

Effects of Music on the Psychopathology of Obsessive Compulsive Disorder (OCD)

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Abstract

Music has shown to be a powerful tool for both treating and enhancing the treatment of various mental health issues such as anxiety and depression. However, whether it can be a potential treatment method for patients with OCD is a topic to be explored in this following review article. OCD is a common psychiatric disorder that affects over 1% of the global population. Its symptoms can be debilitating and hence affect patients on multiple levels of their daily lives, including work, relationships, and physical health. The most common treatment methods remain to be antidepressants and cognitive behavioral therapy (CBT). However, many patients fail to respond well to medication, while CBT poses challenges such as difficulties in reappraisal. In this article, I will explore how music can reduce the symptoms of OCD through reducing the hyperactivity of the association loop, reducing anxiety, and enhancing dopaminergic systems required for extinction learning.

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Introduction

I. Overview

Obsessive Compulsive Disorder (OCD) is a psychiatric disorder characterized mainly by the repetition of anxiety-inducing obsessive thoughts in individuals who then compulsively perform specific rituals to normalize that thought (American Psychiatric Association, 2013). It affects approximately 1-3% of the population worldwide (Hasler et al., 2005). Patients with OCD often display their symptoms in different ways; hence researchers believe that it is a heterogeneous condition (Hasanpour et al., 2017). It generally consists of several core domains including checking, cleaning, rituals, and symmetry. Overlying these domains are the two underlying causes of these behaviors, namely obsessions followed by compulsions driven by the need to relieve excessive anxiety (Stasik, Naragon-Grainey, Chmielewski, & Watson, 2012). In the context of OCD, obsessions are defined as intrusive and unwanted thoughts, ideas, and images. Patients usually experience obsessions in specific areas such as seeing horrific images relating to blasphemy, sexual ideas, or violent images or in the form of thoughts relating to contamination or whether some action is completed or not (McKay et al., 2014). Compulsions, on the other hand, are defined as specific behavioral actions such as ordering, counting, cleaning, checking and even covert mental rituals, all of which are performed in attempt to neutralize the obsessions or to verify behaviors that are in doubt (McKay et al., 2014). Both obsessions and compulsions are forms of cognitive inflexibility that are shown in patients with OCD (Lapidus et al., 2014). Because of these cognitive inflexibilities, the quality of life for patients with OCD are considerably affected. In fact, research has shown that obsession severity significantly predicts patients' quality of life (Masellis, Rector, & Richter, 2003).

II. Diagnostic Criteria:

Stasik et al. (2012) suggest that maladaptive beliefs related to responsibility, overestimation of threat, and intolerance of ambiguity are among the various reasons contributing to the development of OCD symptoms. Because of the heterogeneity as well as complexity of the condition, there are various forms of measurements for the symptomology of OCD. Of the most common and comprehensive types of diagnostic methods is the Yale-Brown Obsessive Compulsive Scale (Y-BOCS) which consists of a symptoms checklist and a severity scale. The checklist includes fifteen categories, the first eight of which are the different manifestation of obsessions and the following seven are the different behavioral compulsions (Hasanpour et al., 2017). Raters are to check all that applies to them and state whether each symptom is current or from the past (Y-BOCS). The severity scale includes ten items anchored on a 5-point scale that assesses distress, frequency, interference, resistance, and symptom control of obsessions and compulsions (Storch, Benito, & Goodman, 2011).

III. Treatment Methods

Though several treatment methods have shown to be beneficial for OCD, large discrepancies between individual responses to these methods remain. The unpredictability of medication effects on individuals can perhaps be explained by the heterogeneity of the disorder. Nevertheless, most patients improve upon taking selective serotonin reuptake inhibitors (SSRI's), most commonly in the form of Sertraline HCl (Stein, 2002). This is the first line treatment for OCD. SSRI's work by inhibiting the reuptake mechanism of serotonin at brain synapses, thereby prolonging the effects of serotonin. Though it is shown that Sertraline HCl can significantly reduce patients' OCD symptoms, the link between its mechanism of action and OCD psychopathology remains uncertain.

Despite being the first line treatment due to its safety and efficacy, SSRI's nevertheless only have a 40-60% response rate, leaving at least 20-30% of the patients untreated by medication alone (Karamah & Khani, 2016). Thus, other treatment methods are developed. Another common method of treatment for OCD is called cognitive behavioral therapy (CBT). This method consists of two components, exposure with response prevention (ERP) and cognitive therapy (CT) (McKay et al., 2014). During ERP, patients list out their symptoms from least to most fear-inducing. They are then exposed to items on this hierarchy accompanied by the prevention of action performances that are normally done to reduce anxiety. In addition to ERP, CT is incorporated to help patients reappraise their beliefs. Many OCD patients have dysfunctional appraisal of certain beliefs, for instance, the perception of inflated responsibility or overestimation of threat, all of which lead them to perform extra behavioral rituals to compensate for the severity of the perceived situation (McKay et al., 2014). With reappraisal, patients can learn that their obsessive thoughts are not a threat nor something that precedes an aversive outcome; hence, their compulsive actions may be omitted (McKay et al., 2014). Nevertheless, just like the challenges encountered with medication treatment, CBT also works on different individuals at various levels, once again reflecting the heterogeneity of OCD (McKay et al., 2014).

On top of CBT, other less common medications have been used to combat patients' lack of response to SSRI's. Clomipramine is one example that patients can either take orally or, in more severe cases, can receive intravenously (Karamah & Khani, 2016). Augmentation of various other medications including buspirone, pindolol, and riluzole on top of SSRI administration can also be helpful in certain cases (Karamah & Khani, 2016). Some single drug alternative therapy includes the use of tramadol, ondansetron, monoamine oxidase inhibitor, or

D-amphetamine (Karamah & Khani, 2016). In more severe cases, transcranial magnetic stimulation (TMS) as well as deep brain stimulation (DBS) can also be applied to patients with poor responses to medication (Karamah & Khani, 2016).

