2010) Dopamine signals for reward value and risk: basic and recent data. *Behav Brain Funct* 6: 24.
27. Zink CF, Pagnoni G, Chappelow J, Martin-Skurski M, Berns GS (2006) Human striatal activation reflects degree of stimulus saliency. *Neuroimage* 29: 977-983.
28. Berridge KC (2007) The debate over dopamine's role in reward: the case for incentive salience. *Psychopharmacology (Berl)* 191: 391-431.
29. Matsumoto M, Hikosaka O (2009) Two types of dopamine neuron distinctly convey positive and negative motivational signals. *Nature* 459: 837-841.
30. Wolf ME (2002) Addiction: making the connection between behavioral changes and neuronal plasticity in specific pathways. *Mol Interv* 2: 146-157.
31. Haass-Koffler CL, Leggio L, Kenna GA (2014) Pharmacological approaches to reducing craving in patients with alcohol use disorders. *CNS Drugs* 28: 343-360.
32. Dackis CA, Gold MS (1985) New concepts in cocaine addiction: the dopamine depletion hypothesis. *Neurosci Biobehav Rev* 9: 469-477.
33. Volkow ND, Wang GJ, Fowler JS, Logan J, Gatley SJ, et al. (1997) Decreased striatal dopaminergic responsiveness in detoxified cocaine-dependent subjects. *Nature* 386: 830-833.
34. Volkow ND, Wang GJ, Telang F, Fowler JS, Logan J, et al. (2007) Profound decreases in dopamine release in striatum in detoxified alcoholics: possible orbitofrontal involvement. *J Neurosci* 27: 12700-12706.
35. Volkow ND, Wang GJ, Fowler JS, Logan J, Hitzemann R, et al. (1996) Cocaine uptake is decreased in the brain of detoxified cocaine abusers. *Neuropsychopharmacology* 14: 159-168.
36. Volkow ND, Wang GJ, Maynard L, Fowler JS, Jayne B, et al. (2002) Effects of alcohol detoxification on dopamine D2 receptors in alcoholics: a preliminary study. *Psychiatry Res* 116: 163-172.
37. Chang L, Alicata D, Ernst T, Volkow N (2007) Structural and metabolic brain changes in the striatum associated with methamphetamine abuse. *Addiction* 102 Suppl 1: 16-32.
38. Wu JC, Bell K, Najafi A, Widmark C, Keator D, et al. (1997) Decreasing striatal 6-FDOPA uptake with increasing duration of cocaine withdrawal. *Neuropsychopharmacology* 17: 402-409.
39. Volkow ND, Fowler JS, Wang GJ, Baler R, Telang F (2009) Imaging dopamine's role in drug abuse and addiction. *Neuropharmacology* 56 Suppl 1: 3-8.
40. Koob GF, Le Moal M (1997) Drug abuse: hedonic homeostatic dysregulation. *Science* 278: 52-58.
41. Melis M, Spiga S, Diana M (2005) The dopamine hypothesis of drug addiction: hypodopaminergic state. *Int Rev Neurobiol* 63: 101-154.
42. Volkow ND, Wang GJ, Telang F, Fowler JS, Logan J, et al. (2006) Cocaine cues and dopamine in dorsal striatum: mechanism of craving in cocaine addiction. *J Neurosci* 26: 6583-6588.
43. McClernon FJ, Kozink RV, Lutz AM, Rose JE (2009) 24-h smoking abstinence potentiates fMRI-BOLD activation to smoking cues in cerebral cortex and dorsal striatum. *Psychopharmacology (Berl)* 204: 25-35.
44. Orsini C, Koob GF, Pulvirenti L (2001) Dopamine partial agonist reverses amphetamine withdrawal in rats. *Neuropsychopharmacology* 25: 789-792.
45. Volkow ND, Wang GJ, Fowler JS, Tomasi D, Telang F (2011) Addiction: beyond dopamine reward circuitry. *Proc Natl Acad Sci U S A* 108: 15037-15042.
46. Volkow ND, Wang GJ, Telang F, Fowler JS, Logan J, et al. (2008) Dopamine increases in striatum do not elicit craving in cocaine abusers unless they are coupled with cocaine cues. *Neuroimage* 39: 1266-7.
