Effects of Musical Pleasure on Dopamine in the Mesolimbic Reward Pathway



By

Jade Nicole Allen

Submitted to the Neuroscience Department at Allegheny College

in partial fulfilment of the requirements for the degree of

BACHELOR OF SCIENCE

Effects of Musical Pleasure on the Mesolimbic Reward Pathway

Senior Comprehensive Project

Presented by:

_____

Jade Nicole Allen

I hereby recognize and pledge to fulfill my responsibilities as defined in the Honor Code and to maintain the integrity of both myself and the College community as a whole.

April 9th, 2021

Approved by:

_____	_____
Dr. Lauren Rudolph	Dr. Lauren B. French

Table of Contents

Acknowledgements……..4

Abstract……..……..5

Reward Pathways……...……..6

Dopamine Transmission……..……..11

Rodent Studies……...……..……..14

Pleasant Music…….……..19

Anhedonia……..21

Music Therapy…….…..25

Conclusions……..……..27

References..……..……..29

Acknowledgements

I want to say a special thank you to Dr. Rudolph for not only being my senior project advisor for the past year, but also for all of the guidance in navigating my sudden project change at the beginning of Fall 2020 due to COVID-19 lab restrictions. In a typical year, I would have done physical rodent research in the lab and collected data to report for my senior project. This unfortunately was not the case this year, but I am so thankful for all of your help and guidance even though this literature review falls outside of your typical research interests. I am glad, in a way, that my original project idea had to be changed because I got to incorporate interests from my Music Performance Minor alongside my Neuroscience Major. I also want to thank Dr. French for your support and guidance throughout this whole process and your willingness to be my second reader.

A special thank you is also owed to my girlfriend, Alexis, for being there for me every step of the way and supporting me the past four years at Allegheny. I don't know where I would be without you and I am forever grateful to have you in my life always encouraging me to be the best version of myself.

Thank you to all of my friends and family for always being there for me and for believing in me, even when I struggled to see the things I have accomplished over the years. I especially thank my grandmother, Cindy, for everything you do for me and for encouraging me to reach for my dreams from day one by not letting anything stand in my way.

Abstract

Music is a powerful stimulus capable of modulating emotional experiences that has roots in the mesolimbic reward pathway, otherwise known as the mesolimbic dopamine pathway or reward pathway. Dopaminergic neurons that project from the ventral tegmental area (VTA) to the nucleus accumbens (NAcc) release dopamine during pleasant musical exposure. Neural responses to pleasurable, rewarding stimuli can be measured by fMRI and PET scans of participants during exposure to pleasant music and the results from these neuroimaging studies seem to show a similar response among participants. Many mesolimbic and cortical structures are activated in response to rewarding stimuli such as the VTA, NAcc, neostriatum (NS), prefrontal cortex (PFC), orbitofrontal cortex (OFC), caudate-putamen (CPu), hypothalamus and insula to name a few. Rodent models are used to investigate dopamine concentrations in these various areas and compared to functional and connective activations in human neuroimaging studies. Anhedonia is the overall loss of feelings of pleasure from otherwise rewarding stimuli and can be seen in healthy individuals with specific music anhedonia as well as in those with depression. Mesolimbic structures are activated less in individuals who experience anhedonia which in turn leads to less dopamine transmission. Therapeutic benefits of music therapy could help individuals with Major Depressive Disorder (MDD) and specific music anhedonia by promoting positive emotional regulation after pleasant music exposure, but this possible therapy needs to be investigated further for clinical success in treating symptoms of anhedonia.

Physiology of the mesolimbic reward pathway

A wide variety of things can affect emotions and humans tend to seek out pleasurable things because of their rewarding nature and avoid aversive things that can invoke negative emotions (Ferrari et al., 2019). This pleasure is modulated by the mesolimbic reward pathway in the brain which is important in invoking feelings of pleasure and responding to reinforcing stimuli. The mesolimbic reward pathway is a dopaminergic system that releases dopamine after pleasurable stimuli from the ventral tegmental area (VTA) of the substantia nigra to the nucleus accumbens (NAcc) to invoke positive emotions and reinforce the behavior (Zatorre & Salimpoor, 2013). These dopaminergic projections also synapse onto the amygdala, pyriform gyrus and lateral septal nuclei and dopamine's release in this pathway has a major role in drug addiction (Ayano, 2016). Another type of dopaminergic pathway is the mesocortical dopamine pathway which involves dopamine projecting from the VTA to the prefrontal cortex (PFC) and this pathway is associated with cognition, decision making and working memory but not reward. Dysfunction in the mesocortical pathway leads to difficulties with concentration and affects one's ability to make decisions whereas dysfunction in the mesolimbic system leads to intense cravings for pleasurable stimuli or an overall loss of pleasure known as anhedonia (Whitton et al., 2015; Hall et al., 2013; Young et al., 2016). Dopamine's effect on the mesolimbic system mediates feelings of satisfaction whereas its effect on the mesocortical pathway mediates cognitive and emotional behavior (Ayano, 2016).