IV. Comorbidity

To add to the complexity of OCD, this multidimensional disorder is also one that can easily be diagnosed with comorbid psychopathologies. Statistically speaking, around 90% of respondents with lifetime OCD meet criteria for another lifetime disorder. The most common comorbid conditions are anxiety disorders (75.8%), followed by mood disorders (63.3%), impulse-control disorders (55.9%), and substance use disorders (38.6%) (Ruscio, Stein, Chiu & Kessler, 2008). There are also other types of comorbidities that are diagnosed due to their overlapping symptoms with OCD. One example of which is Tourette's syndrome, where patients perform unwanted and repetitive motor responses (Nordstrom & Burton, 2002). Another example is attentional deficit hyperactive disorder (ADHD), where patients are often involved in compulsive actions. In one study, impulsivity, symmetry obsessions, and hoarding compulsions strongly predicted the coexistence between OCD and ADHD (Kilic, Dondu, Memis, Ozdemiroglu, & Sevincok, 2016). Another study done by Hofmeijer-Sevink et al. (2017) showed that obsessive compulsive symptoms (OCS) are closely related to both the presence and severity of anxiety and depressive disorders; moreover, they affect the course trajectory of these comorbid disorders. These findings may implicate the need of different combinations of treatment methods for the alleviation of comorbid disorders.

Neural Mechanisms of OCD Psychopathology

I. The CSTC Loop and Cognitive Inflexibility

As mentioned earlier, OCD symptoms are a form of cognitive inflexibility, and this deficiency is revealed through a variety of cognitive flexibility tests. Patients with OCD have shown longer reaction times on the Stroop Task (Stroop, 1935) when compared to healthy participants (Peles, Weinstein, Sason, Adlson & Schreiber, 2013). They have also shown higher rates of perseverative error on the Wisconsin Card Sorting Task (WCST: Berg, 1948) when compared to healthy participants, suggesting the presence of a deficit in attentional set shifting (Gruner & Pittenger, 2017). In addition, patients with OCD showed decreased accuracy and increased perseveration in the Object Alternation Task (OAT) and Delayed Alternation Task (DAT), respectively (Gruner & Pittenger, 2017). Accordingly, out of all the executive functions, patients with OCD showed the greatest deficit in updating working memory, which is a key to cognitive flexibility (Gruner & Pittenger, 2017). Lastly, another measure of cognitive flexibility is the Object Interference Task, in which patients with OCD showed reduced task control and this deficit is shown to be positively correlated with patients' symptom severity (Kalanthroff, Henik, Simpson, Todder & Anholt, 2017).

To understand the underlying causes of cognitive inflexibility, let us explore a type of neural circuit called the Cortical-Striato-Thalamo-Cortical (CSTC) Loop. This type of brain circuit regulates several important cognitive functions including affect, working memory, problem solving, motor control, cognitive inhibition and flexibility (Lapidus, Stern, Berlin, & Goodman, 2014). The three main CSTC circuits are the associative, motor, and affective loops, each of which involves the projection of a cortical region to the striatum, which then projects to the thalamus and back to the original cortical regions. There are two main pathways to the

circuit, the direct and the indirect paths. In the direct path, excitatory glutamatergic signals project from the cortex to the striatum, which then sends inhibitory GABAergic signals to the internal globus pallidus. The internal globus pallidus then disinhibits the thalamus, resulting in an increased excitatory effect on the cortex (Bear, Connors & Paradiso, 2016). Due to its self-reinforcing mechanism, this path is often referred to as the positive feedback loop. On the other hand, striatum in the indirect pathway projects inhibitory signal to the external globus pallidus that normally excites the subthalamic nucleus for the inhibition of the internal segment of the globus pallidus. This ultimately results in the inhibition of the thalamus by the internal segment of the globus pallidus and decreased cortical excitation (Bear et al., 2016). Hence, this pathway is an example of a negative feedback loop that regulates the inhibition and switching of behaviors. These two opposing loops work in concert to regulate several cognitive functions.

Patients with OCD have consistently displayed imbalances between the direct and indirect pathways of several CSTC loops (Heuvel et al., 2015). Most prominently reported is the hyperactivity in their associative CSTC circuit, direct path. Specifically, in this loop, the dorsolateral prefrontal cortex and the lateral orbitofrontal cortex project to the caudate nucleus, which then projects to the striatum. The anteromedial putamen receives direct input from the caudate and innervates the internal globus pallidus that projects to the ventroanterior nucleus of the thalamus. Lastly, the loop ends with the thalamus projecting back to the frontal cortices (Lapidus et al., 2014). Since glutamate is the main neurotransmitter output of cortical pyramidal neurons innervating the striatum, it thus plays a major role in the underlying causes for abnormalities within the CSTC loops (Stahl, 2008).

