NEURAL PROCESSING OF EMOTIONAL MUSIC AND SOUNDS IN DEPRESSION

BY

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Abstract

The present study uses functional MRI and an emotional sound and music paradigm to examine how neural processing of emotionally provocative auditory stimuli is altered in depression. Functional MRI was used to localize the neural response to auditory emotional stimulation, hypothesized to differ between depressed and never-depressed control participants in brain regions known to be involved in reward processing and rumination. Twenty individuals with depression (MDD) and 18 controls (ND) listened to positive and negative emotional musical and nonmusical stimuli during fMRI scanning, and gave subjective ratings of valence and arousal following scanning. ND participants exhibited greater activation to positive versus negative stimuli in the ventral anterior cingulate cortex (vACC), dorsal amygdala, and hippocampus, regions known to be affected in depression. They also showed two distinct processing networks for music versus sounds, with music activating the default mode network (DMN) and sounds activating object identification regions to a greater extent. When compared with control participants, depressed participants showed a different pattern of activation to these emotional stimuli in the ACC. In the rostral part of the ACC, ND participants showed greater activation for positive information, while MDD participants showed greater activation to negative information. In the dorsal and perigenual ACC, the pattern of activation distinguished between the types of sounds, with ND showing greater activation to music compared to sounds, while MDD showed greater activation to sounds, with the greatest response to negative sounds. The anterior cingulate is critical for emotion processing and functions as a relay for diverting cognitive control to demanding tasks. These results suggest that the type of auditory stimulation, as well as the emotional content may be processed differently by people with depression.

Keywords: Music, emotional sounds, depression, emotion, fMRI.

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Chapter 1: Background

Music as an Emotional Probe

Music is a powerful inducer of emotion, and many people use music as a self-medicating tool to alter their emotional state (Juslin & Sloboda, 2001; Meyer, 1956). Music is used for mood change in the population generally, and as a coping strategy specifically in depression. College students diagnosed with depression report using music to reduce stress and anxiety (Aselton, 2012). Additionally, a European survey of public advice for the best self-help measures for dealing with depression placed listening to music near the top of the list, with 69% of respondents agreeing that they would recommend this as a useful self-help method. In this survey, 82% of respondents with depression who were already in treatment agreed that music was helpful in this regard (Holzinger, Matschinger, & Angermeyer, 2012). Because of this effect, music may provide a unique and powerful probe with which to induce mood and study affective processing, and may, therefore, prove to be highly effective for studying depression as well.

Over the last decade, many investigators have been exploring the brain responses to musical stimuli (Blood & Zatorre, 2001; Levitin & Tirovolas, 2009; Menon & Levitin, 2005; Peretz & Zatorre, 2005), and have shown that music triggers brain responses in reward centers (Menon & Levitin, 2005; Salimpoor, et al., 2011). Other researchers have examined the neural responses to other types of emotional stimuli, and although imaging results have shown that emotional sounds produce similar brain responses to other types of emotional stimuli (for example, pictures) (Anders, Eippert, Weiskopf, & Veit, 2008), no study to date has directly

compared a subjectively matched set of music and nonmusical sounds.

This comparison is important, because it may clarify why people choose to engage with music to alter their emotional states, rather than seeking out other, nonmusical emotional sounds. Although several theories have been proposed about why music may be more effective in manipulating emotional states than other emotional sounds (Meyer, 1956; McMullen, 1982; Juslin, 2001), the neural mechanisms that underlie this process are not completely understood. Additionally, these theories do not directly address how this relationship may change when emotional quality is matched between musical and nonmusical sounds. Critically, as music is one tool people with depression use as a coping mechanism, the efficacy of emotional auditory stimuli of different types has not been examined in this population.

Depression is the most prevalent mental disorder throughout adulthood in the United States (16.6% lifetime prevalence) (Kessler, et al., 2005). This debilitating disorder is associated with loss of productivity, social and economic costs (Curkendall, Ruiz, Joish, & Mark, 2010; Sartorius, 2001), and comorbidity with other mental disorders (Kessler & Wang, 2008). Depression is characterized by prolonged negative affect and reduced responsiveness to previously enjoyed activities (American Psychiatric Association, 1994). It has been proposed that negative affect may be the result of increased negative cognitions [that is, attentional biases (Abramson, Seligman, & Teasdale, 1978), outlook (Beck, 2008), rumination (American Psychiatric Association, 1994), and negative self-talk (Ingram & Smith, 1984)] that may stem from disordered brain activity (W. Heller & Nitschke, 1997).

To date, only one study has investigated how the neural responsiveness to music is affected by major depressive disorder, showing that neural responsiveness for one's favorite music is dampened in depression (Osuch, et al., 2009). The lack of investigation in this area is

surprising, as the qualities of music could potentially be very powerful in manipulating mood state. However, the neural responsiveness to emotional music and other sounds in depression is not clearly defined. A clearer understanding of this will inform the use of emotional auditory stimuli in formal treatments for depression, and may shed light on why people turn to music as a way to help themselves deal with depressive symptoms.

Goals of the Current Project

The overall goals of this dissertation project for the degree of Doctor of Philosophy in Cognitive Psychology are first, to outline how "equal" emotionality may be determined between auditory stimuli of different types, and second, to describe the pattern of neural activity that is evoked when healthy adult participants listen to these auditory emotional stimuli that have been matched for emotional quality. This examination will clarify whether the neural representation of emotion is expressed in the same way for music and sounds. Ultimately, understanding the neural responsiveness to these types of auditory stimuli will provide insight into why people engage with music differently than they do with other emotional sounds.

Additionally, this project aims to demonstrate that standardized emotional auditory stimuli evoke different experiences in people with and without major depressive disorder (MDD), and that these experiences are reflected in different patterns of neural activity as measured by functional magnetic resonance imaging (fMRI). The results of this project may ultimately have clinical significance for the treatment of depression, or for the use of music as an affective probe for determining risk of developing the disorder. fMRI is used to increase our understanding of the neural processing of music and other sounds. In conjunction with behavioral differences, this knowledge will inform theories of depression by helping determine the individual contributions of reward, cognitive rumination, and disordered sensitivity in

emotional processing of auditory stimuli. This introduction will describe the neural response to music in healthy control participants, review the overall pattern of cognitive and emotional dysregulation in MDD, and discuss the limited number of studies of musical responsiveness in depression. The following chapters will describe the set of studies that comprise the present project, and provide an interpretation of the results within the broader literature.

This dissertation specifically aims to understand the neural processing for emotionally provocative auditory stimuli (music and nonmusical sounds), and to examine how this may be disordered in depression. The study uses fMRI and a music- and sound-processing probe to determine whether patterns of brain activation elicited by emotionally evocative auditory stimuli differ between groups with MDD and ND controls. Previous research in this area by Osuch and colleagues (Osuch, et al., 2009) used musical stimuli that were well known to participants; as such, familiarity may have modulated the brain responses observed in that study. Differences have not been shown for a standardized, novel set of positive and negative musical stimuli. Additionally, direct comparisons have not been made between responses to music and other nonmusical emotional auditory stimuli in never-depressed control participants, nor have differences been mapped for these types of stimuli in depression. The current study expands on previous research by investigating currently depressed individuals' sensitivity to, and neural processing of, musical excerpts and nonmusical sound clips differing in valence and matched on arousal. These excerpts were played during fMRI scanning to evoke positive and negative emotions. Brain responses to, and emotional ratings for the excerpts are compared between MDD and ND groups. These aims were developed to gain a deeper understanding of how the cognitive and emotional dysregulation seen in MDD may be impacted in auditory processing. The broader area of cognition and emotion in depression already benefits from a large body of

research.

Neural Response to Emotional Music

In the last several years, there has been an explosion of research into the brain responses of healthy control participants to musical stimuli (Blood & Zatorre, 2001; Levitin & Tirovolas, 2009; Menon & Levitin, 2005; Peretz & Zatorre, 2005). A study measuring event-related brain potentials (ERPs) by Koelsch and colleagues showed that musical syntax processing and emotion processing can be separated using this methodology along with psychophysiological measurements (Koelsch, Kilches, Steinbeis, & Schelinski, 2008). In their study, unexpected chords in naturalistic musical examples and musical examples with expressive variables removed elicited both a component that reflects syntactic violations, the early right anterior negativity (ERAN), as well as a component that reflects semantic integration, a negative going component peaking around 500 msec post stimulus (N5). They also measured skin conductance, which was modified only by the naturalistic musical examples. They concluded that the ERAN reflects cognitive, rather than emotional processing of musical stimuli, whereas skin conductance is more sensitive to the emotional response.

Two other brain imaging techniques that have been used to study emotional responses to musical stimuli are positron emission tomography (PET) and functional magnetic resonance imaging (fMRI). Both techniques measure neural activity indirectly, either through receptor binding or cerebral blood flow (PET) or hemoglobin deoxygenation (fMRI). These techniques do not have the precise temporal resolution of ERP/EEG, but have good spatial resolution, which can be 1 millimeter or less at high field strength. Though several thousand neurons are present in 1 mm of brain tissue, neural responses typically consist of many cells firing simultaneously over a local field, suggesting that these techniques are ideal for measuring networks of activity

(Logothetis, 2008).

Both PET and fMRI have been shown to be excellent tools for studying the emotional response to music in healthy, non-depressed participants. Blood and colleagues used both PET (Blood, Zatorre, Bermudez, & Evans, 1999) and fMRI (Blood & Zatorre, 2001) to examine intensely pleasurable responses to music and the associated reward processing networks. They contrasted the brain responses to pleasant music and unpleasant, highly dissonant versions of the same music, and found that regions of the limbic system were activating more to the pleasant music. They found regions of increased cerebral blood flow (CBF) in ventral striatum, midbrain, amygdala, orbitofrontal cortex (OFC), and ventromedial PFC – many of the same regions affected in MDD. They also found increased CBF in parahippocampal gyrus and precuneus in response to increasingly dissonant music, which corresponded to participants' ratings of unpleasantness. The limbic system is implicated in reward processing and motivation. This finding from Blood and colleagues (2001) suggests that similar brain regions are responding to music that also respond to other highly rewarding stimuli, such as food, sex and drugs (Volkow, Wang, Fowler, Tomasi, & Baler, 2012).

In an fMRI study by Koelsch and colleagues (Koelsch, Fritz, Von Cramon, Muller, & Friederici, 2006) of pleasant and unpleasant (dissonant) music, they found that the amygdala, hippocampus, parahippocampal gyrus and temporal pole were activated more during unpleasant music compared to pleasant music. They also found that activity in the ventral striatum was increased during pleasant music compared to unpleasant music, consistent with Blood and Zatorre's (2001) findings. In the Koelsch et al. (2006) study, emotional reactions to pleasant music were not as intense as in Blood and Zatorre's (2001) study, in which 'chills' were elicited, which may explain the differences in amygdala response between the two studies. More recent

work by Viinikainen and colleagues (Viinikainen, Katsyri, & Sams, 2012) has clearly shown that activation in the amygdala follows a u-shaped curve with respect to auditory stimulus valence, with both highly negative and highly positive environmental sounds evoking greater responses in this region bilaterally compared to less emotional sounds.

A third study also using fMRI found that music in a minor key, judged 'sad' by participants, was associated with increases in activation in left medial and left dorsolateral PFC as well as bilateral posterior cingulate when compared with music in a major key, judged 'happy' (Khalfa, Schon, Anton, & Liegeois-Chauvel, 2005). Blood and Zatorre (2001) found responses in these same regions to positive musical stimuli. The discrepant findings may reflect cognitive processes associated with the experience and perception of emotion respectively, as the Blood and Zatorre (2001) stimuli were either pleasant or aversive and both the 'happy' and 'sad' musical examples used in the Khalfa, et al. study (2005) were equally pleasant. Regardless of the valence of the musical passages used in these studies, music consistently activated brain areas implicated in MDD.

In another study using fMRI, Menon and Levitin (2005) presented participants with pleasant music and unpleasant scrambled versions of the pleasant music. This study, which focused on the pleasurable experience of music, found an association between enjoyment of music and activity in the ventral striatal and ventral tegmental areas of the brain, specifically the nucleus accumbens (NAc), corroborating Blood and Zatorre's (2001) findings. The ventral striatal and tegmental areas are major dopamine producing regions of the brain, and have previously been associated with disordered emotional processing in depression (Epstein, et al., 2006). Music listening may be rewarding, Menon and Levitin argue, because it mediates dopamine release, a neurotransmitter of reward, via the nucleus accumbens-ventral tegmental

network.

Salimpoor and colleagues (Salimpoor, Benovoy, Larcher, Dagher, & Zatorre, 2011) have recently shown direct evidence of dopamine release to music using PET, and have localized the timing of the dopamine response using fMRI. In this two-part study, participants who reported experiencing intensely pleasurable 'chills' to specific pieces of music listened to those pieces during PET and fMRI scanning. They were instructed to press a button to indicate when they experienced the 'chills' response. Using this information, the authors identified an anticipation period preceding the 'chills' response, as well as the timing of the 'chills' response itself. Examination of the fMRI signal during these periods revealed that dopamine is released in the NAc during anticipation of the pleasurable response, and during the experience of 'chills,' dopamine is released in the caudate.