The neural response to pleasurable, rewarding stimuli can be measured by fMRI and PET scans of participants during exposure to pleasant music and the results from these neuroimaging

studies seem to show a similar response among participants. These studies tend to use western classical music which is instrumental music from 1750 to 1900 in non-musically trained participants, but they can also use self selected music that the participants already know and report to be pleasurable. These classical music pieces are classified as pleasurable because the participants self-report that they are and brain areas are activated in response to this music in the same areas that are activated during primary reinforcing behaviors. The mesolimbic reward system is typically stimulated in response to primary reinforcing behaviors such as eating, drinking, sex, and caring for offspring in humans and in various animals (Ferrari et al., 2019). Neuroimaging studies in humans have found that various mesolimbic structures are activated in response to pleasurable music as well which includes structures such as the ventral striatum (VS) which is part of the NS, amygdala, hippocampus, hypothalamus, ventromedial prefrontal cortex (VMPFC), and other dorsal midbrain areas (Martinez-Molina et al., 2016; Blood et al., 1999; Blood et al., 2001; Koelsch et al., 2006; and Zatorre & Salimpoor, 2013). These brain regions are associated with reward, motivation, emotional regulation and arousal (Blood et al., 2001). Drugs with addictive properties increase dopamine levels in the reward pathway which could be why they have such strong addictive properties (Feduccia & Duvachelle, 2008). The same brain structures associated with dopamine transmission are involved in the mesolimbic reward pathway as well.

Primary reinforcers are biologically relevant stimuli that modulate the reward pathway when an individual participates in an activity that is needed for survival or reproduction. Secondary reinforcers, like money, are tangible stimuli that are not needed for survival, but elicit a response within the reward pathway as well (Martinez-Molina et al., 2016). These reinforcers

require a learned association between the secondary reinforcer with a primary one (Ayano, 2016). Secondary reinforcers can be abstract, such as music (Ferrari et al., 2019), which stimulates the reward pathway and may be beneficial for our mental and physical well-being since an emotional response to music is not necessarily biologically relevant (Blood et al., 2001). Another reason humans are so attracted to music could be because of rewarding effects from learning the music's structure. One study found that learning about musical structure could be intrinsically rewarding to humans because it contains the same predictive components as learning (Gold et al., 2019). Learning is rewarding due to our ability to predict outcomes and anticipate our wants and needs in order to adapt and survive in our environment (Sutton & Barto, 2018). Predictive errors look at the magnitude of how correct we are in predicting outcomes and specifically reward prediction errors (RPEs) in the NAcc motivate reinforcement learning to maximize rewards and minimize punishments. Participants were told to learn about which choices would lead them to the music they wanted to hear and were given two arbitrary choices of selecting a color (blue or yellow) and then a direction (right or left) that determined which musical stimuli they heard and if it had a consonant or dissonant ending in western music (Gold et al., 2019). Music information software was used to analyze the RPEs that occur when participants were seeking information about which ending the music would end with (i.e. consonant or dissonant) or whether they were uncertain about the outcome of the musical structure. They found that those with low uncertainty and high predictability of the musical ending of the stimuli that those participants were experiencing more rewarding effects from essentially guessing the music ending correctly. This was seen on a functional level by greater blood oxygen level dependent (BOLD) activation in the NAcc which was correlated with improvements in selecting the rewarding consonant musical endings over the punishing

dissonant endings. BOLD responses are a result of the circulatory system responding to firing neurons by sending highly oxygenated blood to that region and an increase in these responses are correlated with activation. These results could possibly only be due to the motivational factor of avoiding the unpleasant dissonant endings and not necessarily pleasure, however; this does further support that abstract musical stimuli activate the same mesolimbic pathway and that cognitive and emotional processing in the NAcc may explain why music is so pleasurable.

Music could also be rewarding because of the sensation of groove which is the motivation to move while listening to music and links the timing of motor response with reward processing (Matthews et al., 2020). This study used both musicians and non-musicians that listened to 36 unique high and medium complexity rhythm and harmony piano sequences in which there were three stimuli for each condition: medium rhythm and harmony, high harmony and rhythm, medium rhythm high harmony and high rhythm medium harmony. Participants rated their sensation of wanting to move while listening to all 36 stimuli in an fMRI scanner and listened to all 36 pieces again at a computer to rate their feelings of pleasure and strength of the beats. Results showed that medium complexity rhythm and harmony elicited the greatest activation in the NAcc, caudate and medial orbital PFC to the musical stimuli. They also found that as harmonic and rhythmic complexity increased from medium to high, that pleasure ratings decreased for both musicians and non-musicians. They also observed that musicians' sensation of wanting to move increased with medium complexity harmonies and chords but that non-musicians' sensation of wanting to move was only influenced by the medium complexity harmonies and not by chords. This could mean that non-musicians do not find chords played in a rhythmic pattern to be rewarding because they have no musical training to be able to predict

what will happen with the rhythm next. The sensation of wanting to move was greater with medium complexity harmonies as compared to high complexity harmonies which could be due to the fact that high complexity harmonies are too complex for our auditory cortex to process properly and makes that complexity of music less pleasurable. The sensation of wanting to move has clear connections to the mesolimbic reward pathway and the prediction of beats in the musical stimuli could have connections to the rewarding nature of learning as well.