The cognitive inflexibilities of patients with OCD are thought to be the results of the hyperactivity within their associative CSTC circuit (Lapidus et al., 2014). Patients with OCD

have been reported to have increased connectivity between their caudate nucleus and orbitofrontal cortex and dorsolateral prefrontal cortex, both of which are part of the associative CSTC circuit (Chen et al., 2016). This is accompanied by the hyperactivation of their orbitofrontal cortex (OFC), caudate nucleus, thalamus, and putamen, all of which together works to regulate cognitive flexibility within the circuit (Goncalves et al., 2016). In fact, increased connectivity between the OFC and putamen is positively correlated with OCD symptom severity (Beucke et al., 2013). This hyper-influence of the OFC over the ventral striatum (VS) is most likely a reflection of increased glutamate release in the OFC (Abe et al., 2015). In accordance to this claim, others also hypothesize that the hyperactivity in the CSTC circuit is induced by elevated level of glutamate in the circuit and this abnormality leads to repetitive thoughts (Simpson et al., 2015). Moreover, it is found that the disinhibition of the circuit ultimately results in hardwired behaviors (compulsions) and cognitions (obsessions) (Wu, Hanna, Rosenberg & Arnold, 2012).

Fortunately, a plethora of research study supports this hypothesis on the glutamatergic influence over the CSTC circuits in patients with OCD. Normally, tonic glutamate activity in the prefrontal cortex (PFC) has an inhibitory effect on the phasic glutamate activity in the striatum. However, disturbances of tonic glutamate in patients with OCD increases the phasic glutamate of the striatum, which is known to be involved in compulsivity (Naaijen, Lythgoe, Amiri, Buitelaar, & Glennon, 2015). A study done by O'Neill et al. (2016) took magnetic resonance spectroscopy measurements of glutamate neurometabolites within patients with OCD and their matched controls. When compared to healthy controls, patients had an elevated level of Glx (glutamate + glutamine) in their thalamus and that this high thalamic glutamate activity within patients correlated positively with their anxiety severity. The greater the Glu receptor stimulation the

more neuronal energy is needed by using creatine and phosphocreatine to produce ATP. As a result, patients' creatine and phosphocreatine levels correlated negatively with their Y-BOCS scores. Consistent with this idea, the substantial neuronal energy needed to drive severe symptoms diverts less glucose to the synthesis of choline-containing molecules. Hence, the choline level within patients is also negatively correlated with their Y-BOCS scores (O'Neill et al., 2016). Another study confirmed that glutamate level in the thalamus of patients with OCD correlates positively with their anxiety severity (Fan et al., 2016). In line with the hyperactive CSTC circuit theory, Glx concentrations are also found to be greater in the left caudate as well as the cerebrospinal fluid of patients with OCD when compared to their matched controls (Wu et al., 2011). Yet another finding that supports the glutamatergic theory of OCD lies in the patients' response to a drug called Riluzole. This drug inhibits voltage-gated Na⁺ channels and P/Q type Ca²⁺ channels, both of which normally inhibit synaptic glutamate release and stimulate glutamate uptake by astrocytes. When treated with Riluzole, more than half of the participants with OCD showed significant symptom improvement (Wu et al., 2011). In addition, memantine, an N-Methyl-D-aspartic acid (NMDA) antagonist has shown to be effective in augmenting the treatment for OCD symptoms (Wu et al., 2011).

II. The Role of Anxiety

Prior to The Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5), OCD was categorized as a type of anxiety disorder (Fontenelle et al., 2011). Despite its new categorization into Obsessive Compulsive and Related Disorders (OCRD), anxiety remains to be key factor in the psychopathology of OCD (Goodwin, 2015). Not only do patients with OCD constantly encounter anxiety-inducing thoughts, the comorbidity of OCD and anxiety disorders are also highlighted (Briggs & Price, 2009). OCD symptoms are often considered to be the result

of high anxiety sensitivity (Calamari et al., 2008). Moreover, patients with OCD generally show significantly higher scores on both the Beck Anxiety Inventory (BAI: Beck, Epstein, Brown & Steer, 1988) and the State-Trait Anxiety Inventory (STAI: Spielberger, 1989) when compared to healthy controls (Parrish & Radomsky, 2009).

Within patients with OCD, anxiety is often associated with obsessions over a feeling that something is incomplete, wrong, or that terrible consequences will ensue if specific actions are not taken (Russo & Pietsch, 2013). This anxiety is the key component of the two major OCD symptoms, obsession and compulsion, without which these symptoms are not fueled. In a study done by Tolin, Worhunsky & Maltby (2004), obsessive beliefs in patient with OCD and anxiety disorder (AD) were assessed in a study using the Obsessional Beliefs Questionnaire (OBQ). Scores for the two groups did not differ, indicating that obsessive beliefs are a result of the psychopathology underlying anxiety (Tolin et al., 2015). Moreover, a study done on 248 OCD patients showed that the OBQ scale was strongly correlated with measures of anxiety and worry (Tolin et al., 2015). Though correlation does not always reflect causation, this strong link between anxiety and obsession suggests that one cannot be present without the other. Surprisingly, when compared to AD, patients with OCD showed an even higher level of anxiety traits when measured by the STAI (Tolin et al., 2015). This should alarm psychiatrists of the massive role that anxiety plays on aggravating obsessions. As directly mentioned by Muller & Roberts (2005), “[obsessive] thoughts are fueled by emotions that emerge effortlessly in response to stressful situations”. Since, “ideas that are fueled by [anxiety] are often distorted and less reliable”, CBT serves to restructure patients’ cognition so that more realistic views of situations can replace distorted views of reality (Muller & Roberts, 2005).