Many of these same neuroanatomical structures that are important for music processing are also implicated in emotion processing more generally, including approach-oriented structures, such as the hypothalamus and medial forebrain bundle (septal area, mammillary bodies, ventral tegmental area [VTA]), avoidance-oriented structures, such as the amygdala and hippocampus, and structures that respond to both approach and avoidance, including several frontal areas (OFC, mPFC, lateral PFC) and the ACC (Reeve, 2009). Some of these regions, specifically those in the ventral areas, function in bottom-up processes, automatically processing pertinent information in the environment, engaging the autonomic nervous system (ANS), and feeding information forward to the frontal regions. The frontal regions in turn exert top-down processes such as appraisal on the ventral regions, and are critical for emotion regulation.

Reeve (2009) summarizes the functions of these areas (p. 54-59). The hypothalamus controls the ANS, stimulating both sympathetic and parasympathetic responses via connections

with all ANS involuntary organs. The medial forebrain bundle connects the hypothalamus to the other limbic structures, and is central in the dopaminergic system. The amygdala detects threatening or uncertain information and sends projections to nearly every part of the brain. Thus, amygdalar activity may be crucial for understanding disorders that stem partially from hypersensitivity to negative information, such as depression. The hippocampus has a monitoring function in emotion regulation, and is activated when events are novel or not as expected. Hyperactivation in the hippocampus may be related to anxiety disorders. The prefrontal regions monitor and evaluate the information from other limbic areas, and are involved in decision making. The mPFC is associated with learning response-outcome contingencies that lead to goal-directed behavior. The OFC maintains reward-related information, and is critical in decision-making tasks. Neurological evidence has shown that lateralized damage to the prefrontal cortices is associated with opposite emotional responses, with the right PFC implicated in negative and avoidance-oriented feelings, and the left PFC responsible for positive and approach-oriented feelings (Sackeim, et al., 1982).

This parallel between the neuroanatomy of emotional music perception and emotion processing more generally provides additional credibility for the argument that music processing is likely affected in patients with mood disorders, and that music may be ideal as an affective probe for studying these disorders. Thus the current research will both add to our understanding of the impact of depression on cognition, but will also provide additional information about how emotion in music is represented in the brain compared with other emotional sounds. Next, I will turn to the discussion of the current theories regarding cognitive risk factors for developing depression.

Depression Risk and Cognitive Susceptibility to Negative Information

As mentioned earlier, the hallmarks of depression are an overall depressed mood and reduced enjoyment to previously pleasurable activities (American Psychiatric Association, 1994). Depression is a mood disorder that represents a change in tonic mood state from a previous, non-depressed baseline. It does not seem to develop inevitably from a predisposition or trait; rather, it is theorized to be a complex interaction of several environmental and cognitive factors that heighten the risk for developing depression. Theories of depression suggest that an increased susceptibility to negative emotional information in the environment could be one of these risk factors (Abramson, et al., 1978; Beck, 2008). Rather than having a neutral outlook, individuals who have never had depression typically show a positivity bias in their cognitive processes (Kakolewski, Crowson, Sewell, & Cromwell, 1999), that is, they allocate greater attentional resources and show greater memory for positive versus negative information. Conversely, depressed individuals show an overall bias toward negative information. This bias could be due to attentional or evaluative differences, and may also be due to either an increased responsiveness to negative information or a decreased responsiveness to positive information. Either would result in a net affective state that was negative. Negative cognitions in depression have been measured in several studies by presenting negative information to participants with MDD in a sort of affective 'stress test', similar in purpose to a cardiac stress test, to evaluate the integrity and functioning of the affective brain networks. In previous studies of affective processing, a variety of neuroimaging techniques have been employed, including electrophysiological measures such as event-related potentials (ERP), magnetic resonance imaging (MRI), and functional imaging (fMRI).

For example, in a functional magnetic resonance imaging (fMRI) study by Epstein and

colleagues (2006), individuals with MDD showed reduced brain responses compared to controls to emotionally positive printed words in reward centers of the brain, including the ventral striatal and dorsomedial prefrontal regions. These structures, along with additional emotional circuitry - involving prefrontal cortex (PFC), anterior cingulate cortex (ACC), hippocampus, and amygdala - are affected by major depression (MDD) (for a review see Davidson, Pizzagalli, Nitschke, & Putnam, 2002). In addition to reduced hippocampal and amygdalar volume, the volume of the lateral habenular nucleus was shown to be reduced in MDD (Savitz, et al., 2011). The habenula is involved in dopamine regulation associated with reward. Although serotonin is the neurotransmitter most commonly associated with depression, the dopaminergic system is also implicated (Cannon, et al., 2009). The dorsomedial PFC has repeatedly been shown to express abnormal functioning in MDD, and increased connectivity between this region and medial temporal cortex has been implicated in rumination, one of the hallmark symptoms of depression (Bar, 2009). Additionally, hyperconnectivity between subgenual ACC and posterior cingulate, or hyperinhibitory control of the medial temporal lobe by the medial PFC (mPFC), may be involved in rumination over negative self-talk (Berman, et al., 2010). Similarly, decreased activity in the ACC has been associated with sadness, inattention to positive stimuli, and depression, and the ability to activate this region may be linked to improved prognosis (Mayberg, et al., 1997).

Evidence from electrophysiological studies also supports this finding of reduced activity to positive information. The P3 is a positive ERP component, peaking around 300 msec post-stimulus onset, which reflects the allocation of attention in novelty processing and cognitive salience. While a reduced P3 has been found in many studies in depression (Bruder, 1992; Bruder, et al., 2009; Bruder, et al., 1998; Diner, Holcomb, & Dykman, 1985; Gangadhar, Ancy,

Janakiramaiah, & Umapathy, 1993; Kayser, Bruder, Tenke, Stewart, & Quitkin, 2000; Sara, et al., 1994), suggesting potential pervasive cognitive deficits, other studies have found a robust P3 to negative, depression-consistent information – a finding that supports cognitive theories of depression. Ilardi and colleagues (Ilardi, Atchley, Enloe, Kwasny, & Garratt, 2007) examined the P3 response to emotional words in depressed and never depressed control participants using a variation of the oddball paradigm, in which negative emotional words were presented infrequently in a series of frequent emotionally neutral words. The results confirm that individuals with MDD show a negativity bias for emotional words; depressed participants had shorter reaction times and larger P3 responses to infrequent negative words compared to controls. This finding was replicated for pain-related words (Nikendei, Dengler, Wiedemann, & Pauli, 2005). Results from other studies (Atchley, Ilardi, & Enloe, 2003; Enloe, Ilardi, Atchley, Cromwell, & Sewell, 2001; Ilardi, et al., 2007) suggest that the overall negativity bias in depression may be comprised of both negative hypersensitivity and positive hyposensitivity: first, negative words are more readily processed by depressed individuals, as evidenced by shorter reaction times and larger evoked brain potentials, and second, responses to positive words are muted compared to controls. These cognitive factors clearly play a role in depression risk by creating an internal environment that is heavily biased toward negative information. It is as though awareness has been shifted in MDD so that negative information is more salient.

Depression Risk and Emotion Regulation

However, although increased sensitivity to negative information is evident in depression, it does not fully explain the chronic negative emotional state that is characteristic of depression. A failure to regulate one's emotional state may also be at play. An fMRI study by Heller and colleagues found that individuals with depression did show brain responses to positive emotion

in the thalamus, hypothalamus, and PFC; however, when instructed to maintain or intensify their emotional response, they were unable to sustain activity in these regions (A. S. Heller, et al., 2009). An emotional response, then, is characterized by at least two factors: the initial response, and the maintenance or reduction of the response. The latter is one of the main components of emotion regulation. As this concept is critical to an understanding of depression, I will now turn to a more thorough discussion of the theoretical underpinnings of this process.

Emotion regulation is the process of manipulating one's own emotional state. Young's (1961) investigations into animal behavior culminated in the theory that all behavior is motivated and driven by emotion. This theory of appetitive motivation states that an individual (animal or human) will seek to increase positive affect and decrease negative affect to attain or sustain an ideal state, and that the individual will approach positive affective stimuli and avoid negative affective stimuli to achieve this. The concept of individual regulation, therefore, implies that there is a variable internal state that is dependent on external stimulation. It also implies that the response to external stimulation is moderated by the individual's internal state – that it is state-dependent. The individual's internal state modulates the affective response to the external stimulus.

Following the presentation of the theory of appetitive motivation, Young (1973) identified eight classes of affective processes that could drive motivation. These are organic feelings, such as hunger and thirst; simple pleasant or unpleasant feelings; activity feelings, leading to the desire for movement; attitudes and beliefs; emotions; moods; temperaments; and pathological affect, such as depression and anxiety. Each of these classes has different time scales and different thresholds for state regulation. Moods, for example, are more transient than temperaments. In addition, the choice of external stimulus for state regulation will be dependent

on the affective process that the individual seeks to regulate. For example, specific feelings such as hunger will lead the individual to seek a specific stimulus, in this case, food. Some of the other affective processes are more generally regulated with many different stimuli leading to similar affective responses. An aesthetic stimulus, like music or art, may serve to regulate some classes of affective processes. Music specifically may be sought to regulate activity feelings, moods, and emotions. In turn, internal affective processes such as attitudes, temperaments, and pathological affect may impact the response an individual makes to those aesthetic stimuli.

Turning now to a discussion of the neural representation of emotion regulation, researchers have sought to understand this by presenting emotional information in many forms, including language, pictures, and music. Each of these forms has distinct qualities that make for a good affective probe. Language, for example, capitalizes on semantic biases that may be present in negative self-evaluations and ruminations. Pictures can represent highly arousing emotional events, and may be processed more quickly than language. Music, however, may serve as an ideal affective probe for several reasons. First, music is pervasive in human experience, and has been argued to predate language evolutionarily (Mithen, 2005). Second, unlike language or pictures which may have a purely descriptive purpose, it has been argued that the purpose of music is to communicate emotion (Meyer, 1956). And finally, as anticipated by Young's theory (1973), many people report using music to regulate their own emotional state (Juslin & Sloboda, 2001; Aselton, 2012; Holzinger, et al., 2012), in other words, people are emotionally self-medicating. Several researchers are currently engaged in studies to elucidate the neural processing of emotional music. Now let's return to the discussion of music, and review the much smaller number of empirical studies that have examined the specific processing of emotion evoking music in depressed patients.

Altered Response to Music in Depression

It seems very reasonable to hypothesize that the negativity bias seen for emotional words may also occur in response to non-linguistic auditory information, such as music. If depressed individuals show a bias for negative musical stimuli – that is, they show increased brain responses or more negative ratings compared to controls – it would be evidence that depression involves general hypersensitivity to negative information not limited to verbal rumination. Furthermore, one possible mechanism that might underlie this negative bias might be controlled by the striatum. As the striatum is one of the areas potentially affected by depression, and as music has been shown to stimulate the release of dopamine in this area, it is possible that the dopamine response to music and other rewarding stimuli may be dampened in people with MDD.

In a recently published study, individuals with MDD were shown to have impaired recognition of emotion in music, similar to the negativity biases seen for facial and vocal prosodic emotion (Naranjo, et al., 2011). Imaging studies confirm this negativity bias for music. Osuch and colleagues (Osuch, et al., 2009) asked participants with MDD and never-depressed controls to provide samples of their favorite instrumental music. They then had participants listen to their favorite music and instrumental music selected by the experimenters that the participants rated as neutral during fMRI scanning. Details about the specific musical examples chosen by each group were not given. Results indicate that MDD participants showed a reduced response in the ventromedial PFC (vmPFC) to their favorite music, compared to controls, even though MDD participants rated their favorite music as highly enjoyable as did controls. This result suggests that even though participants may make the same subjective rating, differential brain responses can point to functional differences in pathological affect, and may help tease

apart individual differences within the normal range of functioning as well. The findings of Menon and Levitin (2005) implicating the dopaminergic system in music processing have, therefore, prompted new research into potential therapeutic implications of music for depression, as well as for addiction and genetically linked reward deficiency syndrome (RDS) (Blum, et al., 2010), which may be characterized by impairments in the dopaminergic system, leading to lessened experience of reward and, consequently, overindulgent behavior.

Summary

Emotional responses to music and other sounds have previously been studied separately in healthy control participants, but these responses have not yet been directly compared for musical and nonmusical stimulus types. The current project will extend previous research by directly comparing neural responses to carefully matched emotional musical and nonmusical stimuli, and examining the relationship of brain activity to subjective emotional ratings of the stimuli. Additionally, from the research presented here, it can be seen that depression is characterized by a general pattern of cognitive and emotional dysregulation, including hypersensitivity to negative information, hyposensitivity to positive information, and a reduced ability to sustain positive emotional states over time. Functional imaging techniques such as fMRI allow for the study of specific patterns of disordered brain activity that might occur in response to music in patients with MDD. Hyper-responsiveness in the amygdala and medial PFC and hyporesponsiveness in dorsolateral PFC to negative information may be indicative of increased susceptibility to negative information in the environment and increased perceived self-relevance of that information. This dysregulation has been shown as decreased activity in vmPFC as an anhedonic response to favorite music, but has yet to be confirmed for novel musical stimuli. The current research seeks to examine each of the cortical and sub-cortical

regions that have been linked to depression.