Dopamine transmission increases following rewarding stimuli

Various mesolimbic areas are activated in response to rewarding stimuli which proposes a significant effect pleasant music can have on an individuals' emotional regulation by stimulation of the reward pathways. Mesolimbic areas activated by pleasant music are also the same areas that are involved in dopamine transmission. Most neuroimaging literature agrees that an increased fMRI response means that a structure is activated which in turn means the level of dopamine has increased because the neurons stimulated in these structures are dopaminergic (Martinez-Molina et al., 2016; Blood et al., 1999; Blood et al., 2001; Koelsch et al., 2006; and Zatorre & Salimpoor, 2013). Specifically dopaminergic neuronal cell bodies projecting from the VTA onto the NAcc can be stimulated in response to rewarding stimuli which promotes dopamine transmission (Menon & Levitin, 2005). Neuroimaging techniques such as functional magnetic resonance imaging (fMRI) and ligand-based positron emission tomography (PET) do not have the ability to directly look at dopamine transmission in the human reward pathway and dopamine does not pass the blood-brain barrier so serum samples cannot be obtained by participants. However, PET and fMRI can indirectly provide important functional and connective information abouts activated brain structures and since these activated structures are associated with dopamine transmission their results can be interpreted as an increase in dopamine transmission. PET scans measure the regional distribution of chemical compounds in the brain that can be labeled by their short-lived positron-emitting isotopes through the application of a radiotracer. In these specific studies, researchers use a radiotracer that labels dopamine receptors, dopamine transporters, dopamine precursors, and compounds that are specific for enzymes involved in degrading synaptic dopamine (Sossi et al., 2002). These results are typically

compared to fMRI results since PET scans are not temporally specific to see if the increase in BOLD activation responses are correlated with the timing of dopamine transmission.

One neuroimaging study investigated the relationship between rewarding musical stimuli and the effective connectivity between the VTA and NAcc with other brain regions (Menon & Levitin, 2005). 13 non-musicians listened to either scrambled or unscrambled classical music stimuli and their fMRI activation results were compared to their responses to a questionnaire on pleasantness ratings of the musical pieces. These results showed that when the VTA was activated the NAcc was activated and when the hypothalamus was activated the NAcc was also activated. Effective connectivity was used to examine VTA-mediated interactions with the NAcc on various mesolimbic structures which found that the NAcc was co-activated with the insula, hypothalamus and OFC following music exposure. This interaction was important to note because it showed a relationship between affective brain regions and regions that are associated with the autonomic nervous system (Menon & Levitin, 2005). The hypothalamus modulates autonomic responses like heart rate and respiration within the autonomic nervous system and this study was the first to find a relationship between the hypothalamus and the response to music. These results do not necessarily describe that pleasant music is mediating these activations, but rather that the difference between normal, unscrambled music is rewarding as compared to unpleasant, scrambled music. Overall, the interactions between the NAcc, VTA and hypothalamus may regulate the emotional responses to rewarding musical stimuli.

Another study used fMRI and PET to look at the time course of dopamine release in response to pleasant music by comparing activations of dopaminergic brain regions (Salimpoor

et al., 2011). The increased level of dopamine was measured by examining the percentage change in the BOLD response in the NAcc and right CPu over time and compared those results to the voxels of interest (VOIs) from their PET scan data (Salimpoor et al., 2011). They did find significant activation in the NAcc and the right CPu right before and during the peak of emotional responses to pleasant music which was characterized by the sensation of “chills" and this indicated that dopamine was being released into the mesolimbic system. Dopamine transmission increases during the sensation of chills because activation in the NAcc is correlated with this increase in dopamine. The CPu is typically associated with feelings of anticipation, so these results could just be showing anticipation of an abstract reward and not actual musical pleasure (Salimpoor et al., 2011). The sensation of chills during dopamine release in the NAcc could be associated with the rewarding effects of learning about music structures and also could be due to conscious evaluation of the music and anticipating the climatic point of the piece (Gold et al., 2019). Human studies surrounding dopamine release and the rewarding effects of music are limited in their direct measurements of their variables, so despite these findings the direct dopamine concentrations in mesolimbic regions cannot be investigated. Post mortem rodent studies on dopamine transmission help researchers to see actual dopamine concentrations following music exposure because in humans this cannot be ethically investigated. The results from rodent studies can be used to compare increasing dopamine concentrations in these mesolimbic regions to what is happening on purely an activational basis in the same structures in humans.