Likewise, compulsions are also driven by anxiety. One study has shown that chronic potentiation of D1 neurons in the amygdala of rats increases anxiety and facilitates certain compulsive behaviors (McGrath, Campbell, Veldman & Burton, 1999). This shows that increases in anxiety parallels with increases in compulsive behaviors in rat models. Again, associations do not always mean causation, and further studies need to be done to confirm this relationship between anxiety and compulsion in rats. Nevertheless, such correlation is also present in human participants. Excessive reassurance seeking (ERS) is a characteristic feature of patients with OCD. It is a strategy that patients use to diminish their obsessional thoughts and is thus a variant of compulsive checking for the reduction of anxiety and minimization of negative outcomes. The most common trigger for this behavior is anxiety, and is continually reinforced by temporary anxiety reduction (Parrish & Radomsky, 2009). That means, if anxiety can be reduced by some therapeutic means, these ERS behaviors can possibly be reduced if not eradicated. This is further supported by the fact that most OCD patients report that their principal reason for checking is for reducing their anxiety. For example, they often claim that it is “to make sure I get a good grade”, or “to make sure no one will enter the house” (Parrish & Radomsky, 2009). These studies all point to the idea that anxiety fuels compulsive behaviors.

This elevated level of anxiety in patients with OCD can be measured physiologically as well. Amygdala is crucial for detecting salient events and can initiate a cascade of psychological and physiological processes that lead to an anxious state. Patients with OCD showed increased amygdala connectivity with the fronto-parietal network during emotional face processing, working memory performance, and response inhibition when compared to healthy controls (Heuvel et al., 2015). Another predictor and indicator of anxiety level is cortisol, a hormone that is released in response to stressful situations (Hakamata et al., 2017). Patients with OCD have an

increased secretion of cortisol when compared to healthy controls (Monteleone, Catapano & Buono, 1994). Moreover, this higher cortisol level in OCD patients is positively correlated with symptom severity (Y-BOCS) scores (Furtada & Katzman, 2015). This correlation extends to young populations of ages 8 – 17, where girls more so than boys at this age show a positive correlation between social anxiety and cortisol level (Schiefelbein & Susman, 2006). Moreover, individuals with chronic anxiety have higher levels of morning cortisol when compared to healthy controls (Greaves-Lord et al., 2007). Interestingly, a study done by Dettmer, Novak, Suomi & Meyer (2010) shows us that hair cortisol is a biomarker of anxiety-related responses. Rhesus monkeys that were reared in stressful environment showed greater anxiety behaviors and higher cortisol level. The link between cortisol and anxiety is further solidified by its generalizability across various stressful situations. A positive correlation was found between anxiety and salivary cortisol levels in patients suffering from oral lichen planus (Nadendla, Meduri, Paramkusam & Pachava, 2014). In addition, Keshavarzi et al. (2014) presented data suggesting that high maternal trait anxiety increases fetus cord blood cortisol. Likewise, correlations between anxiety and cortisol don't fall short in OCD patients, who show an elevated cerebrospinal fluid (CSF) corticotropin-releasing factor (CRF) when compared to healthy controls (Hakamata et al., 2017). The main function of CRF is the stimulation of the adrenocorticotropic hormone (ACTH) synthesis which synthesizes cortisol (Arborelius, Owens, Plotsky & Nemeroff, 1999). Accordingly, the OCD treatment method of using deep brain stimulation at the nucleus accumbens (NAc) reduces cortisol level in patients (Koning et al., 2012). To explore deeper on the effects of stress and cortisol level on patients with OCD, high stress or high cortisol level can in fact decrease the amount of serotonin available for use in the body. Studies on human immune and brain cells suggests that cortisol can decrease serotonin levels in the brain (Tafet, Toister-

Achituv & Shinitzky, 2001). This brings the effects of anxiety to the molecular level, and poses the question on what happens in the brain when serotonin is depleted. Since, SSRI's are the first line treatment for OCD, this rise in the cortisol level due to anxiety implicates the aggravation and induction of OCD symptoms.

III. Dopamine Dysregulation

Glutamate dysregulation at the CSTC circuit is not the only culprit for causing OCD symptoms, dopamine (DA) dysregulation is also manifested in these patients. Wood, LaPalmbara & Ahmari (2017) conducted a study on SAPAP-3 knock-out (KO) mice, a type of animal model for OCD symptoms. They found an increased dihydroxyphenylacetic acid/dopamine ratio as well as HVA/dopamine in the KO mice's lateral OFC when compared to the control mice. These ratios suggest a high dopamine turnover in patients with OCD as well as the presence of monoaminergic dysregulations. Sometimes high turnover rate does not reflect higher activity at synapse, but simply higher rates of neurotransmitter breakdown, and may even lead to lower activity at the synapse. For example, high serotonin turnover rate has been indicated in depression which is treated by SSRI's (Bartoon, Esler, & Dawood, 2007). This may suggest that high DA turnover may require treatment that increases DA. Yet, some researchers would argue that it is the increased activation of DA receptors that leads to OCD-like behaviors. For example, a study was conducted by Campbell et al. (1999) to discover the behavioral role of neurons that contain D1 receptors. They created transgenic mice that expressed an enzyme that chronically activated D1 cells. These transgenic mice expressed a group of compulsive-like behaviors that strongly matched those expressed in patients with OCD. Nevertheless, imaging data suggests that there is both an increased and decreased dopamine transporter binding in patients with OCD (Denys et al., 2004; van der Wee et al., 2004; Hesse et al., 2005; Klanker et al., 2013). D1 and

D2 receptors are very different in nature, and hence this finding within D1 cells may not be generalized to D2 cells. The question lies in what accounts for the discrepancy in these findings.