Current Study

To this end, a series of five experiments was developed, centering on two fMRI experiments examining responses to emotional auditory stimuli in psychiatrically healthy and MDD participants. Experiments 1 and 2 are described in Chapter 2: Stimuli Development and Validation. These two experiments were rating studies to develop and validate the stimuli to be used in the fMRI experiments. Experiment 3 compares brain responses of never-depressed participants to two types of positive and negative emotional auditory stimuli: music and non-music (International Affective Digital Sound set [IADS], Bradley & Lang, 2000), and one type of neutral sounds: pure tones. Experiment 4 is a comparison of subjective ratings to the developed stimuli given by depressed and never-depressed participants. Finally, Experiment 5 compares brain responses of depressed and non-depressed participants to the different sound types.

Specific Aims

Specific aims for this study were 1) to replicate and extend previous research by comparing brain responses of never-depressed participants to emotional musical and nonmusical sounds; 2) to measure and compare the strength of emotions reported to be experienced during music listening by individuals with MDD and ND controls ; and 3) to determine whether the experiences of positive and negative emotion in response to music and nonmusical sounds are differentially represented in brain activity in the mesolimbic system between individuals with MDD and ND controls.

Aim 1: Replicate and extend previous research by comparing brain responses of healthy control participants to emotionally valent musical and nonmusical sounds. This

aim is addressed by Experiment 3. Previous research has shown that emotional sounds, including music activate regions of the brain in healthy control participants known to be involved in emotion processing, such as the amygdala, ACC, ventral striatum, caudate, and mPFC. A direct comparison has not been made to examine how similarly musical and nonmusical auditory stimuli are processed in a healthy population. Although it has been argued that the emotion conveyed by music is not the same as emotion experienced more generally (Scherer & Zentner, 2008), there is little evidence to suggest that recorded emotional sounds would evoke a different emotional experience than recorded music. Therefore, it was hypothesized that the two types of stimuli would show similar patterns of activation in emotion networks of the brain, with negative stimuli evoking greater activation in the amygdala and hippocampus, and positive stimuli evoking greater activation in the mPFC, ACC, ventral striatum, and caudate. Though these musical stimuli were chosen to be unfamiliar to the participants, it is possible that participants found them to be a more rewarding stimulus than the nonmusical sounds. If this were true, we would hypothesize greater activation in the caudate and ventral striatum to musical stimuli.

Aim 2: Measure and compare the strength of emotions reported to be experienced during music listening by individuals with MDD and non-depressed controls. This aim is addressed by Experiment 4. All participants, regardless of diagnosis, were hypothesized to report experiencing both positive and negative emotions while listening to the musical stimuli, but based on previous research, we hypothesized that individuals with MDD would rate positive excerpts as less positive and lower on arousal and rate negative excerpts as more negative and higher on arousal compared to controls. A post-scanner measurement quantified participants' subjective responses to the stimuli. These ratings are used in correlation analyses to examine the relationship between brain activation/inhibition to negative/positive music and self-reported

perceptions of that music.

Aim 3: Determine whether the experiences of positive and negative emotion in response to music and nonmusical sounds are differentially represented in brain activity in the mesolimbic system between individuals with MDD and ND controls. This aim is addressed by Experiment 5. Based on previous research, it was hypothesized that MDD and ND groups would express differential responses in the mesolimbic system – mPFC, ACC, OFC, and ventral striatum — with MDD showing decreased responses to positive stimuli in these areas compared to controls. Additionally, it was hypothesized that MDD would have greater responses to negative stimuli in the amygdala and hippocampus compared to controls, reflecting hyper-responsiveness to, and rumination over, negative information. It was hypothesized that musical and nonmusical sounds would evoke similar patterns of brain activity, which would indicate that all non-verbal emotion-related information is processed similarly. We also allowed for the possibility that the musical sounds could show stronger effects than the nonmusical sounds, as they comprise a more complex stimulus, and are more commonly associated with mood regulation. If music were found to be a more evocative emotional stimulus, this could help guide future decisions in the research and therapy domains.

Chapter 2: Stimuli Development and Validation

Need for a Standardized Emotional Musical Stimuli Set

Experiments 1 and 2 were designed to develop a standardized set of musical stimuli and match them for emotional quality to an existing auditory stimuli set, the majority of which are nonmusical in nature (International Affective Digital Sound set [IADS]; Bradley & Lang, 2000). The parameters and characteristics of a musical stimulus (for example, tempo, and instrumentation) can each modulate the emotional processing of that stimulus. These parameters may either be measured directly in an objective manner following the methods of empirical aesthetics (Berlyne, 1974), or manipulated or restricted by experimental design. As many of these parameters are unique to music, a discussion of the theory and previous research in this area is warranted, as this work informed the experimental considerations used in developing these stimuli.

Elements Affecting Emotional Processing

Musical elements. For example, tempo and rhythmic structure seem to play an important role in communicating emotion (Gomez & Danuser, 2007). Music in a quick tempo is judged to be happier than music in a slow tempo. This may be explained by McMullen's activation/evaluation model (1982), in that tempo and rhythm may convey the arousal level of the music. According to this model, arousal or 'activation' will determine which evaluative concepts a person will use to describe a stimulus. Similar to Juslin's super-expressive voice theory (2001), that states that music is potentially a more powerful inducer of emotion compared to the human voice due to the increased range of emotional prosodic cues that are possible, some researchers have argued that rhythmic information in music is responsible for entrainment of the

heartbeat and respiration, thus allowing the listener to differentiate between happy and sad musical emotions (Etzel, Johnsen, Dickerson, Tranel, & Adolphs, 2006). However, other researchers, by carefully manipulating both tonal and rhythmic information in their musical samples (that is, creating multiple samples from the same piece of music with either the tonal information or the rhythmic information kept constant and varying along the other element), determined that tempo and rhythm alone cannot account for emotion distinctions (Khalfa, Roy, Rainville, Dalla Bella, & Peretz, 2008).

Performance cues. Many elements of music are manipulated in subtle ways during a performance. The effects of these expressive manipulations of tempo, dynamics, and sustain on emotion processing have been examined by researchers. Recent studies have used new technologies in instrumentation to measure real-world musical examples. Certain acoustic pianos have been equipped with digital recording and playback equipment (for example, Yamaha Disklavier, Yamaha Corporation of America, Buena Vista, CA) that allow for exact replication of a performance, or for discrete modeling of various parameters of that performance. Psychophysiological and behavioral research using this type of instrument from Bhatara and colleagues (Bhatara, et al., 2010) has shown that by systematically reducing or removing the variation in expressive timing (that is, deviations from notated timing values), pedaling, and amplitude (a measure of key depression velocity) in a professional pianist's recorded performance, the experience of expressivity or emotionality is reduced in children with normal functioning, but that these variations do not affect ratings of emotionality by children with autism spectrum disorder (ASD). Though these experimental manipulations are useful for particular research questions, the stimuli chosen here are professional recordings that have the expressive elements preserved.

Connotative associations. In addition to the emotional cues present in the musical stimulus, the connotative associations or evaluations (McMullen, 1982) an individual makes with the stimulus are likely to alter the affective response. Various methods for measuring these associations have been used in previous research. In visual aesthetics research, for example, measurement of these types of connotative associations has led to increased understanding of color preference, such that associations people make between particular colors and objects can account for differences in valence judgments of the color itself (Palmer & Schloss, 2010). It is likely that the specific associations may vary widely between individuals, but that themes may emerge that could be used as variables in later studies. In the current research, we used these common themes to create a standardized set of musical stimuli, and to match that stimuli set to a subset of the IADS (Bradley & Lang, 2000).

Measuring emotion

In previous research, connotative associations with music have been studied using a variety of methods, from matching emotion words like happy and sad to musical excerpts (Hevner, 1936; Krumhansl, 1997), to having participants judge whether two samples are expressing the same emotion or different emotions (Filipic & Bigand, 2005), to asking participants to freely give emotional labels to the music (Gosselin, et al., 2005). Many studies of affective states induced by music involve categorization of music into 'happy' and 'sad' selections (Baumgartner, Esslen, & Jancke, 2006; Krumhansl, 1997; Mitterschiffthaler, Fu, Dalton, Andrew, & Williams, 2007; Peretz, Gagnon, & Bouchard, 1998). Though this categorization seems stable both within and between participants, there are some limitations to this method. Music classified as 'happy' is generally fast and in a major mode, whereas music classified as ''sad' tends to be slow and in a minor mode (Krumhansl, 1997). Tempo variation alone could

account for differences in arousal, and therefore, classification between the two categories. The valence-arousal circumplex model of emotion (Hevner, 1936; Posner, Russell, & Peterson, 2005; Russell, 1980) has been used in studies of emotionally evocative nonmusical sounds as well as in other modalities (for example, visual scenes) (Bradley & Lang, 2000; Lang, Greenwald, Bradley, & Hamm, 1993). In a study using musical stimuli to evoke feelings of liking and facial electromyography (EMG), Witvliet and Vrana (Witvliet & Vrana, 2007) varied both valence and arousal of the music, thereby controlling for arousal as a potential confound.

Vines and colleagues (Vines, Krumhansl, Wanderley, Dalca, & Levitin, 2005) asked participants to rate their experienced emotions to either audio, visual, or audio-visual clarinet performances using Likert scales of 19 representative emotions. They conducted a factor analysis, and found that four factors explained most of the variance in responses: active positive, active negative, passive positive, and passive negative. Additionally, the level of visual performance cues (that is, exaggerated or suppressed body gestures) was a better predictor of factor loading than were auditory cues. These four factors map well onto Russell's 'circumplex model' of emotion (Posner, et al., 2005; Russell, 1980), and many recent studies (Bailes & Dean, 2009; Egermann, Grewe, Kopiez, & Altenmuller, 2009) have used this model directly by having participants rate musical examples for valence and arousal level by indicating where the example would map on a biaxial (*x*=valence, *y*=arousal) diagram (Figure 1). The method of rating used in a particular study can have a profound impact on study outcomes, and could potentially be impacted by participants' linguistic or musical abilities (Scherer, 2004). The circumplex model has the benefit of allowing participants to rate music without relying on specific linguistic representations. It also allows researchers to carefully control for valence and arousal as separate variables – features that are highly confounded when participants rate music as happy versus sad

(Witvliet & Vrana, 2007), and that, evidence suggests, are experienced separately by participants (Vines, et al., 2005).

Effects of expertise

Musical expertise and experience may also affect how an individual responds to a musical stimulus. Researchers have used ERP techniques to study the degree to which musical syntax violations are detected by both highly trained and musically naïve participants (Leino, Brattico, Tervaniemi, & Vuust, 2007). The authors had participants listen to a series of chords that either matched or violated the Western rules of harmonic progression. At the violating chord, even musically naïve participants responded with an early right anterior negativity (ERAN) ERP inflection. This indicates that intense musical training is not necessary for people to learn the rules of musical syntax of their culture. These rules are learned implicitly through enculturation. Because of this, musical expertise is not the focus of this project. However, as differences may exist, musical knowledge and experience was recorded for all participants.

Experiment 1: Stimuli development

Introduction

As demonstrated above, emotional valence in music is highly confounded by different arousal level between examples categorized as 'happy' or 'sad'. To control for potential arousal effects, a standardized stimuli set was developed. Emotionally evocative musical stimuli were identified from previous literature (Witvliet & Vrana, 2007) (Table 1). Musical examples were edited into ten-second clips according to phrase boundaries, and were programmed for presentation and response collection in E-Prime 2.0 (Psychology Software Tools, Inc., Sharpsburg, PA). Individual clips were rated for valence (positive-negative) and arousal (active-passive), and the most positive and negative examples, matched for arousal, were selected for a

secondary stimuli validation study (Experiment 2).

Methods

Site of study. This experiment was conducted in the Psychology department of the University of Kansas. This study was approved by the University of Kansas Human Subjects Committee (Appendix A).

Participant population. Participants were 24 undergraduates at the institution ($Mean_{AGE}$ = 20.87, $Range_{AGE}$ = 18-51) selected from the undergraduate Psychology subject pool.

Materials. ***Stimuli.*** The musical examples were taken from Witvliet and Vrana (2007). Though they used the musical examples for a facial EMG study, the rating system used for this study was similar, and the musical examples were expected to evoke comparable emotions. In their study, twelve pieces of instrumental music were selected from a pilot study of over 300 pieces. The three most extreme examples of each of four categories (positive – high arousal [for example, joyful], positive – low arousal [peaceful], negative – high arousal [angry], and negative – low arousal [sad]) were selected for use in the EMG study. These pieces varied in instrumentation (that is, solo to full orchestra), loudness, and key (that is, major-minor). These parameters varied across all quadrants; however, tempo was faster for the high compared with the low arousal pieces. In the current study, each of these twelve pieces was segmented into 10-second samples, beginning at musical phrase boundaries, resulting in 404 samples. The exact segments used in the Witvliet and Vrana (2007) study were unknown. As emotionality can vary within a piece of music, each piece was fully segmented allowing the samples most characteristic of each category to be determined. A symmetric onset and offset fade of 80 msec was added to each of the samples with Amadeus Pro software (HairerSoft, New York, NY) to avoid startling participants.