Rodent Studies Focus on Neuroendocrine Effects of Music

Dopamine is the most prevalent catecholamine neurotransmitter synthesized from the amino acids tyrosine and phenylalanine and action potentials release it from the synaptic vesicles into the synaptic gap. When dopamine binds to the postsynaptic neuron it can act upon five different types of receptors: D1, D2, D3, D4 and D5 (Ayano, 2016). These receptors can be grouped into D1-like (includes D1 and D5 receptors) and D2-like (includes D2, D3 and D4 receptors). One main difference between the two classes of dopamine receptors is that D1-like receptors can excite or inhibit its target neuron whereas D2-like receptors typically only inhibit target neurons (Ayano, 2016). D1 receptors are mostly found in the NAcc, CPu, substantia nigra, olfactory bulb, and striatum and these receptors are important in working memory and attention. D2 receptors are important in mood and emotional regulation in limbic structures such as the VTA and NAcc and movement control in the basal ganglia. *Taq* 1 A1 is an allele in the D2 receptor gene that has been correlated with lower D2 receptor density expression rates and has been found in those with severe alcoholism (Blum et al., 1990). This specific allele is considered a general reward gene specifically in those with alcoholism and has been associated with reduced release of dopamine from the NAcc to the VTA in the mesolimbic reward pathway. This can lead to Reward Deficiency Syndrome (RDS) which increases the likelihood of drug seeking behaviors to compensate for the low density of D2 receptors that mediate feelings of pleasure at normal concentrations (Blum et al., 1990). The direct concentration of dopamine in the mesolimbic reward pathway is able to be investigated using rodent models.

Non-human mammal studies have the potential to give insight into how dopamine affects human mesolimbic structures on a neurochemical level by investigating direct dopamine

turnover ratios. Dopamine effect on mesolimbic structures following musical exposure can be directly investigated in rodents to compare and contrast to activation data from human neuroimaging studies. Dopamine turnover is the ratio of dopamine to its metabolites which are 3,4-dihydroxyphenylacetic acid (DOPAC) and homovanillic acid (HVA) and can be measured post-mortem in rodent brain tissue to see if this ratio is increasing to overcompensate for reward pathway dysfunction (Sossi et al., 2002). In other words, the reward pathway dysfunction could be due to an increased level of dopamine metabolites and a lower level of actual dopamine in the brain. This overcompensation was seen early in those with Parkinson's disease which is characterized by a loss of dopaminergic neurons in the striatum and the increased rate of dopamine turnover in the remaining neurons. This increased turnover rate was estimated in humans with early Parkinson's disease by using dopamine precursors as the radioactive tracer in a PET scan study (Sossi et al., 2002). One study investigated the direct dopamine turnover ratios in rodents in the CPu and the NAcc, along with other monoamine neurotransmitters such as serotonin, within the reward pathway (Moraes et al., 2018). Rats exposed to classical melodic music as compared to a group not exposed to music showed an increase in dopamine turnover in both the NAcc and CPu (Moraes et al., 2018). These results should be looked at cautiously because the release of dopamine in the CPu is also associated with anticipation of rewards. Since the rats underwent seven music exposure sessions this could mean the rats were anticipating the musical stimuli to happen and that activation in the NAcc is not necessarily because this stimuli is rewarding to them (Salimpoor et al., 2011). The increase in dopamine turnover between the VTA and NAcc could be reflective of their peak emotional response to the music similar to the sensation of chills in humans (Blood et al., 2001; Salimpoor et al., 2011). The emotional response in rodents cannot be recorded with the use of self-report surveys as is done in human

studies which raises the question on why rodents respond similarly to musical stimuli. Similar areas are activated in the rodent reward pathway during pleasant music exposure as compared to humans, so this could mean that rodents are capable of experiencing similar pleasurable feelings from rewarding musical stimuli.

Rodent models using psychoactive drugs such as 3,4-Methylenedioxymethamphetamine or commonly known as MDMA or ecstasy, which strongly stimulate reward pathways, and D2 antagonists such as haloperidol allow researchers to investigate the direct concentrations of various neurotransmitters in the reward pathway which is unobtainable in humans (Feduccia & Duvachelle, 2008; Tasset et al., 2012). Stimulant drugs such as MDMA and other amphetamines are used in addiction research because of their ability to increase dopamine transmission which modulates the reward pathway. Opioids are not used as much in reward research because opioid receptors are located in similar brain regions as dopamine receptors (Feng et al., 2012). Opioid receptors are known for their role in addiction and pain modulation along with other physiological effects on respiration and homeostasis. There are more gaps in research about how dopamine functions in the mesolimbic reward pathway and its implications for various disorders, so that is why stimulants are used more often than opioids in reward pathway investigations.

The use of D2 dopamine receptor antagonists in rodents affects dopamine release and its effects can be looked at during pleasant musical stimuli by comparing untreated to treated rodents to see if blocking D2 receptors eliminates or lowers classical musics' effect on the reward pathway (Tasset et al., 2012). Rats were placed into either a control group not exposed to music or haloperidol which is a D2 antagonist, a group just exposed to music, a group just

treated with haloperidol, or a group treated with haloperidol and exposed to music. Rats in the music only condition had decreased plasma levels of prolactin and corticosterone and increased dopamine content in the PFC and MS whereas rats in the haloperidol condition had increased plasma levels and decreased dopamine content in the PFC, MS and SN. It is important to note that the rats that were treated with haloperidol and exposed to music experienced a slight increase in plasma concentrations, but they had significantly higher levels of dopamine in the PFC, MS and SN (Tasset et al., 2012). This shows that music has the powerful ability to modulate dopamine transmission in the mesolimbic reward pathway even when a D2 receptor antagonist is actively blocking dopamine. Rodents can be used to investigate the effects that different drugs such as MDMA have on the mesolimbic pathway and see if music heightens the activation of structures after drug treatment instead of blocking their activation as seen with D2 receptor antagonists (Feduccia & Duvachelle, 2008). These results could show researchers if music exposure along with drug treatment elicits greater activation in mesolimbic brain regions which could mean that rewarding stimuli can increase dopamine transmission even more when stimuli are used in conjunction with each other.