D1 and D2 are two main opposing types of DA receptors. The D2-like receptor subfamily includes D2, D3 and D4 receptors, which are specifically coupled to $G_{\alpha i}$ and $G_{\alpha o}$ proteins. Upon ligand binding, G_{α} proteins promote the replacement of GDP by GTP and the α -subunit dissociates from the $\beta\gamma$ complex. At this point both the α -subunit and the $\beta\gamma$ -complex are free to transduce a signal and activate several effector systems. The $G_{\alpha i}$ and $G_{\alpha o}$ subfamilies downregulate the production of cyclic AMP via the inhibition of adenylyl cyclase (AC), leading to a reduced activation of protein kinase A (Missale, Nash, & Robinson, 1998). On the other hand, D1-like receptor subfamilies consists of D1 and D5 receptors, which are coupled to G_s proteins. This ultimately leads to the stimulation rather than the inhibition of AC, leading to increased activation of protein kinase A (Koshikawa, Fujita & Adachi, 2011). Due to the differences in nature of D1 and D2 receptors, the way they effect OCD symptoms are also distinctive. For example, D1 agonists were needed to cause super-stereotypy of syntactic grooming chains within mice, while D2 agonists reduced initiation and completion of these grooming chains (Berridge, Aldridge, Houchard & Zhuang, 2005). More recent findings show that it is rather the antagonism of DA that can exacerbate symptoms (Denys et al., 2004; Klanker et al., 2013; Simpson et al., 2013). A meta-analysis done by Ducasse et al. (2014) looking at five different OCD antipsychotic drugs and 13 randomized controlled trials showed that increases in D2 and D3 dopamine binding affinities can enhance antipsychotics' effects in OCD treatment. Yet, there people who argue that OCD is induced by the activation of D2 receptors due to research done on the induction OCD-like behavior by quinpirole, a D2 agonist (Szechtman, Sulis & Eilam, 1998). However, we must note it had to be chronic not just temporal injection of

quinpirole that was able to produce this observed OCD-like behavior within subject mice. Moreover, D2 receptors are present in many different brain circuits, and hence this may be the effect on the D2 receptors within the nigrostriatal pathway as opposed to the reward pathway that produced OCD-like behavior. To further counter argue this claim that D2 receptor activation induces OCD behaviors, the most effective antipsychotic found to work against OCD symptoms happen to be Aripiprazole, a D2 partial agonist that has the same affinity to D2 as does dopamine (Dold, Aigner, Lanzenberger & Kasper, 2015). Aripiprazole is thought to stabilize DA and serotonin activity within the nucleus accumbens (NAc). Hence, it could be that D2 agonists within the NAc could reduce OCD symptoms, while the induction of dopamine receptors within D1 and perhaps D2 receptors within other brain regions may display opposite effects. These studies point to the possibility that D1 and D2 receptors within distinct neural circuits may play different roles in the alteration of OCD symptoms.

Because of the prevalence of D2 receptors within the NAc, let's explore the role of NAc on OCD symptoms as well. Complimentary to DA dysregulation in OCD pathophysiology, there are quite a few evidences pointing to the effects of treating OCD through the activation of the NAc. The NAc stores and projects DA to various cortical areas in the brain, primarily the mPFC (Bear et al., 2016). By performing DBS on the NAc, compulsive checking in rats are significantly reduced, which shows that the NAc core and shell constitute potential target structures for the treatment of OCD (Mundt et la., 2009). When done on humans, bilateral DBS of the NAc resulted in a 50% reduction in participants' OCD symptoms (Denys et al., 2010). Also, a recent study by Figeet al. (2013) showed that DBS targeted at the NAc normalizes the previously blunted activity of NAc in patients with OCD, when compared to healthy controls. Moreover, this normalization and increase in activity of the NAc upon DBS is accompanied by reduction in

OCD symptoms (Figuee et al., 2013). Though some argue that activities in the NAc are responsible for compulsions, Denys et al., (2010) showed that lesions in the NAc core did not reduce compulsivity. Likewise, even after NAc lesion, quinpirole still induced OCD-like behaviors, showing that the induction of OCD-like behavior lie outside the NAc (Gonzalez, Dvorkin-Gheva, Silva, Foster & Szechtman, 2015).

Proposals for the Effects of Music on OCD

I. Effects of Music on other Psychopathologies

The purpose of this thesis is to explore the positive effects that music could potentially bring to the alleviation of OCD symptoms and the treatment of this psychopathology. Music therapy has been around since the end of World War I and II, when musicians performed at Veterans hospitals for those who were physically and emotionally traumatized by the wars. From that point, the effects of music therapy began to be apparent and this practice continued to move forward from both an educational and organizational standpoint up till today (Horden, 2000). Many current studies indicate that music therapy benefits multiple psychopathologies and mental health issues. One study showed that both active and receptive music therapy served as an adjunct therapy for patients with major depressive disorder (MDD). Patients who received music therapy on top of their primary treatment reached their peak therapeutic effects faster than those who did not receive the adjunct therapy (Atiwannapat, Thaipisuttikul, Poopityastaporn & Katekaew, 2015). Similarly, a randomized control trial conducted on 79 patients with depression, aged 25-60 showed that those who underwent music therapy had fewer depressive symptoms when compared to those who underwent psychotherapy (Castillo-Perez, Gómez-Perez, Velasco, Perez-Capos & Mayoral, 2010). Since depression is often comorbid with other psychopathologies, the effects of music therapy can extend to the improvement of symptoms in

patients with other mental health disorders as well. An example is the effects of music therapy on the reduction of depressive symptoms in patients with schizophrenia (Kavak, Unal & Yilmaz, 2016). This is an example for which the benefits of music therapy are not limited to the most common disorders but may extend to improving those that affect specific cohorts of people, possibly even patients with OCD, as I will discuss in the following subsections.