Measures. Participants completed a paper and pencil questionnaire that included musical training and listening habits, as well as psychological health information (Appendix B). Auditory stimuli were presented through Sentry multi-media gaming headsets, model HMM10 (Hillburn, NY) using E-Prime 2.0 software running on Dell PC computers. Participants were allowed to adjust the volume to a comfortable level during a practice session. The musical samples were rated according to Russell's circumplex model of emotion (Posner, et al., 2005). Participants rated valence and arousal on a biaxial diagram centrally presented on the screen after each trial (x=valence, y=arousal; black on white background: Figure 1) by left-clicking with a Dell three-button optical mouse on the appropriate location in the diagram at the completion of each sample. Coordinates (x, y) of the selected location were recorded.

Procedure. Participants were tested in groups of one to three. After completing informed consent, subjects completed the musical training questionnaire. They were then escorted to the testing room, which housed three testing stations with dividers between them. Instructions were visually presented on the screen and aurally presented through the headsets. A practice session followed, in which participants practiced recording their responses using the diagram for emotional words, pictures, and music selected from pieces not included in the testing set. The 404 trials were presented in random order, with an optional break given after every 100 trials. Each trial was preceded by a warning screen ("Get Ready"). The screen was blank during the auditory stimulus, and the recording diagram was presented after each trial. The experimental procedure lasted approximately two hours. Following testing, participants were debriefed about the purpose of the experiment and were given course credit for participation.

Analysis methods. Mean valence and arousal ratings were calculated for each sample. Samples were then ranked by mean valence rating, and split into quartiles. Eighteen segments

from each of the highest (that is, most positively rated) and lowest (most negatively rated) quartiles for valence were selected for inclusion in the fMRI stimuli set. Separate two-sample *t*-tests were run for valence and arousal to confirm that positive and negative selected samples differed on valence, but were not significantly different on arousal.

Results

Questionnaire. Five participants (21%) reported a history of psychiatric diagnosis (Depression = 2; Depression/Anxiety = 1; ADD = 1; Schizophrenia = 1). Inclusion of these participants did not significantly change the results; therefore, the results reported here include data from these five participants. Eighty-seven percent (n = 21) reported at least one year of musical training. Twenty-five percent (n = 6) reported some dance training. Eighty-three percent (n = 20) reported listening to music every day, and all participants reported listening four or more days per week. Thirty-eight percent (n = 9) affirmed that they liked classical music, and 13% (n = 3) that they disliked classical music.

Ratings. One piece was not represented in the outer quartiles (Kevin Volans, "White Man Sleeps IV"), and samples from this piece were used for practice in the fMRI experiments. Samples from a second piece were represented in both quartiles (Bedrich Smetana, "Ma' Vlast: Vysehrad"), suggesting that this method was sensitive to variations within a single piece. The selected positive and negative samples differed significantly on valence (t (34) = -43.96, $p <$ .001), but did not differ on arousal (t (34) = 1.09, p = .28). High and low arousing stimuli were, therefore, combined for the fMRI analyses (Experiments 3 and 5).

Discussion

Experiment 1 was used to select the most evocative moments from the pieces identified from Witvliet & Vrana (2007) for use as emotional probes in the imaging experiments which

follow. As expected, the emotional ratings given by participants in this experiment varied widely across each piece, with examples from one piece being among the most positive and the most negative samples of the set as a whole. Thus, it is clear that this was an important first step in stimulus selection. However, the ratings given by this first set of participants could have been influenced by comparison of the highly emotional segments with the less emotional segments with which they were presented. Therefore, Experiment 2 was run to confirm that ratings for the selected subset of musical segments would be rated similarly by a second, independent sample of participants when they were presented in isolation.

Experiment 2: Stimuli validation

Introduction

To ensure that the emotional ratings for the sounds as a set were reliable, the selected sounds from Experiment 1 were validated in the manner they would be presented in the imaging study in a separate sample of participants. Additionally, a subset of the IADS (Bradley & Lang, 2000) was included in this rating study.

Methods

Site of study. This experiment was conducted in the Psychology department of the University of Kansas. This study was approved by the University of Kansas Human Subjects Committee.

Participant population. Participants were 21 undergraduates (7 males; $Mean_{AGE}$ = 18.90, $Range_{AGE}$ = 18-26) selected from the undergraduate Psychology subject pool.

Materials. ***Stimuli.*** The musical stimuli selected from Experiment 1 were matched for valence and arousal with IADS (nonmusic) sounds (Bradley & Lang, 2000), and were programmed into the fMRI blocked stimuli presentation paradigm. Bradley and Lang (Bradley

& Lang, 2000) developed the IADS, a set of emotionally evocative sounds rated for valence and arousal, for use in research. This set represents a wide variety of sounds, ranging from infant cries to nature sounds. A subset of the IADS was selected for use in these experiments using methods similar to that for selecting the musical examples (Table 2). Using the published ratings for the IADS (Bradley & Lang, 2000), samples were ranked according to valence rating, and 24 samples were selected from the outer quartiles. The IADS samples are five seconds long; to match the musical stimuli they were looped for 10 seconds. Musical samples, violence and erotica were excluded from the selected subset.

The selected emotional stimuli from Experiment 1, plus additional neutral sounds (pure tones) were also programmed for presentation using the same paradigm as Experiment 1, so that valence and arousal ratings could be collected for each sample within the set. The pure tones, created with Audacity music editing software (Sourceforge.net) were composed of step-wise increments of a C major scale, beginning on A_3 (220 Hz); these tones serve as a baseline condition. Pure tones were hypothesized to be an adequately neutral auditory sound, but other neutral sounds (long instrumental tones, white noise, and so on) were presented as well to test this empirically.

Measure. Stimuli were presented using E-Prime 2.0 software (Psychology Software Tools, Pittsburgh, PA). Two tasks were presented in this experiment. First (2a), using the same equipment as in Experiment 1, blocks of positive or negative sounds were presented through the headsets, interleaved with neutral (pure tones) blocks. To ensure they were attending to the sounds, participants were asked to respond via left mouse click when the type of sound had changed (music to tones, IADS to tones). Response time was recorded. Second (2b), valence and arousal ratings were collected for each sample using the methods from Experiment 1. The

musical training questionnaire was also collected during this experiment.

Procedure. Participants were tested in groups of one to three. After completing informed consent, subjects completed the musical training questionnaire. They were then escorted to the testing room. Instructions were visually presented on the screen. A practice session followed, in which participants were familiarized with the types of sounds they would hear during the experiment via an example run. Musical stimuli in the practice run were selected from Kevin Volans, "White Man Sleeps IV", which was rated as neither explicitly positive nor negative during Experiment 1. A blank gray screen was presented during the rest of the experiment.

Music and IADS stimuli were presented in separate runs. A series of five runs was presented: three music and two IADS. During each run, two repetitions of each block type were alternated between positive and negative stimuli, with a baseline block between each, and beginning and ending each run. Valence order was counterbalanced so that half of the participants heard positive stimuli first, and the other half heard negative stimuli first. Participants heard 30-second blocks of positive, negative, and pure tone (baseline) samples. Each block contained three 10-sec samples of the same stimulus type (Figure 2). Participants clicked the left mouse button to indicate when they experienced the stimulus type as having changed. No visual stimulation or feedback was presented.

When the five runs of the first task were completed, participants were again presented with each of the sounds they had heard in random order, plus the additional neutral sounds, and asked to give ratings for each using the methods from Experiment 1. The experimental procedure lasted approximately one hour. Following testing, participants were debriefed about the purpose of the experiment and were given course credit for participation.

Analysis methods. To confirm that the selected IADS sounds were matched on valence and arousal to the musical stimuli, a multivariate analysis of variance (MANOVA) was run. Mean valence ratings were also compared between all samples classified as positive, negative, and neutral in a one-way analysis of variance (ANOVA). Valence and arousal ratings for the pure tones were compared to the alternative neutral examples using a MANOVA with post-hoc univariate tests.

Results

Questionnaire. One participant (5%) reported a history of psychiatric diagnosis (Depression). As in Experiment 1, inclusion of this participant in the analysis did not significantly change the results. The results reported here include data from this participant. Eighty-one percent (n = 17) reported at least one year of musical training. Forty-eight percent (n = 10) reported some dance training. Ninety-five percent (n = 20) reported listening to music every day. Thirty-three percent (n = 7) affirmed that they liked classical music, and 24% (n = 5) that they disliked classical music.

Matching of music & IADS. A non-significant Type by Valence interaction in the MANOVA confirmed that the selected IADS sounds were adequately matched on valence and arousal to the musical stimuli (F (2, 55) = 0.23, p = .79).

Valence comparisons. The positive, negative, and neutral sounds were rated significantly different on valence (F (1, 64) = 15.56, p < .001). The positive sounds were rated significantly higher on valence than both the neutral and negative sounds, and the neutral sounds were rated significantly higher than the negative sounds, confirmed with Tukey's Honestly Significant Different (HSD) post hoc tests. The pure tones were not rated significantly differently on valence compared to the alternative neutral sounds (F (1, 14) = 1.63, p = .22).

They were, however, rated significantly lower on arousal compared to the alternative neutral tones (F (1, 14) = 19.09, p = .001). To keep the neutral condition as consistent as possible, the pure tones were used as the neutral stimulus in Experiments 3-5.

Discussion

The results of Experiment 2 confirmed that the emotional musical stimuli were rated similarly as they had been in Experiment 1. Additionally, the selected IADS sounds were rated as equally emotionally positive or negative and equally arousing as the musical stimuli. We can, therefore, conclude that the selected stimulus set is matched for subjective ratings of valence and arousal, and should be rated similarly by a third set of participants (that is, participants in the imaging studies). Consequently, any differences in neural activity that are seen in the imaging studies should be due to differences in processing of the stimulus type, rather than differences in emotional quality between the stimulus types.

Chapter 3: Neural Responses to Musical and Nonmusical Emotional Sounds in Psychiatrically Healthy Control Participants – Experiment 3

Introduction

Though imaging results have shown that IADS sounds produce similar brain responses to other types of emotional stimuli (for example, pictures) (Anders, Eippert, Weiskopf, & Veit, 2008), and that music also triggers brain responses in reward centers (Menon & Levitin, 2005; Salimpoor, et al., 2011), no study to date has directly compared a subjectively matched set of music and nonmusical sounds. Experiment 3 addresses the first specific aim: replicate and extend previous research by using fMRI to compare neural responses to positive and negative emotional auditory stimuli in healthy, never-depressed individuals.

Psychiatrically healthy adult participants listened to the previously selected emotionally evocative musical and nonmusical stimuli during fMRI scanning. However, rather than simply monitoring for a change in sound type (music to tones, IADS to tones) as described in Experiment 2a, participants were instructed to think about whether each sound was emotionally positive or negative while listening, and to press a button when prompted to indicate whether the block was positive or negative. Brain responses to positive and negative musical stimuli and nonmusical emotional sounds (IADS) were compared to see if brain regions implicated in emotion processing (amygdala, subgenual ACC, ventral striatum) were differentially responding to these distinct types of emotional auditory stimuli.

Methods

Site of study. This experiment was conducted at the Hoglund Brain Imaging Center at the University of Kansas Medical Center. This study was approved by the University of Kansas

Medical Center Human Subjects Committee (Appendix C).

Participant population. Never Depressed Control participants (ND: n = 19; 8 males; $Mean_{AGE}$ = 28.53; SD_{AGE} = 11.31; $Range_{AGE}$ = 18-59) with no history of depression or other psychiatric disorder, determined by administration of the Structured Clinical Interview for DSM Disorders, non-patient version (SCID-I/NP) (First, 2002), were recruited from flyers posted on university campuses throughout the immediate metro area, through online advertisements, and through the University undergraduate subject pool. In addition to screening for any past history of depressive episodes during the diagnostic interview, participants' frequency and severity of depressive symptoms were assessed with the Accuracy of Past Memories Test (PASTEP: Ingram, unpublished), a 20-item questionnaire that asks respondents to note how often (Never – Very Frequently) they have had particular depressive symptoms in the past, and how much distress those symptoms caused (None – A lot). Participants' dysphoria was assessed on the day of testing with the Beck Depression Inventory - Second Edition (BDI-II; Beck, Steer, & Brown, 1996). The BDI-II is a widely used and validated self-report measure of severity of depression symptoms. A score of greater than 18 on the BDI-II would indicate high levels of dysphoria. One participant scored greater than 18 on this measure on the day of testing, and was, therefore, excluded from further analyses.

Participants were paid $50 for their time and travel expenses, and participants recruited through the undergraduate subject pool also received course credit. As handedness could affect brain function lateralization, participants were all right-handed. Participants had no contraindications for MRI (metal implanted in body, pregnancy), conditions and medications affecting blood flow (hypertension, diabetes), or brain function (psychiatric illness or medications), or neurological conditions (head injury, stroke). Participants all had at least a high

school education ($Mean_{ED}$ = 15.53 years; SD_{ED} = 3.29 years), and were within the normal range of IQ ($Mean_{IQ}$ = 120.42; SD_{IQ} = 12.17) as assessed by the Vocabulary and Matrix Reasoning subtests of the Wechsler Abbreviated Scale of Intelligence (WASI) (Wechsler, 1999).

Materials. ***Stimuli.*** The musical, nonmusical, and neutral stimuli were those selected and used in the first task (2a) described in Experiment 2.

Procedures. Participants underwent a single fMRI scanning session with five functional scanning runs. Study procedures are summarized in Figure 3. During three functional runs, participants listened to alternating groups of positive music, negative music, and pure tones. During the other two functional runs, participants listened to alternating groups of positive and negative nonmusical stimuli selected from the International Affective Digital Sound set (IADS) (Bradley & Lang, 2000) and pure tones.