47. Volkow ND, Wang GJ, Ma Y, Fowler JS, Wong C, et al. (2005) Activation of orbital and medial prefrontal cortex by methylphenidate in cocaine-addicted subjects but not in controls: relevance to addiction. *J Neurosci* 25: 3932-3939.
48. Volkow ND, Wang GJ, Fowler JS, Hitzemann R, Angrist B, et al. (1999) Association of methylphenidate-induced craving with changes in right striato-orbitofrontal metabolism in cocaine abusers: implications in addiction. *Am J Psychiatry* 156: 19-26.
49. Schultz W (2004) Neural coding of basic reward terms of animal learning theory, game theory, microeconomics and behavioural ecology. *Curr Opin Neurobiol* 14: 139-147.
50. Kalivas PW, Volkow ND (2005) The neural basis of addiction: a pathology of motivation and choice. *Am J Psychiatry* 162: 1403-1413.
51. Barnes TD, Kubota Y, Hu D, Jin DZ, Graybiel AM (2005) Activity of striatal neurons reflects dynamic encoding and recoding of procedural memories. *Nature* 437: 1158-1161.
52. Everitt BJ, Robbins TW (2005) Neural systems of reinforcement for drug addiction: from actions to habits to compulsion. *Nat Neurosci* 8: 1481-1489.
53. Ungless MA, Whistler JL, Malenka RC, Bonci A (2001) Single cocaine exposure in vivo induces long-term potentiation in dopamine neurons. *Nature* 411: 583-587.
54. Chen BT, Bowers MS, Martin M, Hopf FW, Guillory AM, et al. (2008) Cocaine but not natural reward self-administration nor passive cocaine infusion produces persistent LTP in the VTA. *Neuron* 59: 288-297.
55. Pu L, Liu QS, Poo MM (2006) BDNF-dependent synaptic sensitization in midbrain dopamine neurons after cocaine withdrawal. *Nat Neurosci* 9: 605-607.
56. Sutton MA, Schmidt EF, Choi KH, Schadt CA, Whisler K, et al. (2003) Extinction-induced upregulation in AMPA receptors reduces cocaine-seeking behaviour. *Nature* 421: 70-75.
57. Modell JG, Mountz JM, Glaser FB, Lee JY (1993) Effect of haloperidol on measures of craving and impaired control in alcoholic subjects. *Alcohol Clin Exp Res* 17: 234-240.
58. Hutchison KE, Swift R, Rohsenow DJ, Monti PM, Davidson D, et al. (2001) Olanzapine reduces urge to drink after drinking cues and a priming dose of alcohol. *Psychopharmacology (Berl)* 155: 27-34.
59. Shaw GK, Waller S, Majumdar SK, Alberts JL, Latham CJ, et al. (1994) Tiapride in the prevention of relapse in recently detoxified alcoholics. *Br J Psychiatry* 165: 515-523.
60. Croissant B, Klein O, Gehrlein L, Kniest A, Hermann D, et al. (2006) Quetiapine in relapse prevention in alcoholics suffering from craving and affective symptoms: a case series. *Eur Psychiatry* 21: 570-573.
61. Drake RE, Xie H, McHugo GJ, Green AI (2000) The effects of clozapine on alcohol and drug use disorders among patients with schizophrenia. *Schizophr Bull* 26: 441-449.
62. Myrick H, Li X, Randall PK, Henderson S, Voronin K, et al. (2010) The effect of aripiprazole on cue-induced brain activation and drinking parameters in alcoholics. *J Clin Psychopharmacol* 30: 365-372.

63. Anton RF, Kranzler H, Breder C, Marcus RN, Carson WH, et al. (2008) A randomized, multicenter, double-blind, placebo-controlled study of the efficacy and safety of aripiprazole for the treatment of alcohol dependence. *J Clin Psychopharmacol* 28: 5-12.
64. Martinotti G, Di Nicola M, Janiri L (2007) Efficacy and safety of aripiprazole in alcohol dependence. *Am J Drug Alcohol Abuse* 33: 393-401.
65. Kosten TR, George TP, Kosten TA (2002) The potential of dopamine agonists in drug addiction. *Expert Opin Investig Drugs* 11: 491-499.
66. Dackis CA, Gold MS, Sweeney DR, Byron JP Jr, Climko R (1987) Single-dose bromocriptine reverses cocaine craving. *Psychiatry Res* 20: 261-264.