II. Music and Cognitive Flexibility

It has been reported that musical training has a large association with executive functions. An instrument player in a band or orchestra must constantly listen and attend to multiple auditory streams of music to coordinate with the group. They also continuously adjust their volume, tempo, and timbre according to the music piece. Simultaneously, they're reading the sheet music with extra notes that they have written, all of which must be held in their short-term memory before playing them out. These parallel processes require extensive cognitive flexibility (Okada & Slevc, 2016). The term "Mozart Effect" was first introduced in a study showing how passive music exposure can lead to improvement in cognitive functioning (Okada & Slevc, 2016). Accordingly, studies have shown that musicians out-perform non-musicians in several cognitive flexibility tests, including the Trail-Making Test (Hanna-Pladdy & Mackay, 2011) and in cued task-switching (Moradzadeh, Blumenthal & Wiseheart, 2015). Adjusting one's own playing to that of other performers not only require the shifting of attention, but also exercise inhibitory control to monitor for conflict as well as control one's performance (Jentzch, Mkrtchian, & Kansal, 2014). The skills required of musicians likely call upon cognitive flexibility skills. Hence, playing a musical instrument may potentially benefit patients with OCD by improving their major source of symptom, cognitive inflexibility.

While playing in a band or an orchestra can train instrument players to be cognitively flexible, patients with OCD may not have the advantage to excel in such settings. Fortunately, instrumental playing is not the only way music can help with OCD. Studies have found that melodic music can increase the release of serotonin in the brain (Moraes et al., 2018). In fact, SSRIs are the first line treatment for OCD (Kellner, 2010). Yet little connection or implication has been attributed to the neural mechanisms whereby SSRIs work in patients with OCD. Interestingly, the associative CSTC loop as previously mentioned is modulated by external serotonergic projections arising from the raphe nucleus (Geyer & Vollenweider, 2008). The raphe nucleus projects serotonin to the frontal cortex, globus pallidus, as well as the thalamus in the CSTC circuit. In one study, not only did 5-HT₆ receptor agonists attenuate stimulated glutamate levels, but it also displayed anti-OCD-like behavior in rats (Schechter et al., 2008). Moreover, paroxetine, an SSRI, is found to reduce caudate glutamate (Rosenberg et al., 2000). In addition, SAPAP, a type of postsynaptic protein directly binds to a protein family known to regulate the trafficking of both NMDA and AMPA glutamate receptors, which make up the core of the CSTC loop synapses. Mice with SAPAP mutation have displayed OCD-like symptoms, which are reversed by fluoxetine administration (Welch et al., 2007). These evidence all points to the serotonergic effects on the regulation of glutamate levels. Thus, music therapy could potentially alleviate OCD symptoms by increasing serotonin levels for the regulation of glutamate hyperactivity in the CSTC loop.

Another avenue for music to improve cognitive flexibility within patients with OCD is through the induction of positive mood. “One of the most robust and widely confirmed findings in the affect literature is that positive affect increases cognitive flexibility” (Isen, 2002). Results from a study done by Dreisbach and Goschke (2004) showed that increases in positive affect as

opposed to neutral or negative affect, promoted cognitive flexibility and reduced perseveration. Moreover, another study suggests that the explanation for the hedonic contingency theory is the link between positive mood and cognitive flexibility. In their study, the happy participants exhibited measurements of greater cognitive flexibility in all three scenario cases (Hirt, Devers & McCrea, 2008). The effect of positive affect on cognitive flexibility is rather comprehensive, it even contributes to consumer investment behaviors. A study done by Emich and Pyone (2017) showed that inducing positive affect increases cognitive flexibility as shown through the reduction of sunk cost bias within participants. Sunk cost bias occurs when people continue to invest their resources towards unsuccessful outcomes simply because they previously invested in them. Individuals with induced positive mood were less affected by the sunk cost bias as opposed to the control group (Emich and Pyone, 2017). Another study done with 120 participants showed that the group assigned to positive affect conditions showed reduced switch cost during the switch task, a measure of cognitive flexibility; moreover, the same group also showed enhanced performance on two other measures of creativity (Lin, Tsai, Lin & Chen, 2014).

While much research has been dedicated to solidifying the effects of positive mood on cognitive flexibility, it is just as common to find literature presenting the effects of music on positive mood induction. Karreman, Laceulle, Hanser & Vingerhoets (2017) showed that music has an enhancing effect on mood, whether it is positive or negative depends on the type of music. Within their study, the group that underwent music intervention showed a much greater post emotional intensity when compared to the control group. It is not surprising to see such results, since the creation of mood within a movie is most often contingent upon the music that accompanies the dramatic scenes. Similarly, another study showed that participants who listened

to positive music reported more positive mood in comparison to those who listened to aversive or neutral music. Moreover, the reported positive mood was correlated with less anger shown during provocation, further indicating the powerful effects of music on mood (Krahe & Bieneck, 2012). Not only does music effect people's mood in face of aggressive, it also alleviates stress. In a study conducted by Koelsch et al. (2016), participants who listened to music showed greater positive mood when compared to those who did not listen to music, when both groups underwent CO₂ stress test. Knowing that music can be used to manipulate and adjust mood, many researches were done to show the effects of music on creating positive mood in patients who are suffering from different medical conditions. For example, music therapy was shown to improve the mood of stroke patients as measured by the BAI as well as the Beck Depression Inventory (BDI) (Kim et al., 2011).