Several self-report measures were collected for comparisons with the MDD group (Experiment 5). In addition to the BDI-II and PASTEP, described above, participants' current anxiety level was assessed with the Beck Anxiety Inventory (BAI) (Beck & Steer, 1990). This twenty-one item questionnaire is used to assess severity of anxiety symptoms over the previous week. Current affect was assessed on the day of testing with the Profile of Mood States (POMS). The POMS is a comprehensive set of scales, widely used to assess current mood state. The POMS scoring returns six subscale scores (Tension, Depression, Anger, Vigor, Fatigue, and Confusion), and a Total Mood Disturbance score, and is consistent and stable over repeated measurements (McNair, Heuchert, & Shilony, 2003). The Affect Intensity Measure (AIM), a brief, validated self-report tool for measuring strength of positive and negative emotions, was collected to assess the role of affect intensity in rating and brain activity differences. The AIM returns a total score and three subscale scores: Positive Affectivity, Negative Intensity, and

Negative Reactivity (Diener, Larsen, Levine, & Emmons, 1985). Participants also rated their music listening habits (that is, frequency, styles, reasons for listening, and so on) using the Brief Music Experience Questionnaire (MEQ) (Werner, Swope, & Heide, 2006). The Brief MEQ is a 53 item self-report measure of music centrality in the respondent's life (Commitment subscale), musical aptitude (Innovative Musical Aptitude subscale), and experience with and reaction to music (Social Uplift, Affective Reactions and Depth of Reactions, Positive Psychotropic Effects, and Reactive Musical Behavior subscales). This scale was used to confirm whether participants reported experiencing strong emotions with music, and was used in comparisons of musical experience between MDD and control groups in Experiment 5.

fMRI methods

Scanning parameters. Scanning was conducted at the Hoglund Brain Imaging Center at the University of Kansas Medical Center on a 3 Tesla Siemens Skyra scanner (Siemens, Erlangen, Germany). Participants' heads were immobilized with cushions. Following automated scout image acquisition and shimming procedures to optimize field homogeneity, a structural scan was completed. High-resolution T1-weighted anatomic images were acquired with a 3D MPRAGE sequence (TR/TE = 23/4 msec, flip angle = 8 degrees, FOV = 256 mm, matrix = 256 x 192, slice thickness = 1 mm), used for slice localization for the functional scans, Talairach transformation, and coregistration with fMRI data. Participants were given the option to have their de-identified structural images included in a database accessible to researchers at the University of Kansas Medical Center, reducing the cost of future studies. Following structural scans, five gradient echo blood oxygen level dependent (BOLD) sequences were acquired in 50 interleaved oblique axial slices at a 40 degree angle (repetition time/echo time [TR/TE] = 3000/25 msec, flip angle = 90 degree, field of view [FOV] = 220 mm, matrix = 64 x

64, slice thickness = 3 mm, 0 mm skip, in-plane resolution = 2.9 x 2.9 mm, 105 data points, 5 min: 24 sec).

To minimize susceptibility artifact and optimize signal in ventromedial prefrontal regions, participants were positioned in the scanner with the angle of the AC-PC plane between 17 and 22 degrees in scanner coordinate space, verified with a localization scan. This careful positioning ensured that the 40 degree slice acquisition angle was applied the same way for all subjects. These procedures were developed in collaboration with MR physicist at the Hoglund Brain Imaging Center, Dr. Phil Lee. Head positioning and slice orientation parameters were verified in pilot tests and are now applied routinely at the Hoglund Brain Imaging Center in all fMRI studies targeting ventromedial regions of the brain.

Stimuli were presented using E-Prime 2.0 software (Psychology Software Tools, Pittsburgh, PA) in a block-design paradigm (Figure 2). During each functional run, two repetitions of each block type were alternated between positive and negative stimuli, with a baseline block between each, and beginning and ending each run. Participants heard 30-second blocks of positive, negative, and pure tone (baseline) samples. Each block contained three 10-sec samples of the same stimulus type. After each block, participants saw a plus and a minus on the computer screen for three seconds. The plus and minus were randomly presented to the right or left of the screen. Participants were asked to press a button (fORP eight-button response pad, Current Designs, Inc., Philadelphia, PA) with either their right or left thumb when they saw this screen to indicate whether they thought the previous block of sounds was positive or negative. This button press served as a measure of response time, which was used to quantify potential cognitive slowing in MDD that might affect the data. If response time were found to differ between the MDD and control groups, it would have been entered into the analyses as a

covariate. Each participant had five functional runs: three music, and two IADS processing. The order of the three music processing runs, and the order of the two IADS processing runs, was counterbalanced between subjects, with half of the subjects receiving positive stimuli first, and the order of stimulus type (music or IADS) was also counterbalanced between subjects. Stimuli were presented through MR compatible earbuds (Sensimetrics Corporation, Malden, MA) at 70dB, or as loud as comfortably possible to ensure the stimuli was heard over the noise of the scanner. In addition, noise-canceling headphones were placed over the earbuds to block some scanner noise. This system was designed specifically to present audio stimuli in the noise of the MR scanning environment. It has been used successfully during fMRI scanning at the imaging center in previous studies.

Analysis methods. Though power analyses are limited with fMRI pilot data from only two subjects, published estimates indicate that 80% power can be achieved using a threshold of .002 with approximately 20 subjects for fMRI experiments with medium effect sizes, and a conservative random effects model (Desmond & Glover, 2002). Further, fMRI studies of emotional responses to music activated the amygdala with fewer than 20 subjects (Koelsch, et al., 2006; Osuch, et al., 2009).

fMRI data were analyzed using the Analysis of Functional NeuroImages (AFNI) statistical package (Cox, 1996) and random effects. Preprocessing steps included trilinear 3D motion correction, 3D spatial smoothing to 4-mm with a Gaussian filter, and high pass filter temporal smoothing. Each participant's structural image was realigned to the first functional image obtained within the participant's scanning session, and normalized to the space defined by Talairach and Tournoux's (1988) stereotaxic atlas with the AFNI <@auto-tlrc> algorithm. Any functional runs with motion of more than 3 mm along any axis (x, y, or z) were discarded.

Additionally, motion of greater than 1 mm between successive TRs resulted in the censoring of that TR and the two adjacent TRs. Any functional runs with more than thirty percent of TRs censored were discarded. No functional runs were discarded for motion. fMRI data were analyzed using whole brain and region of interest analyses.

Whole brain statistical analyses. Activation maps were analyzed using statistical parametric methods (Friston, Frith, Frackowiak, & Turner, 1995) contained within the AFNI software (Cox, 1996). Statistical contrasts were conducted using multiple regression analysis with the general linear model (GLM). Regressors representing the experimental conditions of interest were modeled with a hemodynamic response filter and entered into the multiple regression analysis using a two-stage mixed-effects model. Motion estimates were also entered into the model as nuisance regressors. Contrasts between conditions of interest were assessed with *t* statistics using the <3Dttest++> command. Main effects of Valence (Positive, Negative) and Type (Music, IADS), and the interaction of Valence and Type were assessed. Statistical parametric maps were then overlaid on three-dimensional renderings of the Talairach template brain (TTN27). Activations in *a priori* regions of interest – ventral striatum, midbrain, amygdala, OFC, ACC and vmPFC – were considered significant if they survived a statistical threshold of $\alpha < .05$ (corrected for multiple comparisons). Other areas were considered significant if they exceed a threshold of $\alpha < .01$ (corrected).

Region of interest (ROI) data analyses. Follow-up analyses of *a priori* ROIs were conducted in regions noted above that achieved statistical significance in the whole brain analyses. The maximally activated voxel within each of the six *a priori* ROIs was inspected bilaterally. Mean percent signal change for each condition (Positive music, Negative music, Positive IADS, Negative IADS) for each individual was exported to SPSS/PASW 20.0 (IBM

Corporation, Somers, NY). These data were used to examine potential relationships between degree of activation and stimuli ratings, gender, age, scores on the AIM, and MEQ. These six *a priori* ROIs were anticipated to show differential brain responses based on the valence of the stimuli, with greater activation to positive stimuli in all regions except the amygdala, where activation was expected to be greater for negative stimuli. Further, activation in these regions was expected to be positively correlated with stimuli ratings and AIM scores, and for musical stimuli, to be positively impacted by MEQ score.

Results

Questionnaires. As the scores on the AIM and MEQ are used in correlation analyses with the imaging data, descriptive statistics for these measures are provided in Table 3. The results of the BDI-II, BAI, POMS, and PASTEP group comparisons are described in Chapter 5.

Scanner responses. Participants' responses (in msec) collected during the scanning session were analyzed in terms of accuracy and response time, to determine whether there was any difference in how the participants were classifying the sounds during the blocked forced choice task. Accuracy was defined as a classification of positive or negative for the block of stimuli (that is, three stimuli from a particular category) that corresponded to the ratings given in Experiments 1 and 2, and is expressed as percent correct. Separate Valence (Positive, Negative) by Type (Music, IADS) ANOVAs were run for the accuracy and response time measures. It has been established that gender (Campanella, Rossignol, Mejias, Joassin, Maurage, Debatisse, et al., 2004; Glaser, Mendrek, Germain, Lakis, & Lavoie, 2012) and age (Vieillard, Didierjean, & Maquestiaux, 2012) can impact emotional responsiveness. Therefore, gender and age, as well as musical training were included as covariates in the model.

The results of the ANOVA for accuracy revealed a trend toward a significant main effect

of Valence (F (1, 14) = 3.84, p = .07, η^2 = .22), with Positive stimuli being rated accurately somewhat more frequently than negative stimuli ($Mean_{POS}$ = .81, SE_{POS} = .04; $Mean_{NEG}$ = .79, SE_{NEG} = .04). There was also a significant interaction of Valence by Type by Age (F (1, 14) = 10.15, p < .01, η^2 = .42). This three-way interaction was characterized by younger participants (< 29 years) rating Positive IADS accurately more frequently than did older participants (t (16) = -4.13, p = .001, Mean difference = -.51, $SE_{MeanDiff}$ = .12), but no difference was found for Negative IADS (t (16) = -0.01, p = .26, Mean difference = .05, $SE_{MeanDiff}$ = .05), Positive Music (t (16) = -0.03, p = .98, Mean difference = -.002, $SE_{MeanDiff}$ = .07) or Negative Music (t (16) = -0.09, p = .93, Mean difference = -.01, $SE_{MeanDiff}$ = .16). All other effects and interaction terms were non-significant (All F's < 3.50)

Results of the response time ANOVA revealed no significant effects or interactions (all p's > .10); however, some trends emerged. The main effect of Age was marginally significant (F (1, 14) = 3.78, p = .07, η^2 = .21), with younger participants (< 29) responding somewhat more quickly than older participants overall (t (16) = 0.89, p = .38, Mean difference = 81.66, $SE_{MeanDiff}$ = 91.32). There was also a trend toward significance for the interaction of Type by Age (F (1, 14) = 3.79, p = .07, η^2 = .21), with younger participants (< 29) responding slightly faster than older participants to musical stimuli (t (16) = 1.35, p = .20, Mean difference = 126.77, $SE_{MeanDiff}$ = 94.08), but not to IADS sounds (t (16) = 0.13, p = .90, Mean difference = 14.00, $SE_{MeanDiff}$ = 109.12). There was also a marginally significant interaction of Valence by Type by Gender (F (1, 14) = 3.54, p = .08, η^2 = .20). Though not significant, this three-way interaction was characterized by men responding somewhat faster than women to Negative IADS sounds (t (16) = 1.12, p = .28, Mean difference = 110.38, $SE_{MeanDiff}$ = 98.56), but not to Positive Sounds (t (16) = -0.78, p = .45, Mean difference = -112.06, $SE_{MeanDiff}$ = 144.29), Negative Music (t (16) = -0.48,

p = .64, Mean difference = -63.30, $SE_{MeanDiff}$ = 131.82),or Positive Music (t (16) = 0.48, p = .66, Mean difference = 43.20, $SE_{MeanDiff}$ = 96.62).

fMRI results. ***Main effect of Valence.*** When all positive stimuli were compared to all negative stimuli, the left auditory cortex showed significantly greater activation to positive stimuli, while bilateral occipital gyri showed significantly greater activation to negative stimuli ($\alpha < .05$ [$p < .05$, $k > 113$ voxels]). There was a trend for significantly greater activation to positive stimuli in the ventral anterior cingulate ($\alpha = .11$ [$p < .05$, $k = 101$ voxels]), and the right hippocampus ($\alpha = .13$ [$p < .05$, $k = 97$ voxels]) (Table 4, Figure 4). Activation focused in the hippocampus also spread into the right dorsal amygdala. As these two regions – the vACC and the amygdala – were among our *a priori* regions of interest, degree of activation was extracted from the maximally active voxel in the vACC, hippocampus, and amygdala for correlation analyses, assessed with Pearson's *r*.

Activity in the vACC (All Positive > All Negative) was significantly positively correlated with Negative Reactivity scores on the AIM (r = .64, p = .005), which means that as self-reported reactivity to negative situations increased, greater activity in the vACC was observed to positive compared with negative stimuli. Positive Affectivity was significantly positively correlated with activation in the amygdala (r = .47, p = .05), which means that those participants who reported greater affective responsiveness and intensity for positive stimuli on the AIM had greater neural response to positive versus negative stimuli in the amygdala. All other correlations between AIM scores and activity in these two regions were non-significant (all $r <$ .35).