Other rodent studies also investigated dopamine's effects on different regions of the brain also involved in the mesolimbic reward pathway. Music and MDMA exposure in rodents activate some of the same regions that are also stimulated by dopamine such as the NAcc (Feduccia & Duvachelle, 2008). Rats exposed to music and MDMA showed an increase in dopamine levels in the NAcc whereas rats in the white noise condition and the music only condition did not show any change in their dopamine or serotonin levels. Serotonin increased in the NAcc after music and MDMA treatment, but to a lesser extent than did dopamine within the NAcc. This shows that

strong stimuli like drugs increase dopamine levels in the NAcc which could explain the overwhelming feeling of pleasure humans get in response to pleasant music exposure.

Pleasant Music Activates Mesolimbic Structures

Pleasant music exposure has the ability to modulate the mesolimbic reward pathway and its stimulation induces feelings of pleasure (Blood et al., 2001). Pleasure that individuals experience during music listening can also co-occur with changes in multiple physiological markers such as blood pressure, body temperature, skin conductance, heart rate and respiration (Salimpoor et al., 2011; Zatorre & Salimpoor, 2013). This is because the autonomic nervous system is modulating these physiological changes after music exposure and shows how the body can physically react to emotions. Most of the literature focuses on how pleasant music indirectly stimulates the mesolimbic reward pathway because of similar activations between brain regions that also exhibit higher levels of dopamine transmission in rodents (Blood et al., 1999; Blood et al., 2001; Koelsch et al., 2006). Pleasant music typically consists of western classical music pieces which are from European composers (i.e. Bach, Mozart) between the years 1750 and 1900 and these pieces elicit intense emotional responses as a result of pleasure in humans. The pleasure felt by individuals has been correlated with activations found by fMRI and PET scans in numerous studies and they have found activation in areas that also are activated during positive emotional regulation following pleasant music exposure (Martinez-Molina et al., 2016; Blood et al., 1999; Blood et al., 2001; Koelsch et al., 2006; and Zatorre & Salimpoor, 2013). Mesolimbic structures that are activated during pleasant music exposure include the VTA, NAcc and striatum across multiple neuroimaging studies that have slight experimental variations. This shows that pleasant music has the overall ability to stimulate the reward pathway regardless of individual differences between imaging studies.

Unpleasant music is correlated with negative emotions like fear, discomfort or annoyance and this type of musical stimuli activates different brain regions than pleasant music. The use of unpleasant music in neuroimaging studies typically consists of dissonant, clashing musical tones to invoke these negative emotional states (Blood et al., 1999). These negative emotional states are associated with unpleasant music because participants self-report these as their emotions during the music exposure. The areas that are associated with negative emotional states include the amygdala, parahippocampal gyrus and the temporal poles (Blood et al., 1999; Koelsch et al., 2006). The amygdala is typically associated with feelings of fear and dissonant music can cause participants to experience a wide variety of negative emotions. There was not any activation in the amygdala in their specific study which could just imply that their participants were not experiencing fear during the unpleasant music condition (Blood et al., 1999). These results show there is a clear distinction in the brain between pleasant and unpleasant music in which the latter does not activate structures associated with the mesolimbic reward pathway.

Anhedonia is Negatively Correlated with Musical Reward

Anhedonia, which is known as the overall loss in pleasure from otherwise rewarding stimuli, is a phenomenon seen in individuals with Major Depressive Disorder (MDD) and in healthy individuals with specific music anhedonia where the loss of pleasure is explicitly seen in regard to music (Martinez-Molina et al., 2016; APA, 2017). Specific music anhedonia seems to be a result of the inability to appropriately process pleasant musical stimuli rather than an underlying abnormality within the reward pathway (Young et al., 2016). This specific music anhedonia tends to occur in about 5% to 10% of the population in those without brain damage or mental disorders such as MDD, schizophrenia and substance abuse disorders (Belfi et al., 2020). People who exhibit specific music anhedonia do show typical pleasurable responses to other types of stimuli such as monetary tasks and do not show any pleasurable responses to music (Mas-Herrero et al., 2014). These individuals do not show anhedonia on a general anhedonia scale but do on the Barcelona Musical Reward Questionnaire (BMRQ) (Belfi et al., 2020).