67. Lawford BR, Young RM, Rowell JA, Qualichefski J, Fletcher BH, et al. (1995) Bromocriptine in the treatment of alcoholics with the D2 dopamine receptor A1 allele. *Nat Med* 1: 337-341.
68. Naranjo CA, Dongier M, Bremner KE (1997) Long-acting injectable bromocriptine does not reduce relapse in alcoholics. *Addiction* 92: 969-978.
69. Amato L, Minozzi S, Pani PP, Solimini R, Vecchi S, et al. (2011) Dopamine agonists for the treatment of cocaine dependence. *Cochrane Database Syst Rev* : CD003352.
70. Donny EC, Brasser SM, Bigelow GE, Stitzer ML, Walsh SL (2005) Methadone doses of 100 mg or greater are more effective than lower doses at suppressing heroin self-administration in opioid-dependent volunteers. *Addiction* 100: 1496-1509.
71. Silagy C, Lancaster T, Stead L, Mant D, Fowler G (2004) Nicotine replacement therapy for smoking cessation. *Cochrane Database Syst Rev* : CD000146.
72. Kant I (1914) *Kants Critique of Judgement*, translated with Introduction and Notes by J.H. Bernard (2nd edn) Macmillan Publishers, London.
73. Leder H, Belke B, Oeberst A, Augustin D (2004) A model of aesthetic appreciation and aesthetic judgments. *Br J Psychol* 95: 489-508.
74. Vartanian O, Goel V (2004) Neuroanatomical correlates of aesthetic preference for paintings. *Neuroreport* 15: 893-897.
75. Ishizu T, Zeki S (2011) Toward a brain-based theory of beauty. *PLoS One* 6: e21852.
76. Cela-Conde CJ, Marty G, Maestú F, Ortiz T, Munar E, et al. (2004) Activation of the prefrontal cortex in the human visual aesthetic perception. *Proc Natl Acad Sci U S A* 101: 6321-6325.
77. Brown S, Gao X, Tisdelle L, Eickhoff SB, Liotti M (2011) Naturalizing aesthetics: brain areas for aesthetic appraisal across sensory modalities. *Neuroimage* 58: 250-258.
78. Kringsbach ML (2005) The human orbitofrontal cortex: linking reward to hedonic experience. *Nat Rev Neurosci* 6: 691-702.
79. Salimpoor VN, Benovoy M, Longo G, Cooperstock JR, Zatorre RJ (2009) The rewarding aspects of music listening are related to degree of emotional arousal. *PLoS One* 4: e7487.
80. Huron D (2001) Is music an evolutionary adaptation? *Ann N Y Acad Sci* 930: 43-61.
81. Wilford, JN (2012) Flute's revised age dates the sound of music earlier. *The New York Times*.
82. Nunn, JF (2002) *Ancient Egyptian Medicine*. University of Oklahoma Press, Norman, OK.
83. Iamblichus (1818) *Life of Pythagoras* (T. Taylor, Trans.). J M Watkins, London.
84. Wigram T, Pedersen IN, Bonde LO (2002) *A Comprehensive Guide to Music Therapy: Theory, Clinical Practice, Research and Training*. Jessica Kingsley Publishers, London and Philadelphia.
85. Plato (1997). *Plato complete works* (G.M.A Grube, Trans.). Hackett Publishing Company, Cambridge, UK.
86. Zatorre, R.J., Peretz, I. (Eds.) (2001) *The Biological Foundations of Music*, vol. 930. *Annals of the New York Academy of Sciences*, New York.
87. Zatorre RJ, Salimpoor VN (2013) From perception to pleasure: music and its neural substrates. *Proc Natl Acad Sci U S A* 110 Suppl 2: 10430-10437.
88. Sloboda JA (1991) Music structure and emotional response: some empirical findings. *Psychology of Music* 19: 110-120.
89. Grewe O, Nagel F, Kopiez R, Altenmuller E (2007) Listening to music as a re-creative process: physiological, psychological, and psychoacoustical correlates of chills and strong emotions. *Music Perception* 24: 297-314.
90. Nusbaum EC, Silva PJ (2010) Shivers and timbres: personality and the experience of chills from music. *Social Psychological and Personality Science* 2: 199-204.
91. Brown S, Martinez MJ, Parsons LM (2004) Passive music listening spontaneously engages limbic and paralimbic systems. *Neuroreport* 15: 2033-2037.