For stimuli ratings, there was a significant negative correlation between activity in the amygdala (All Positive > All Negative) and valence ratings for negative stimuli (r = -.54, p =

.02), so that those participants who gave higher (less negative) valence ratings for the negative stimuli had greater neural responsiveness to negative, compared to positive, stimuli in the amygdala. There was no significant correlation between activity in the vACC (r = .01, p = .97) or the hippocampus (r = .003, p = .99) and Negative Valence ratings. There was a trend toward a significant positive correlation between activity in the hippocampus (All Positive > All Negative) and Positive Valence ratings (r = .45, p = .06), such that those participants who rated the positive stimuli as more positive showed greater activation to positive versus negative stimuli in the hippocampus. There was no significant correlation between activity in the vACC (r = .29, p = .24) or the amygdala (r = .31, p = .21) and Positive Valence ratings. Negative Arousal (vACC: r = -.37, p = .13; hippocampus: r = -.07, p = .77, amygdala: r = -.04, p = .88), and Positive Arousal (vACC: r = -.33, p = .18; hippocampus: r = -.13, p = .62; amygdala: r = -.19, p = .45), were not significantly correlated with activity in any of the three regions. Neither were Gender and Age significantly correlated with activity in these regions (Gender-vACC: r = -.23, p = .37; Gender-hippocampus: r = -.13, p = .60; Gender-amygdala: r = .37, p = .14; Age-vACC: r = -.02, p = .94; Age-hippocampus: r = -.38, p = .12; Age-amygdala: r = -.39, p = .11).

The relationships between ratings for Musical stimuli and activation for Positive and Negative Music, as well as MEQ scores and activation in these regions were also examined. Valence ratings for Positive Music were significantly positively correlated with activation to Positive Music in the hippocampus (r = .52, p = .03). Those participants who had rated the Positive Music as more positive also had greater activation in the hippocampus to Positive Music during scanning. All other correlations between valence and arousal ratings and activity in these two regions were non-significant (all r < .30, except Negative Music in vACC and Negative Music Valence Rating: r = -.33, p = .18; and Positive Music in amygdala and Positive Music

Valence Rating: $r = .38$, $p = .12$). MEQ scores were not significantly correlated with activation in the hippocampus (all $r < .30$). In the vACC, however, there were marginally significant negative correlations between activation to Positive Music and Affective Reactions to Music ($r = -.43$, $p = .08$), and between activation to Negative Music and Social Uplift from Music ($r = -.41$, $p = .09$). Participants who reported stronger affective reactions to music had somewhat less activation to Positive Music in the vACC, and those who reported feeling a greater sense of social uplift from music had marginally less activation to Negative Music in this region. There was also a trend for a significant positive correlation between activity to Positive Music in the amygdala and Innovative Musical Aptitude ($r = .45$, $p = .06$). All other correlations were non-significant (all $r < .30$, except activity to Positive Music in the amygdala and Commitment to Music: $r = .37$, $p = .13$).

Main effect of Sound Type. In stark contrast to the Valence results, which were very focal, the main effect of sound type revealed broad differences in activation across the brain. Activation foci are listed in Table 5; however, clusters were large and encompassed several regions. Activation to music was stronger in left middle frontal gyrus, anterior and dorsal cingulate gyrus, bilateral precuneus, bilateral inferior parietal lobule, bilateral occipital gyrus, and bilateral fusiform gyrus. Activation to sounds was greater in thalamus spreading into left amygdala, dorsomedial prefrontal cortex (DMPFC), bilateral dorsolateral prefrontal cortex (DLPFC), bilateral ventrolateral PFC (VLPFC), auditory cortex bilaterally (middle temporal gyrus, superior temporal gyrus), and bilateral cerebellum (Figure 5).

Interaction of Valence by Sound Type. In the interaction of Valence by Sound Type, only bilateral auditory cortex showed significant activation. This interaction was characterized by greater activity to positive music versus negative music, with no difference in activation to

positive versus negative IADS sounds (Figure 6; Table 6).

Discussion

In Experiment 3, healthy, never-depressed control participants' brain activations to emotional music and sounds were compared. First, brain responses to emotionally positive versus emotionally negative stimuli were examined. Then, brain responses to emotionally matched musical and nonmusical sounds were compared. Negative stimuli showed greater activation in bilateral occipital gyrus, or Brodmann area 18. This occipital cortex is the seat of visual processing; area 18 is part of the associative visual cortex, and has previously been shown to activate in response to auditory stimuli as part of the auditory network (Goycoolea, Mena, & Neubauer, 2011).

There was a trend for greater activation to positive stimuli compared to negative stimuli in the ventral anterior cingulate cortex. The ACC is generally divided into two main areas. The ventral ACC encompasses the perigenual, or rostral, and subgenual portions of the ACC, while the dorsal ACC is defined posterior to the crossing of the corpus callosum to the motor cortex. The vACC is also described as the emotional ACC, in contrast to the dorsal, or cognitive ACC, because activation in the vACC is typically found to emotional stimuli, whereas the dorsal ACC is more often activated in cognitive tasks (Bush, Luu, & Posner, 2000; Devinsky, Morrell, & Vogt, 1995). The ventral ACC receives projections from dopaminergic neurons in the nucleus accumbens, and has previously been shown to be activated in response to pleasant music (Menon & Levitin, 2005; Salimpoor, et al. 2010). In this study, activation in the vACC was displaying a true valence effect, with no differences in activation for stimulus type. The rostral anterior cingulate was more active in the current sample of participants to music compared to sounds. These findings suggest, in keeping with the work of Menon & Levitin and Salimpoor and

colleagues, that the dopaminergic system is active during music listening, and is actually more active during music listening than when listening to other emotional sounds.

Though a trend, the dorsal amygdala was also activated by this paradigm. The amygdala is comprised of several nuclei, each with distinct functions. While the ventral nuclei monitor for potentially threatening stimuli, the dorsal part of the amygdala contains the central nucleus, which signals the thalamus to activate the autonomic nervous system, and initiate physiological responses to emotional stimuli (Reeve, 2009). The amygdala is often thought to be sensitive to fearful or otherwise negative stimuli; however, it has previously been shown to activate to strong emotional responses to positive musical stimuli (Blood, Zatorre, Bermudez, & Evans, 1999; Blood & Zatorre, 2001). In this study, as in the work from Blood and colleagues, the amygdala showed greater activation to positive stimuli. This finding was driven by a small, but consistently greater response to positive versus negative musical stimuli, compared to a larger magnitude, but highly variable response to negative sounds; however, this was not reflected in differences in the ratings of these stimuli (See Chapter 4). One possible explanation for this finding could be that the emotional stimuli used in this study were mild compared to other studies of emotion processing, and the negative music was not unpleasant or dissonant, as in the study by Koelsch and colleagues (2006) that found greater activity to unpleasant music in this region. Additionally, the IADS sounds were specifically selected to match the emotional content of the musical stimuli. Consequently, some of the most extreme emotional sounds from the IADS set, such as erotic sounds and physical violence, were not included. It is possible that for these milder negative stimuli the emotional experience is more variable between individuals. While the data from this study do not address this question, it is possible that the positive stimuli used in this study may also evoke greater physiological responses, such as change in heart rate,

respiration, or skin conductance. Additional work is needed to determine if the pattern of activation in the amygdala is mirrored in these physiological measures.

The responses to music versus sounds were described by very different patterns of activation, contrary to our hypotheses. Greater activation to sounds compared to music in thalamus, amygdala, cerebellum and auditory cortex – regions associated with early emotion processing – suggests that sounds activate primary emotion networks more than music. However, greater activation to sounds was also found in lateral and dorsomedial prefrontal cortex, areas associated with top-down executive control, object recognition, language processing, and reappraisal. Music, on the other hand, activated rostral anterior cingulate cortex, precuneus, and bilateral parietal and occipital cortices more than sounds. These regions, collectively, are associated with the default mode network (DMN), a network of regions that tend to be more active when a person is focused more on their own internal state, rather than engaged in an external task (Golland, Bentin, Gelbard, Benjamini, Heller, Nir, et al., 2007; Greicius, Krasnow, Reiss, & Menon, 2003). These two systems have been described in models of voluntary and automatic reappraisal strategies (Phillips, Ladouceur, & Drevets, 2008). The DMN has been implicated in autobiographical processing (Buckner & Carroll, 2007; Spreng, Mar, & Kim, 2009). The fact that music activates the DMN, while sounds show greater activation in the network generally associated with tasks of executive function, is neural evidence that supports Myer's (1956) theory that the ambiguity in music is what allows it to be what he called a "metaphorizing medium," a scaffold that provides structure, but not content, that allows individual listeners the freedom to impose personal meaning onto this structure.

These stimuli were matched for valence and arousal (Experiments 1 and 2); therefore, the differences seen here cannot be attributed to differences in the emotional qualities of the stimuli,

and must, therefore, be interpreted in terms of cognitive identification and appraisal strategies. Together, these findings show that even when carefully matched for emotional content, separable brain networks process music compared with other emotional sounds. Emotional sounds activate early emotion monitoring systems (thalamus, amygdala, and cerebellum). Executive control areas, such as DLPFC, VLPFC, and DMPFC are activated as well, suggesting that object identification and voluntary reappraisal may be taking place. Music activates DMN and reward processing areas, such as ACC, suggesting that emotional processing in music relies more on autobiographical memory, idiosyncratic meaning assignment, and automatic appraisal, than does emotional processing in everyday sounds, which are more concrete and activate linguistic processing areas to a greater degree.

Chapter 4: Subjective Emotional Ratings – Experiment 4

Introduction

Experiment 4 was designed to test the third specific aim: measure and compare the strength of emotions reported to be experienced during music listening by individuals with MDD and ND controls. A significant Valence-by-Group interaction was predicted, with ND rating the Positive examples of both Types as more positive than MDD, and MDD rating the Negative examples of both Types as more negative than ND. Differences were not expected for arousal ratings between the Groups, neither were main effects or interactions involving Type.

Methods

Using the methods described for Experiments 1 and 2, participants from Experiments 3 (ND) and 5 (MDD) gave valence and arousal ratings for the stimuli selected in Experiment 1 and validated with Experiment 2. Experiment 4 was conducted following fMRI scanning of Experiments 3 and 5 so that the stimuli novelty was ensured during scanning. Ratings for musical and nonmusical stimuli were compared between MDD and ND groups.

Site of study. This experiment was conducted at the Hoglund Brain Imaging Center at the University of Kansas Medical Center. This study was approved by the University of Kansas Medical Center Human Subjects Committee.

Participant population. Participants were the eighteen ND participants described in Experiment 3 (Chapter 3) and the twenty MDD participants described in Experiment 5 (Chapter 5).

Materials. ***Stimuli.*** Stimuli were the music and IADS samples selected from Experiments 1 and 2. Participants heard the samples in the scanning environment prior to this testing session.

Measure. Ratings of valence and arousal of the stimuli were taken following fMRI testing, using the methods described in Experiments 1 and 2b, thus allowing for comparisons of emotion rating between MDD and ND participants for this previously validated stimuli set. Auditory stimuli were presented through computer speakers, using E-Prime 2.0 software running on a PC computer outside the scanning environment. Participants were allowed to adjust the volume to a comfortable level during a practice session. Responses were collected via mouse click, with valence rating coded on the *x* axis, and arousal coded on the *y* axis (Figure 1).

Procedure. Immediately following fMRI testing (Experiments 3 and 5), participants were escorted to a testing room within the imaging center. They were presented with each of the stimuli they had heard during the scanning session in random order, and asked to give valence and arousal ratings for each using the methods from Experiment 1. The procedure lasted approximately twenty minutes.

Analysis methods. Average valence and arousal ratings for each condition (Valence – Positive, Negative: Type – Music, IADS) given by participants in the two diagnosis Groups (MDD, ND), were compared using separate 2x2x2 mixed model analysis of variance (ANOVA) tests to determine whether the groups were responding to the two stimuli types differently. As with the analysis of classifications for the blocked forced choice task collected during scanning, gender, age, and years of musical training were included as covariates in each analysis. Planned analyses using one-tailed *t*-tests directly tested whether MDD participants rated the negative stimuli as more negative and the positive stimuli as less positive compared to ND participants by

comparing average ratings of valence across the diagnostic groups. Individual subject's ratings were also entered into correlation analyses with brain activation in *a priori* regions of interest (Chapters 3 and 5).

Results

The results of the ANOVA for Valence rating revealed a significant main effect for Valence (F (1, 33) = 11.79, $p < .01$, $\eta^2 = .26$), with Positive stimuli being rated as more positive than negative stimuli ($Mean_{POS} = 359.40$, $SE_{POS} = 3.78$; $Mean_{NEG} = 267.42$, $SE_{NEG} = 4.28$). No other effects or interactions passed significance criteria.