One study looked at the heart rate (HR) and skin conductance responses (SCR) of individuals with musical anhedonia and found that they had less of a response during high pleasure moments in the music than those that scored normally on the BMRQ (Mas-Herrero et al., 2014). Another key finding was that individuals with specific musical anhedonia and the control group with normal BMRQ scores showed similar responses in HR and SCR during a monetary reward task. This shows that those with specific musical anhedonia have functional reward system processing in regard to primary reinforcing stimuli and have dysregulation in regard to processing musically rewarding stimuli only. The loss of the ability to derive pleasure from music in humans can have clinical applications to symptoms of depression and

abnormalities in the reward pathway (Whitton et al., 2015; Hall et al., 2013; Young et al., 2016). It is currently unknown if individuals with specific music anhedonia are more likely to develop symptoms of depression or not. Individuals with MDD may display general anhedonia along with other symptoms such as fatigue, inability to concentrate, overall depressed mood and suicidal ideations (APA, 2017). Individuals must show either anhedonia or prolonged sadness along with at least five other depressive symptoms for a consecutive period of at least two weeks in order to be diagnosed with clinical MDD. Anhedonia can also be a symptom in other disorders such as schizophrenia and is the key factor in relapse in substance abuse disorders which both involve dopamine and reward system dysfunctions (APA, 2017).

Reward system functioning is typically diminished in patients with MDD characterized by reduced activation following a reward contingency, such as a monetary gambling task, in the left NAcc, ventromedial prefrontal cortex (VMPFC) and dorsal anterior cingulate (ACC) which is within the PFC (Whitton et al., 2015; Hall et al., 2013). Reward contingencies typically involve a monetary gambling task in order to stimulate the reward pathway. The ventral and dorsal striatum show an overall diminished activation in those with MDD which could be viewed as a potential neurochemical precursor to depressive symptoms, but more research is needed to investigate this (Whitton et al., 2013). Patients who recently developed depressive symptoms show fewer functional abnormalities in activation than those who have suffered at least 3 depressive episodes in the NAcc, VMPFC and ACC (Hall et al., 2013). This means that those who have had depressive episodes over time have a more severe impact on their ability to experience pleasure and could indicate that MDD has degenerative characteristics. These regions show the greatest amount of activation following a reward contingency in healthy controls, so

individuals with MDD will exhibit less activation in these same areas. Another study also found a lack of connectivity between the VMPFC and reward pathways in those who experience specific musical anhedonia (Young et al., 2016). Individuals with and without MDD listened to scrambled and unscrambled classical music pieces to examine the effects of anhedonia on the reward pathway. Individuals with MDD showed less connective activations than those without MDD between the VMPFC and mesolimbic structures such as the NAcc and VTA after pleasant musical stimuli as compared to the unpleasant scrambled music (Young et al., 2016). Individuals without MDD showed typical activation to the pleasant music in frontal and mesolimbic areas and typical activation in the other brain regions associated with unpleasant music.

Studies that look at specific music anhedonia are trying to investigate its effects on the mesolimbic reward pathway because many studies that use those with MDD have trouble separating anhedonia from other depressive symptoms. These studies give important information on the neuroanatomical basis for anhedonia in the reward pathway and can be applied to those with mental illnesses such as depression to see if music therapy would be beneficial in emotional regulation. Specific music anhedonia was investigated in healthy individuals using the typical pleasant, neutral and unpleasant paradigm as well as using a monetary reward task to make sure they are only exhibiting anhedonia to music and not other rewarding stimuli (Martinez-Molina et al., 2016). A questionnaire was used to evaluate the participants' level of sensitivity to music prior to the musical stimuli within the fMRI. In another study, they looked at another group of healthy individuals using fMRI to examine connectivity within the reward pathway (Keller et al., 2013). They found that specific music anhedonia was correlated with lower activation in key reward pathway structures such as the NAcc, basal

forebrain and hypothalamus. They also found that limbic areas associated with processing emotional regulation showed reduced activation in those with anhedonia which include the insula and OFC. The rationale behind these studies was to look at anhedonia in general and try to see its effects because many studies that use those with MDD have trouble separating anhedonia from other symptoms. These give important information on the neurological basis for anhedonia and can be applied to those with mental illnesses such as depression to see if music therapy would be beneficial in emotional regulation.

Possible Roles for Music Therapy-mediated Changes in Emotional Regulation

Recently, research has begun to look at the potential benefits to mental health that music therapy can provide to those with MDD to induce positive emotions and reflect on those feelings. Receptive music therapy is when the patient listens to music and then reflects on their thoughts and responses to the music with their therapist (Grocke et al., 2007). Although music therapy is not one of the first lines of action in a treatment plan, it has been effective in children and adult patients with a wide variety of disorders and some therapists use it to help begin engaging with their patients. One study found that music therapy as a treatment for depression has been shown to help with emotional regulation in the short term (Aalbers et al., 2017). They looked at those with depression receiving treatment as usual typically through talk therapy and/or medication and compared self-reported emotional scores to those who received music therapy in addition to typical treatment. Self-selected music is more likely to activate the reward pathway to give the listener feelings of pleasure than novel, unknown music like classical music that is typically used methodically (Grocke et al., 2007; Blood et al., 2001). However, in clinical practice music therapists may use classical music rather than self-selected music to help eliminate individual differences in musical preference (Grocke et al., 2007). This could limit the pleasurable effect music can have on emotional regulation during music therapy since self-selected music has been shown to activate reward pathways more often. Music that is familiar is more rewarding to individuals which has been characterized by neuroimaging studies, so therapists should keep this in mind when selecting the type of music for the session. The patients will experience the greatest amount of activation in their mesolimbic reward system if they are listening to their own music and the use of classical music in music therapy may only be helpful to those who enjoy or play classical music. One study looked at the effects of self-selected favorite music in those with