92. Menon V, Levitin DJ (2005) The rewards of music listening: response and physiological connectivity of the mesolimbic system. *Neuroimage* 28: 175-184.
93. Salimpoor VN, Benovoy M, Larcher K, Dagher A, Zatorre RJ (2011) Anatomically distinct dopamine release during anticipation and experience of peak emotion to music. *Nat Neurosci* 14: 257-262.
94. Richards T, Johnson J, Sparks A, Emerson H (2007) The effect of music therapy on patients' perception and manifestation of pain, anxiety, and patient satisfaction. *Medsurg Nurs* 16: 7-14.
95. Evans D (2002) The effectiveness of music as an intervention for hospital patients: a systematic review. *J Adv Nurs* 37: 8-18.
96. Sung HC, Chang AM (2005) Use of preferred music to decrease agitated behaviours in older people with dementia: a review of the literature. *J Clin Nurs* 14: 1133-1140.
97. Hsu WC, Lai HL (2004) Effects of music on major depression in psychiatric inpatients. *Arch Psychiatr Nurs* 18: 193-199.
98. Hayashi N, Tanabe Y, Nakagawa S, Noguchi M, Iwata C, et al. (2002) Effects of group musical therapy on inpatients with chronic psychoses: a controlled study. *Psychiatry Clin Neurosci* 56: 187-193.
99. Gold C, Wigram T, Elefant C (2006) Music therapy for autistic spectrum disorder. *Cochrane Database Syst Rev* : CD004381.
100. Silverman MJ (2003) Music therapy and clients who are chemically dependent: a review of literature and pilot study. *The Arts in Psychotherapy* 30: 273-281.
101. Dougherty KM (1984) Music therapy in the treatment of the alcoholic client. *Music Therapy* 4: 47-54.
102. Gallagher LM, Steele AL (2002) Music therapy with offenders in a substance abuse/mental illness treatment program. *Music Ther Perspect* 20: 117-122.
103. Ross S, Cidambi I, Dermatis H, Weinstein J, Ziedonis D, et al. (2008) Music therapy: a novel motivational approach for dually diagnosed patients. *J Addict Dis* 27: 41-53.
104. Baker FA, Gleadhill LM, Dingle GA (2007) Music therapy and emotional exploration: exposing substance abuse clients to the experiences of non-drug-induced emotions. *The Arts in Psychotherapy* 34: 321-330.
105. Silverman MJ (2011) Effects of music therapy on change readiness and craving in patients on a detoxification unit. *J Music Ther* 48: 509-531.
106. Gallant WA, Gallant MD, Gorey KM, Holosko MJ, Siegel S (1997) The use of music in group work with outpatient alcoholic couples: a pilot investigation. *Groupwork* 10: 155-174.
107. Cevasco AM, Kennedy R, Generally NR (2005) Comparison of movement-to-music, rhythm activities, and competitive games on depression, stress, anxiety, and anger of females in substance abuse rehabilitation. *J Music Ther* 42: 64-80.
108. Perkins KA, Karelitz JL, Giedgowd GE, Conklin CA (2013) Negative mood effects on craving to smoke in women versus men. *Addict Behav* 38: 1527-1531.
109. Garavan H, Pankiewicz J, Bloom A, Cho JK, Sperry L, et al. (2000) Cue-induced cocaine craving: neuroanatomical specificity for drug users and drug stimuli. *Am J Psychiatry* 157: 1789-1798.
110. Goldstein A (1980) Thrills in response to music and other stimuli. *Physiol Psychol* 8: 126-129.
111. Peciña S, Smith KS, Berridge KC (2006) Hedonic hot spots in the brain. *Neuroscientist* 12: 500-511.

-
112. Huang ST, Good M, Zauszniewski JA (2010) The effectiveness of music in relieving pain in cancer patients: a randomized controlled trial. *Int J Nurs Stud* 47: 1354-1362.
113. Vaajoki A, Pietilä AM, Kankkunen P, Vehviläinen-Julkunen K (2012) Effects of listening to music on pain intensity and pain distress after surgery: an intervention. *J Clin Nurs* 21: 708-717.
114. Blum K, Gardner E, Oscar-Berman M, Gold M (2012) "Liking" and "wanting" linked to Reward Deficiency Syndrome (RDS): hypothesizing differential responsivity in brain reward circuitry. *Curr Pharm Des* 18: 113-118.