There was a trend toward significance for the interaction of Valence by Type (F (1, 33) = 3.01, $p = .09$, $\eta^2 = .08$), with Positive Music being rated as slightly more positive than Positive Sounds, with no difference for Negative Music and Sounds. There was also a trend for the interaction of Valence by Type by Gender (F (1, 33) = 2.59, $p = .12$, $\eta^2 = .07$), with women rating the Positive Music as slightly more positive than did men (t (36) = 1.79, $p = .08$, Mean difference = 17.78, $SE_{MeanDiff} = 9.94$), but no differences were found for ratings of Negative Music (t (36) = -0.92, $p = .36$, Mean difference = -11.01, $SE_{MeanDiff} = 11.92$), Positive IADS (t (36) = -0.10, $p = .92$, Mean difference = -1.25, $SE_{MeanDiff} = 12.68$), or Negative IADS (t (36) = -0.14, $p = .89$, Mean difference = -1.71, $SE_{MeanDiff} = 12.19$). Finally, there was trend toward a significant interaction of Valence by Type by Age (F (1, 33) = 3.07, $p = .09$, $\eta^2 = .09$). Though not significant, this three-way interaction was characterized by younger participants (< 32 years) rating Positive IADS as more positive than did older participants (t (36) = -2.36, $p = .02$, Mean difference = -29.77, $SE_{MeanDiff} = 12.62$), but no difference was found for Negative IADS (t (36) = -0.40, $p = .69$, Mean difference = -5.18, $SE_{MeanDiff} = 13.02$), Positive Music (t (36) = 0.41, p =

.43, Mean difference = 8.82, $SE_{MeanDiff}$ = 11.00) or Negative Music (*t* (36) = 0.18, *p* = .92, Mean difference = 1.36, $SE_{MeanDiff}$ = 12.90).

Contrary to our hypotheses, there was not a significant interaction of Valence by Group (*F* (1, 33) = 0.08, *p* = .79, $\eta^2 < .01$), which means that diagnostic group was not a factor in how the participants were rating the valence of these stimuli. The planned *t*-tests comparing Valence ratings of Positive (*t* (36) = 0.45, *p* = .65, Mean difference = 3.46, $SE_{MeanDiff}$ = 7.62) and Negative stimuli (*t* (36) = -0.51, *p* = .61, Mean difference = -4.45, $SE_{MeanDiff}$ = 8.68) between the two groups were non-significant, confirming this result. All other effects and interaction terms in the ANOVA were non-significant (All *F*'s < 2.5).

The results of the ANOVA for Arousal rating revealed a significant interaction of Type by Age (*F* (1, 33) = 4.94, *p* = .03, η^2 = .13), with younger participants (< 32 years) rating IADS stimuli as more arousing than did older participants (*t* (36) = -2.04, *p* = .05, Mean difference = -27.35, $SE_{MeanDiff}$ = 13.38), but no difference was found for Musical stimuli (*t* (36) = 0.78, *p* = .44, Mean difference = 9.04, $SE_{MeanDiff}$ = 11.60). No other effects were significant; however, there were trends for the main effects of both Valence (*F* (1, 33) = 3.06, *p* = .09, η^2 = .09) and Age (*F* (1, 33) = 2.62, *p* = .12, η^2 = .07). Though not significant, the pattern of arousal ratings for these trends indicated that Negative stimuli were rated slightly more arousing than were Positive stimuli ($Mean_{NEG}$ = 226.98, SE_{NEG} = 4.13; $Mean_{POS}$ = 216.62, SE_{POS} = 5.55), and younger participants rated all stimuli as slightly more arousing than did older participants ($Mean_{<32}$ = 224.43, $SE_{<32}$ = 5.03; $Mean_{>=32}$ = 215.30, $SE_{>=32}$ = 8.35). All other effects and interaction terms were non-significant (All *F*'s < 2.5), which means that diagnostic group and musical training did not significantly change the pattern of responding for Arousal ratings.

Discussion

Self-reported ratings for Valence and Arousal given by participants in the imaging studies indicate that depression status did not systematically influence how participants rated the stimuli. Indeed, gender and age were the only factors to influence participants' responses, though most of these findings were marginal. In this group of participants women gave marginally more positive ratings for music than did men, but no other ratings were different between men and women. Age was a contributing factor for both valence and arousal ratings, with younger participants rating positive IADS sounds as slightly more positive, and the IADS as a whole significantly more arousing than did older participants. These findings do support previous literature that suggests gender and age are important variables to consider (Campanella, et al., 2004). Indeed, the diagnostic groups were carefully matched for gender and age to balance the effects of these variables in the imaging data.

Though we had predicted differences in Valence ratings, depression status did not significantly change the pattern of responses. This means that the results of Experiment 5, the imaging study, are comparable to the work from Osuch and colleagues (2009). In that study, participants gave equivalent enjoyment ratings for their favorite music, yet they showed reduced activity in reward centers of the brain, suggesting a potential neural marker of anhedonia. As participants in this study are also rating the stimuli equivalently, differences in brain activity, therefore, cannot be directly attributed to changes in subjective experience.

Chapter 5: Differential Neural Responses to Emotional Music and Sounds Between Currently Depressed and Never Depressed Participants – Experiment 5

Introduction

Experiment 5 address the second specific aim: 1) determine whether the experiences of positive and negative emotion in response to music and nonmusical sounds are differentially represented in brain activity in the mesolimbic system between individuals with MDD and ND controls.

The fMRI responses of depressed (MDD) participants to emotional musical and nonmusical stimuli were compared with ND participants' responses to determine whether the brain regions known to be affected in depression (amygdala, subgenual ACC, VTA, thalamus, mPFC) were responding differentially to emotionally evocative stimuli in the auditory domain. It was hypothesized that depressed individuals would show greater responsiveness to negative stimuli and reduced responsiveness to positive stimuli in these areas when compared with non-depressed controls.

Methods

Site of study. This experiment was conducted at the Hoglund Brain Imaging Center at the University of Kansas Medical Center. This study was approved by the University of Kansas Medical Center Human Subjects Committee.

Participant population. Twenty individuals with major depressive disorder (MDD) (n = 20; 9 males; $Mean_{AGE}$ = 34.15; SD_{AGE} = 13.64; $Range_{AGE}$ = 18-56), experiencing a current depressive episode at the time of scanning, determined by administration of the Structured Clinical Interview for DSM Disorders, non-patient version (SCID-I/NP) (First, 2002), were

scanned using the same paradigm as Experiment 3. Participants had no current or past manic episodes, no comorbid anxiety disorders, and no current alcohol abuse or dependence. Six participants were currently being treated for depression (Counseling: n = 5, Medication (Sertraline): n = 1), and 13 had received treatment in the past (Counseling: n = 7, Medication: n = 6). Four participants had a history of alcohol or drug dependence, fully remitted a minimum of one year prior to participation. One participant had a history of PTSD in full remission. Participants were recruited from flyers posted on university campuses throughout the immediate metro area, through online advertisements, and through the University undergraduate subject pool. The Never Depressed participants from Experiment 3 served as control participants for Experiment 5. The groups (ND: n = 18, MDD: n = 20) were matched for age (t (36) = -1.25, p = .22, $Mean_{DIFF}$ = -5.15, $SE_{MEANDIFF}$ = 4.11), gender (X^2 (1) = 0.001, p = .97), years of education (t (36) = 1.29, p = .21, $Mean_{DIFF}$ = 1.12, $SE_{MEANDIFF}$ = 0.87), IQ as estimated by the Vocabulary and Matrix Reasoning subtests of the WASI (Wechsler, 1999) (t (36) = 0.86, p = .40, $Mean_{DIFF}$ = 3.27, $SE_{MEANDIFF}$ = 3.81), and years of musical training (X^2 (4) = 3.89, p = .42). All participants were right handed.

Materials. ***Stimuli.*** Stimuli were the same as those described in Experiment 3.

Scanning parameters and procedures. Scanning parameters and procedures were the same as those used in Experiment 3.

Analysis methods. Preprocessing was identical to Experiment 3. Anatomic data from one participant (MDD group) was not able to be successfully normalized using the <@auto-tlrc> algorithm, and was transformed manually in AFNI by defining key anatomic points (anterior commissure, posterior commissure, anterior point, posterior point, superior point, inferior point, right point, left point, and two points on the mid-sagittal plane). No functional runs were

discarded for excessive motion.

Whole brain analyses were conducted as for Experiment 3. Additional analyses adding Group as a between-subjects measure were also performed. ROI analyses were conducted, exporting percent signal change data as described in Experiment 3 to SPSS/PASW for correlation analyses using Pearson's *r*. These six *a priori* ROIs were anticipated to show differential brain responses for MDD and ND participants based on the valence of the stimuli, with MDD showing greater activation to negative stimuli and ND showing greater activation to positive stimuli. Further, activation in these regions was expected to be negatively modulated by higher BDI and POMS scores and positively correlated with stimuli ratings and AIM scores, and for musical stimuli, to be positively impacted by MEQ score. Correlations were run in the groups separately.

Results

Questionnaires. Group differences on each of the self-report measures were assessed using t-tests. A full table of these results is available in Table 7. Depressed participants reported higher total BDI-II score, total BAI score, and PASTEP total score, confirming that this group was experiencing greater depressive symptoms at the time of testing, as well as higher incidence of depression over their lives. Current mood was also different, as depressed participants had higher scores on the Depression, Anger, Fatigue, Confusion, and Total Mood Disturbance subscales of the POMS. Control participants had higher scores on the Vigor subscale of the POMS, the only subscale that measures positive mood states. Depressed participants also had higher scores on the AIM Negative Intensity subscale, indicating that they experience negative situations with greater intensity than do Never Depressed participants. Interestingly, depressed participants reported greater Positive Psychotropic Effects from music, as measured by the MEQ.

As this was an unexpected finding, this should be treated cautiously, and will need to be replicated in a larger sample. The finding is supported by public opinion, however. In a large survey of the public's recommendations for dealing with depression, 82% of those respondents with depression who were currently in treatment agreed that music was effective as a coping strategy, compared with only 67% of those who were not in treatment (Holzinger, et al., 2012).

Scanner Responses. As in Experiment 3, participants' responses collected during the scanning session were analyzed in terms of accuracy and response time, to determine whether the groups were classifying the sounds differently during the blocked forced choice task. Separate Group (Depressed, Never Depressed) by Valence (Positive, Negative) by Type (Music, IADS) ANOVAs were run for the accuracy and response time measures. Gender, age, and years of musical training were included as covariates in each analysis.

The results of the ANOVA for accuracy revealed no significant main effects or interactions by diagnostic group (All F's < 3.0). There was a significant main effect of Valence (F (1, 33) = 8.64, $p < .01$, $\eta^2 = .21$), with Negative stimuli being rated accurately more frequently than Positive stimuli ($Mean_{NEG} = .79$, $SE_{POS} = .03$; $Mean_{POS} = .75$, $SE_{NEG} = .03$), the opposite effect of the Valence effect found in the ND group alone (Chapter 3). Age significantly affected the ratings in several comparisons. There was a significant interaction of Valence by Age (F (1, 33) = 5.68, $p = .02$, $\eta^2 = .15$), with younger participants (< 32 years) rating Positive stimuli accurately more frequently than did older participants (t (36) = -2.60, $p = .01$, Mean difference = -.17, $SE_{MeanDiff} = .06$), but no difference was found for Negative stimuli (t (36) = -0.35, $p = .73$, Mean difference = -.03, $SE_{MeanDiff} = .09$). There was also a significant three way interaction of Valence by Type by Age (F (1, 33) = 8.81, $p < .01$, $\eta^2 < .01$). This three-way interaction was characterized by younger participants rating the Positive IADS accurately significantly more

often than older participants (t (36) = -2.90, p < .01, Mean difference = -.30, $SE_{MeanDiff}$ = .10), but there were no differences for Negative IADS (t (36) = 1.21, p = .23, Mean difference = .07, $SE_{MeanDiff}$ = .06), Positive Music (t (36) = -1.12, p = .27, Mean difference = -.08, $SE_{MeanDiff}$ = .07), or Negative Music (t (36) = -0.78, p = .44, Mean difference = -.10, $SE_{MeanDiff}$ = .12). There were also significant interactions with Gender and Musical Training. There was a significant interaction of Gender by Type (F (1, 33) = 5.67, p = .02, η^2 = .15), with men rating the music accurately somewhat more often than did women (t (36) = -1.66, p = .11, Mean difference = .13, $SE_{MeanDiff}$ = .08), and women rating the IADS accurately marginally more often than did men (t (36) = 1.00, p = .33, Mean difference = .06, $SE_{MeanDiff}$ = .06). Finally, There was a significant interaction of Valence by Musical Training (F (1, 33) = 4.05, p = .05, η^2 = .11), with participants who had more years of musical training rating Negative stimuli accurately more frequently than did participants with less training (t (36) = 2.14, p = .04, Mean difference = 0.17, $SE_{MeanDiff}$ = 0.08), but no difference was found for Positive stimuli (t (36) = 0.45, p = .66, Mean difference = 0.03, $SE_{MeanDiff}$ = 0.07). All other effects and interaction terms were non-significant (All F's < 3.0).