MDD and compared them to healthy controls through fMRI (Osuch et al., 2009). Healthy controls showed greater activation in the medial orbitofrontal cortex and NAcc than in individuals with depression when listening to their self-selected music. The use of music therapy as a supportive therapy for individuals with MDD is typically researched for an acute period of time due to the difficulty of maintaining contact with participants and long term data collection and analysis, so long-term therapeutic benefits for emotional regulation are currently unknown (Zatorre et al., 2013). It is important to note that music therapy alone is unlikely to help those with depression because it may not treat all of their symptoms, so it should be used alongside typical interventions such as cognitive behavioral therapy and antidepressants.

Other disorders related to reward system dysfunction may also experience mental health benefits from music therapy. Individuals with substance use disorder could benefit from music therapy, especially in those who express the *Taq* 1 A1 allele in their D2 receptors (Blum et al., 1990). The A1 allele is associated with lower D2 receptor density which in turn reduces the amount of dopamine transmission in the reward pathway and those with this allele tend to experience greater activation of the reward pathway in response to music only. This exaggerated response to music may allow them to overcome their deficits in reward system functionality if music therapy is used in these individuals. These individuals show reduced response to primary reinforcers and only show a heightened response to music similar to effects from D2 receptor agonists (Blum et al., 1990). Music therapy may provide natural benefits by increasing dopamine transmission and stimulate the reward pathway of individuals who typically only experience that activation through drug use.

Conclusion and Future Directions

Various mesolimbic structures are activated in response to the rewarding nature of pleasant music exposure in human neuroimaging studies. The most important structures and their effects on dopamine transmission in the mesolimbic reward pathway are the VTA and NAcc. Rodent models can be used to see what is happening on a neurochemical level to dopamine receptors in the reward pathway to compare and contrast to human anatomical data. Pleasant classical music has a greater ability to modulate dopamine transmission in these regions than dissonant, unpleasant music which tends to affect different structures. Individuals with specific music anhedonia do not experience pleasurable effects from music, but they have the capacity to normally respond to rewarding stimuli such as food or money. MDD is characterized by the common symptom of anhedonia and understanding how the reward pathway functions in healthy individuals can help explain dysfunctions within these structures in MDD. The powerful ability of music to stimulate the reward pathway and increase dopamine transmission could have implications for using musical therapy in those who struggle with anhedonia.

There are various limitations to this type of neuroimaging research in humans that should be addressed in future studies. The types of populations that are typically studied are not a good representation of the entire population because they tend to use college aged adults with no musical training and tend to use musical stimuli that would not necessarily be rewarding to them. These studies also tend to occur in western countries which is the basis for using western classical music, so it would be interesting to see if eastern music has a similar effect on the mesolimbic reward system in individuals who live in those areas. Eastern music would not be rewarding to individuals from western countries and vice versa because they would not be used

to the different intervals between notes and musical modes that are used in the opposing culture. Another limitation to this research is the indirect nature of neuroimaging because researchers cannot ethically measure activation and dopamine concentrations in human participants. This direct measurement is only able to be obtained in rodent models by analyzing their brain tissues after musical exposure, so it would be interesting to compare and contrast the same exact study to humans and rodents. Various studies have been done on rodents and humans separately, however; no group of researchers has used the same study in both groups. A longitudinal study could investigate the cumulative effects of increased dopamine transmission within the reward pathway to see if receptive music therapy is beneficial in the long term on emotional regulation. This type of a study could use fMRI and/or PET scans to measure brain activation and/or the level of dopamine transmission before and after each therapy session to see if transmission increases over repeated sessions. Dopamine transmission has clear links to the mesolimbic reward pathway and the rewarding nature of processing pleasant musical stimuli could be fundamental in further understanding the concept of anhedonia in individuals with MDD.

References

Aalbers S; Fusar-Poli L; Freeman RE; Spreen M; Ket JC; Vink AC; Maratos A; Crawford M; Chen XJ; Gold C;. (2017). Music therapy for depression.

Ayano, G. (2016). Dopamine: Receptors, Functions, Synthesis, Pathways, Locations and Mental Disorders: Review of Literatures. *Journal of Mental Disorders and Treatment, 2*(2).

Belfi, A. M., & Loui, P. (2020). Musical anhedonia and rewards of music listening: Current advances and a proposed model. *Annals of the New York Academy of Sciences, 1464*(1), 99-114. doi:10.1111/nyas.14241

Blood, A. J., Zatorre, R. J., Bermudez, P., & Evans, A. C. (1999, April). Emotional responses to pleasant and unpleasant music correlate with activity in paralimbic brain regions.

Blood, A. J., & Zatorre, R. J. (2001, September 25). Intensely pleasurable responses to music correlate with activity in brain regions implicated in reward and emotion.