When considering music therapy strategies, music composition and improvisation are preparatory activities for training cognitive flexibility. They both involve arranging and rearranging the elements of pitch and rhythm over time, which is believed to exercise executive functions and promote cognitive flexibility. Also, it is suggested that the reason why our ancestors could sing and dance for hours on end, creating variations on themes was primarily to show their cognitive flexibilities and fitness to their mates. Both skills are essential when food supply runs out or when there's a need to build a new shelter or escape from predators within a short period of time (Levitin & Tirovolas, 2009). Another effective practice for increasing cognitive flexibility would be sight-singing exercises. The triplet and duple organization of notes forces participants to switch and process information in novel ways (Bugos & Mostafa, 2011). In addition to composition and improvisation, playing an instrument is also a great way to increase cognitive flexibility. Piano playing was shown to have direct influence on the improvement of

cognitive flexibility in participants of all ages. Older adults have shown improvements on the Stroop Task performance following a piano learning program that lasted for four months, while the control group who did not undergo the piano program did not show such a pattern of improvement (Seinfeld, Figueroa, Ortiz-Gil & Sanchez-Vives, 2013). Another study compared the cognitive flexibility between adult musicians (total participants = 15; pianists = 6) and adult non-musicians as well as that between children musicians (total participants = 15; pianists = 5) and children non-musicians. Both groups of adult and children musicians showed better performances on a series of cognitive flexibility tests including the trail-making test, verbal fluency, and design fluency (Zuk, Benjamin, Kenyon, & Gaab, 2014). Moreover, piano lessons decreased depression severity and induced positive mood states, within elderly participants (Seinfeld et al., 2013). The comprehensive effects of piano playing make it an incredible incorporation for music therapy.

III. Music and Anxiety Reduction

As previously argued, anxiety is the ultimate fuel for OCD symptomology, mainly obsessions and compulsions. It is thus essential to focus on the reduction of anxiety for the treatment of OCD symptoms. Music has proven to be effective in reducing anxiety as shown through a series of research studies on the effects of music therapy on patients suffering from various forms of anxiety. For example, music therapy was shown to reduce anxiety in generalized anxiety disorder (GAD) (Gutierrez & Camarena, 2015). It can also reduce anxiety in patients with Alzheimer's Disease and breast cancer (Guetin et al., 2009; Bulfone et al., 2009). Recall the last time you were at a dentist, there most likely was some mellow classical music playing in the background. It is not by chance that many dental clinics play classical music, because low arousal classical music can shift subjects into a relaxation state (Lynar et al., 2017).

In fact, a study conducted by Chen (2018) shows that Mozart regulates the Glu/GABA ratio in rat hippocampus and thereby reduces anxiety. This effect extends to humans as well, where music is often used as an adjunct therapy for anxiety reduction. Bidabadi & Mehryar (2015) conducted a study on seeing the effects of music therapy on OCD symptomology. The group that underwent music therapy had a significantly greater reduction in total obsessive scores as well as anxiety when compared to the group of patients that did not undergo music therapy. While listening to music can reduce anxiety, playing a musical instrument can also have the same effect (Matney, 2017). In a study done by Toyoshima, Fukui & Kuda (2011), 57 college students were divided into four groups, each participated in 30-minute sessions of either piano playing, non-musical creative activities or control activities. Those who participated in piano playing had the greatest reduction in stress as measured by the STAI and cortisol level when compared to all the other groups. While we are on the topic of cortisol level, recall back to the supporting evidence on how the physiological underlying factor for anxiety is an increase in cortisol level. In agreement with the idea that music therapy reduces anxiety, Bach's Magnificat has shown to reduce cortisol level in patients with infectious lung conditions (Le Roux, Bouic & Bester, 2007). Moreover, salivary cortisol after stress induction can be reduced by listening to music (Khalifa, Bella, Roy, Peretz & Lupien, 2003).

IV. Music and the Dopaminergic System

Lastly, some people might wonder why patients with OCD can't just stop associating irrelevant events together or simply cut off these illogical mindsets. The answer could very well lie in the dysregulation of DA in these patients that leads to their difficulty in reversal learning. However, by recognizing the problem, we can find potential treatment methods to overcome this deficit. Though it may seem far stretched to claim that music can reduce the symptoms of OCD

through the mediation of fear extinction, there are evidence supporting the necessity of DA for both extinction learning and OCD symptoms reduction. Before we delve deeper into evidence on the role of DA receptors and NAc in extinction learning, let's look at why extinction learning is a topic of interest when looking at treatment methods for OCD. Currently, the most effective method of OCD treatment is CBT. OCD was once considered as a disorder acquired through classically conditioned fear responses, and maintained through negatively reinforced avoidance response (Mowrer, 1960). Fortunately, extinguishing negative conditioned associations via exposure to symptom provoking stimuli has proven efficacious in OCD patients (Foa et al., 2005; Franklin and Foa, 2011; Simpson et al., 2013; Lewin et al., 2014; Ludvik et al., 2015). Hence, exposure therapy, a common technique used in CBT is developed for treating OCD patients who didn't respond well to medication. The central target in exposure treatment is the fear structure that is stored in memory (Foa & Kozak, 1986). Such treatment is conducted in a way that sufficiently arouses the fear structure but not so much that near learning cannot be accomplished (McKay et al., 2014). Thus, patients start off with fear-inducing stimuli from the lower end of the hierarchy and slowly advance. The reason for preserving the ability to accomplish fear learning is because the action of CBT overrides a previously learned association with a newly learned association (Hofmann & Smits, 2008). This is in fact comparable to the idea of extinction learning. Ever since Pavlovian learning was discovered almost a century ago, researchers have found that extinction of classical conditioned association does not erase the previous learning, rather the change in context or presentation can easily trigger the relapse of the previously learned behavior (Dunsmoor, Niv, Daw & Phelps, 2015). This strengthens the idea that extinction is in fact a new learning rather than the elimination of a previous learning. "Like other forms of learning, extinction occurs in three phases: acquisition, consolidation,

and retrieval” (Quirk & Mueller, 2008). Similar to Pavlovian learning, fear extinction involves learning a new appetitive association to override a previous association to a fearful stimulus (VanElzakker, Dahlgren, Davis, Dubois & Shin, 2013). In many cases of fear extinction, the “reward” is usually the absence of a fearful stimuli, or the presence of pleasant stimuli in one form or another. Thus, the underlying concept of CBT and extinction learning converge. However, extinction learning is impaired in patients with OCD (Milad & Rauch, 2012). When compared to healthy controls, patients with OCD have lower extinction recall index scores (VanElzakker et al., 2013). Moreover, patients have impairments in reversal learning (Tezcan, Tumkaya & Bora, 2017). It is therefore difficult for patients to break unhealthy associations without extended periods of CBT. However, the antipsychotic medication, aripiprazole, as mentioned previously for treating OCD, can reverse this deficit in extinction learning (Tuplin & Holahan, 2017). This further suggests that the treatment of OCD involves the need for increasing patients’ ability for extinction learning.