Blum, K., Noble, E. P., Sheridan, P. J., Montgomery, A., Ritchie, T., Jagadeeswaran, P., . . . Cohn, J. B. (1990). Allelic association of human dopamine D2 receptor gene in alcoholism. *JAMA: The Journal of the American Medical Association, 264*(14). doi:10.1001/jama.264.14.1807b

Diagnostic and statistical manual of mental disorders: DSM-5. (2017). Arlington, VA: American Psychiatric Association.

Feduccia, A. A., & Duvauchelle, C. L. (2008). Auditory stimuli enhance MDMA-conditioned reward and MDMA-induced nucleus accumbens dopamine, serotonin and locomotor responses. Brain Research Bulletin, 77(4), 189-196.

Feng, Y., He, X., Yang, Y., Chao, D., Lazarus, L. H., & Xia, Y. (2012). Current research on opioid receptor function. Current Drug Targets, 13(2), 230–246.

Ferreri, L., Mas-Herrero, E., Zatorre, R. J., Ripollés, P., Gomez-Andres, A., Alicart, H., . . . Rodriguez-Fornells, A. (2019, February 26). Dopamine modulates the reward experiences elicited by music.

Gold, B. P., Pearce, M. T., Mas-Herrero, E., Dagher, A., & Zatorre, R. J. (2019). Predictability and Uncertainty in the Pleasure of Music: A Reward for Learning? *The Journal of Neuroscience, 39*(47), 9397-9409.

Grocke, D., Wigram, T., & Dileo, C. (2007). Pgs. 15-16. In Receptive Methods in Music Therapy: Techniques and clinical applications for music therapy clinicians, educators and students. London: Jessica Kingsley.

Hall, G. B., Milne, A. M., & Macqueen, G. M. (2013). An fMRI study of reward circuitry in patients with minimal or extensive history of major depression. European Archives of Psychiatry and Clinical Neuroscience, 264(3), 187-198.

Keller, J., Young, C. B., Kelley, E., Prater, K., Levitin, D. J., & Menon, V. (2013). Trait anhedonia is associated with reduced reactivity and connectivity of mesolimbic and paralimbic reward pathways. Journal of Psychiatric Research, 47(10), 1319-1328.

Koelsch, S., Fritz, T., V Cramon, D. Y., Müller, K., & Friederici, A. D. (2006, March). Investigating emotion with music: An fMRI study.

Mas-Herrero, E., Zatorre, R., Rodriguez-Fornells, A., & Marco-Pallarés, J. (2014). Dissociation between Musical and Monetary Reward Responses in Specific Musical Anhedonia. Current Biology, 24(6), 699-704.

Matthews, T. E., Witek, M. A., Lund, T., Vuust, P., & Penhune, V. B. (2020). The sensation of groove engages motor and reward networks. NeuroImage, 214.

Moraes, M. M., Rabelo, P. C., Pinto, V. A., Pires, W., Wanner, S. P., Szawka, R. E., & Soares, D. D. (2018, February 27). Auditory stimulation by exposure to melodic music increases dopamine and serotonin activities in rat forebrain areas linked to reward and motor control.

Menon, V., & Levitin, D. (2005, July 14). The rewards of music listening: Response and physiological connectivity of the mesolimbic system.

Osuch, E. A., Bluhm, R. L., Williamson, P. C., Théberge, J., Densmore, M., & Neufeld, R. W. (2009). Brain activation to favorite music in healthy controls and depressed patients. NeuroReport, 20(13), 1204-1208.

Salimpoor, V. N., Benovoy, M., Larcher, K., Dagher, A., & Zatorre, R. J. (2011). Anatomically distinct dopamine release during anticipation and experience of peak emotion to music. Nature Neuroscience, 14(2), 257-262.

Sossi, V., Fuente-Fernández, R. D., Holden, J. E., Doudet, D. J., Mckenzie, J., Stoessl, A. J., & Ruth, T. J. (2002). Increase in Dopamine Turnover Occurs Early in Parkinsons Disease: Evidence from a New Modeling Approach to PET 18F-Fluorodopa Data. *Journal of Cerebral Blood Flow & Metabolism, 22*(2), 232-239.

Sutoo, D., & Akiyama, K. (2004, June 19). Music improves dopaminergic neurotransmission: Demonstration based on the effect of music on blood pressure regulation.

Sutton, R. S., & Barto, A. (2018). *Reinforcement learning: An introduction*.

Tasset, I., Quero, I., García-Mayórgaz, Á D., Río, M. C., Túnez, I., & Montilla, P. (2012, February 28). Changes caused by haloperidol are blocked by music in Winstar rat.

Whitton, A. E., Treadway, M. T., & Pizzagalli, D. A. (2015, January). Reward processing dysfunction in major depression, bipolar disorder and schizophrenia.

Young, C., Chen, T., Nusslock, R., Keller, J., Schatzberg, A., & Menon, V. (2016, May 17). Anhedonia and general distress show dissociable ventromedial prefrontal cortex connectivity in major depressive disorder.

Zatorre, R. J., & Salimpoor, V. N. (2013, June 18). From perception to pleasure: Music and its neural substrates.

Zatorre, R. J. (2015). Musical pleasure and reward: Mechanisms and dysfunction. Annals of the New York Academy of Sciences, 1337(1), 202-211. doi:10.1111/nyas.12677