In this section I will describe how music might help with the process of CBT through the augmentation of extinction learning. But first, I need to establish the mechanism by which this deficit of extinction learning is displayed in OCD. Tying the idea of DA receptors to extinction learning, studies have found that infralimbic D2 receptors are shown to be necessary for fear extinction, while the disruption of D2 impairs extinction learning (Mueller, Bravo-Rivera & Quirk, 2010). Moreover, methylphenidate, an inhibitor of DA and norepinephrine (NE) reuptake seem to be effective in treating a significant number of patients with OCD. This drug increases the DA and NE activity in patients, thereby allowing them to identify obsessional beliefs and improve learning associated with exposure-based therapy (King, Dowling & Leo, 2017). Dopamine receptors are mainly concentrated in two areas, the NAc core and shell. Evidence

have shown that the DA projection responsible for fear extinction are those directed to the NAc shell (Luo et al., 2018). One study has demonstrated that direct infusion of flupenthixol (DA receptor antagonist) into the NAc shell attenuated place conditioning, while injection into the core attenuated cue conditioning as well as conditioned place preference (Ito & Hayden, 2011). Furthermore, DA receptor blockade disrupts acquisition and performance of conditioned approach to stimuli associated with reward (Di Ciano, Cardinal, Cowell, Little, & Everitt, 2001). In addition to findings on the importance of DA receptor activation for extinction learning, NAc activation is also essential for learning. Lesions in the NAc impairs Pavlovian auto shaping and produce deficits in reestablishing pre-lesion Pavlovian approach (Parkinson, Olmstead, Burns, Robbins & Everitt, 1999). This suggests that the NAc is necessary for the re-structuring and re-learning of a stimulus, which is the basis of fear extinction. The study done by Luo et al. (2018) showed that inhibition of the NAc shell projection cells reduces the long-term retention of extinction. Moreover, blocking the rewards pathway mediated by dopaminergic projection from the NAc shell prevented fear extinction. Lastly, reducing dopaminergic inputs to the NAc with 6-hydroxydopamine impairs acquisition of Pavlovian approach behavior and post-training infusion of D1 dopamine receptor antagonists blocks consolidation of Pavlovian associations (Parkinson et al., 2002; Dalley et al., 2005). These evidences all point to the idea that extinction and association learning require dopaminergic activity in the NAc, which was previously argued to be deficient in patients with OCD. Moreover, these findings all resonate the previously mentioned research on OCD symptom reduction through DBS of the NAc (which increases SE and DA levels). In addition to learning an appetitive association, extinction learning also requires the weakening of the previous association. Picture a patient with OCD who has developed excessively strong associations between a certain stimulus (ex. unorganized wardrobe) and an

aversive outcome (ex. death of a family). The patient would perform a compulsive behavior (ex. organizes the wardrobe) selected through Pavlovian Instrumental Transfer (PIT) of aversion association. This behavioral selection could be enhanced by the abnormally strong amygdala activation in patients with OCD. Both fear and anxiety involve the activation of amygdala projections to the hypothalamus and brainstem, which leads to their consequent autonomic and behavioral responses (VanElzakker et al., 2013). During the weakening of this unwanted association, the infralimbic regions of the mPFC excites the intercalated neurons of the amygdala, which is a group of GABA producing cells that have inhibitory effect on amygdala output. Through the inhibition of the amygdala (which is overactive in patients with OCD, as previously mentioned), the association between the conditioned stimulus (CS) and the non-conditioned stimulus is slowly weakened (Luo et al., 2018).

Now, the question is what role does music play in all this? It is shown that music can increase cerebral blood flow (rCBF) at the NAc and decrease rCBF to the amygdala (Chanda & Levitin, 2013). This effect seems to be accentuated when participants listen to music that gives them “chills down the spine” as opposed to neutral music. In support of this finding, Salimpoor, Benovoy, Larcher, Dagher & Zatorre (2011) found significant increases in D2 binding within the NAc during chills, when listening to music. Moreover, since music can increase positive affect, it is also possible to use music as an appetitive stimulus for the enhancement of extinction learning. Lastly, since patients’ overactive amygdala is also associated with anxiety, the effects of music in reducing amygdala activity may counteract anxiety as well. By increasing D2 binding within the NAc, reducing amygdala activity, and lastly acting as an appetitive stimulus, music is an ideal candidate to be used during CBT for enhancement of extinction learning.

Conclusion

OCD is undoubtedly an extremely complex condition in which its neural mechanisms certainly needs further elucidation on. However, from many researches that supports each other, the ideas of the hyperactive association CSTC circuit, anxiety display, and DA dysregulation seem to be robust in the psychopathology. While many treatment methods have been developed to combat this disorder, the heterogeneity of the disease render it difficult to be treated with just one method. This review has provided another non-medical alternative to the improvement of OCD symptoms through the power of music.

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