The results of the ANOVA for response time also revealed no significant main effects or interactions by diagnostic group (All F's < 3.0). There was a significant interaction of Type by Musical Training (F (1, 33) = 9.10, p < .01, η^2 = .22), with those participants who had more musical training responding somewhat more quickly to the musical stimuli (t (36) = -1.57, p = .13, Mean difference = -142.23, $SE_{MeanDiff}$ = 90.80), but not to the IADS sounds (t (36) = 0.84, p = .41, Mean difference = 59.29, $SE_{MeanDiff}$ = 70.31). There was a marginally significant interaction of Gender by Type (F (1, 33) = 3.08, p = .09, η^2 = .09), with men responding slightly more quickly to musical stimuli (t (36) = 0.62, p = .54, Mean difference = 55.68, $SE_{MeanDiff}$ =

90.56), and women responding somewhat more quickly to IADS sounds (t (36) = -0.62, p = .54, Mean difference = -42.30, $SE_{MeanDiff}$ = 68.52). There was also a marginally significant three-way interaction of Valence by Gender by Type (F (1, 33) = 3.87, p = .06, η^2 = .11). Though not significant, this three-way interaction was described by men responding somewhat more quickly to Positive Music (t (36) = 1.32, p = .19, Mean difference = 118.28, $SE_{MeanDiff}$ = 89.46), and women responding somewhat more quickly to Positive IADS (t (36) = -1.26, p = .21, Mean difference = -111.91, $SE_{MeanDiff}$ = 88.55), but no differences were found for Negative IADS (t (36) = 0.40, p = .69, Mean difference = 27.32, $SE_{MeanDiff}$ = 68.39), or Negative Music (t (36) = -0.61, p = .95, Mean difference = -6.91, $SE_{MeanDiff}$ = 113.23). All other effects and interaction terms were non-significant (All F's < 3.0).

fMRI results. ***Interaction of Group by Valence.*** Comparing all positive to all negative stimuli, no significant differences were found between Depressed and Never Depressed groups (all $\alpha > .10$). One region, the rostral ACC, did show a trend toward significance ($\alpha = .20$ [$p < .05$, $k = 90$ voxels]), with Never Depressed participants showing no difference from baseline to positive stimuli accompanied by a decrease in activation to negative stimuli, while Depressed participants showed the opposite pattern in this region: no difference from baseline to negative stimuli, with a significant decrease to positive stimuli (Figure 7; Table 8).

Interaction of Group by Sound Type. Comparing group responses to music versus IADS sounds, only one region survived thresholding ($\alpha < .05$ [$p < .05$, $k > 113$ voxels]; Table 9). Never Depressed Control participants showed greater activation in the anterior cingulate cortex to music versus sounds, while Depressed participants showed relatively greater activity to sounds, with the greatest activation to negative sounds, followed by positive sounds, then positive music, and finally, negative music (Figure 8). The area of activation covers both the

ventral and dorsal ACC; however, the maximally activated voxel was in the dorsal ACC. Percent signal change for each condition and for the contrast (All Music > All IADS) in this voxel was exported for correlation analyses with self-report measures, including the BDI-II, BAI, PASTEP, POMS, AIM, and MEQ. As this region was identified from a group comparison, correlation analyses were run in the groups separately.

Correlation analyses: ND Control Participants. Correlation analyses of the mood measures in the Never Depressed Group revealed a significant negative correlation between activation in the dACC to Negative IADS and BDI-II score (r = -.48, p = .04), and a significant negative correlation between the Total Mood Disturbance score of the POMS and activation to Negative IADS (r = -.56, p = .02). Those participants who reported more negative mood states on these measures were exhibiting greater activation in this region specifically for the Negative IADS. There was also a trend toward a significant positive correlation between activation to Positive Music and the Vigor subscale of the POMS (r = .43, p = .08), such that those participants who reported greater feelings of vigor had greater activation to Positive Music in this region. All other correlations between activation in this region and measures of mood were nonsignificant, as were all correlations with valence and arousal ratings (All p's > .10). There was a significant negative correlation between AIM Negative Reactivity score and activation in this region (All Music > All IADS) (r = -.52, p = .03), such that as Negative Reactivity scores increased, activation in the contrast decreased. There was also a marginally significant negative correlation between AIM Negative Intensity score and Negative IADS activation (r = -.33, p = .07). In this case, as self-reported Negative Intensity increased, activation to Negative IADS decreased. Finally, there was a marginally significant negative correlation between activity to Positive Music in this region and Affective Reactions to Music, as measured by the MEQ (r = -

.44, p = .07). As self-reported affective reactions to music decreased, activation to Positive Music increased. As this region of the ACC is more cognitive and less emotional, this finding is perhaps not too surprising. All other correlations with AIM and MEQ scores were nonsignificant (All p's < 0.10).

Correlation analyses: MDD Participants. In the Depressed group, activation in the dACC to Positive Music was marginally negatively correlated with BAI scores (r = -.44, p = 06), such that as anxiety symptoms increased, activation to Positive Music decreased. BDI-II scores were not significantly correlated with activity in this region (All p's < 0.10). Mood scores on the POMS were significantly correlated with activity for positive stimuli, with the Vigor subscale being significantly positively correlated with activation to Positive IADS (r = .48, p = .03), and the Tension (r = -.62, p < .01) and Fatigue subscales (r = -.47, p .04) being significantly negatively correlated with activation to Positive IADS, and the Fatigue subscale trending toward a significant negative correlation with activation to Positive Music (r = -.40, p .08). With negative mood state, there was reduced activation to positive stimuli in this region, while positive mood (that is, vigor) was associated with increased activation to positive stimuli.

In this group, activation was significantly correlated with ratings given outside the scanner. Activity to Positive Music was significantly positively correlated both to arousal ratings for Positive Music (r = .46, p = .04), and marginally significantly correlated with arousal ratings for positive stimuli overall (r = .43, p = .06). Activation to Negative IADS was significantly negatively correlated with valence ratings for negative stimuli (r = -.50, p = .02), such that as valence ratings increased (were less negative), activation in this region to negative sounds increased. Activation in the contrast (All Music > All IADS) was positively related to arousal ratings generally and for sounds specifically. There were significant positive correlations

between activation and arousal for Negative IADS (r = .53, p = .02), and arousal for Positive IADS (r = .47, p = .04), and trends toward significant correlations with arousal for negative stimuli (r = .39, p = .09), and arousal for all stimuli (r = .41, p = .08). Finally, activation to Positive IADS was significantly positively associated with scores on the AIM Positive Affectivity subscale (r = .56, p = .01), and activation to Negative Music was marginally positively correlated with Positive Psychotropic Effects of Music measured by the MEQ (r = .41, p = .07). All other correlations were nonsignificant (All p's < .10).

Three-way interaction. No areas of the cortex were significantly activated in the Group by Valence by Sound Type interaction (all $\alpha > .20$).

Discussion

Comparing brain responses to emotional musical and nonmusical sounds between those participants currently experiencing depression and those who have never had depression, one broad region was found to show different patterns of activation – the anterior cingulate cortex. Never Depressed Control participants showed significantly greater activity compared to Depressed participants in the dorsal ACC for music compared to sounds. Depressed participants were showing comparatively greater activity, or hyperactivity, in this region for sounds.

The ventral part of the ACC also showed a trend for greater activation to all positive stimuli in ND participants compared to MDD participants. This activation was characterized by both a hypoactivation to positive and a hyperactivation to negative stimuli. The ventral ACC is anterior to the subgenual ACC, which is the most effective stimulation site for deep brain stimulation in treatment-resistant depression (Hamani, Mayberg, Stone, Laxton, Haber, & Lozano, 2011). Although the activation found in this study is not the exact location targeted for stimulation, the entire ACC receives projections from the midbrain dopaminergic neurons

(VTA), and is implicated in emotional functioning in depression (Drevets, 2000, 2001; Drevets, Price, & Furey, 2008). The current findings using standardized emotional auditory stimuli replicate those found by Osuch and colleagues (2009), showing reduced activity in this region by depressed participants to their favorite music.

Chapter 6: General Discussion

Summary

Never depressed control participants. ***Positive versus Negative stimuli.*** This set of studies was designed to determine whether music and nonmusical emotional sounds could be used in a neuroimaging paradigm as a probe for investigating neural circuitry of emotion and reward in depression. First, the paradigm was tested in never depressed control participants to determine whether the musical and nonmusical sounds activated these circuits. Across both stimulus types, positive stimuli activated the dorsal amygdala, hippocampus, and ventral ACC to a greater extent than negative stimuli. Activity in the dorsal amygdala showed reliable differences in activation to positive versus negative music, compatible with the results from Blood and colleagues (Blood, et al., 1999; Blood & Zatorre, 2001). Interestingly, the negative nonmusical sounds showed the greatest magnitude of activation, but also the greatest variability; therefore, contrasts with negative sounds were not statistically significant. The dorsal amygdala triggers physiological responses to emotional stimuli by activating the thalamus (Reeve, 2009). In this study, the emotional stimuli were milder than stimuli used in other studies, which may have contributed to the variability to negative sounds found here.

Positive stimuli also activated the hippocampus to a greater degree than negative stimuli. Activity in this region was characterized by a significant decrease in activity to negative sounds. The role of the hippocampus in emotion processing is to encode memory traces of the critical stimuli, and is involved in learning associations between the stimulus and the emotional response. It is also involved in monitoring emotional regulation, and is activated to anticipation of pleasure, as well as pain (Reeve, 2009). Never depressed participants often show a positivity

bias in memory for emotional stimuli (Kakolewski, et al. 1999). Participants' memory for and experience with these stimuli were not tested in this study; however, it is possible that the relatively greater activation seen for positive stimuli in the hippocampus may be a mechanism by which this positivity bias in memory develops.

Finally, as hypothesized, there was greater activation in the vACC for positive versus negative stimuli. Activation in this area was characterized by a true valence effect. No differences were seen based on stimulus type. The vACC receives dopamine projections from the ventral tegmental area, and sends projections dorsally and laterally to executive control areas of the cortex (Reeve, 2009). Blunted activity in this region has been associated both with transient sadness (Devinsky, et al., 1995) and with depression (Davidson, et al., 2002), suggesting that this region is critical for the experience of positive emotions.

Musical versus Nonmusical stimuli. Next the study compared responses to musical and nonmusical stimuli directly, to determine whether these emotionally matched stimuli evoked different brain responses. Valence and arousal ratings for these two stimuli types were not different; however, there were some effects of age and gender, as anticipated. Contrary to our hypothesis that matching for emotional quality would lead to similar patterns of neural activity, music and sounds activated distinct networks in the brain. Music activated the reward network and default mode network to a greater extent than sounds, whereas sounds activated early emotion processing areas and object recognition areas. These networks also map very nicely onto Phillips and colleagues' model of automatic versus voluntary emotion regulation. Music activates midline regions that are included in this model's automatic regulatory system, while sounds activate lateral prefrontal areas that make up the voluntary regulatory system. Interpreted in light of this model, the emotional response to music seems to be driven by the automatic,

internal processes, while that to sounds incorporates more of a top-down, object-oriented appraisal process. Importantly, these results suggest that emotion processing within the same sensory domain is clearly not equivalent. Different brain networks are recruited for different types of stimuli, and these may reflect different appraisal or reappraisal strategies that may be evoked.

Comparison of Depressed versus Never-depressed participants. ***Positive versus Negative stimuli.*** After confirming the paradigm evoked activity in the areas known to be affected in depression, activity was directly compared in a group of participants experiencing a current depressive episode. Both groups reported similar emotional experiences from the stimuli; however activation in the anterior cingulate cortex did show differences in activation. When all stimuli were compared based on emotional valence, the ventral ACC showed relatively more activation to positive stimuli in never-depressed participants. This relative difference was actually driven by never-depressed participants showing no difference from baseline to positive stimuli, with a significant decrease from baseline to negative stimuli. Depressed participants showed the opposite pattern: no difference from baseline for negative stimuli, and a significant decrease from baseline to positive stimuli. The present results are comparable to those found by Epstein, and colleagues, that showed comparatively greater striatal and medial PFC activation in controls when viewing emotional words (2006). The ventral ACC inhibits amygdala response (Jackson & Moghaddam, 2001), and has been shown to deactivate to cognitive tasks (Bush, et al., 2000). Activity in this region could be monitoring for a change from current mood state, as controls showed a change in activity only to negative stimuli and depressed participants showed a change only to positive stimuli. More cognitive resources would be required to integrate emotional information that represents a change from the current state.

Musical versus Nonmusical stimuli. Comparing musical to nonmusical stimuli between the groups, activation was found in the perigenual and dorsal ACC. In this region, never depressed participants showed greater activation to all music compared to all sounds. When emotional content is mild, as in this study, and stimuli are pleasant, yet evoke negative emotions, as in the negative music, emotional classification for the music requires a decision between competing streams of information. Activity in the dACC in ND controls could represent a neural representation of the enjoyment of negative music. Depressed participants showed greater activation to sounds in this region, with the biggest response for negative sounds, followed by positive music, positive sounds, and negative music showing the smallest response.

A large body of research has implicated the anterior cingulate as one of the main regions to be affected by depression (Pizzagalli, 2011). Volumetric studies have repeatedly shown that a decrease in the size of the ACC to be associated with depression (Lai, 2013), and has sufficient sensitivity and specificity as a secondary means of diagnosis (Niida, Niida, Matsuda, Inada, Motomura, & Uechi, 2012). Unlike studies showing atrophy of affected brain regions with psychiatric disorders – for example, studies showing reduced hippocampal volume following post-traumatic stress disorder (PTSD) (Admon, Leykin, Lubin, Engert, Andrews, Pruessner, et al., 2012) – the size of the ACC in depression does not change either with the course of the disorder, or with treatment (Niida, et al., 2012). This suggests that ACC volume may be a marker of depression vulnerability, in addition to its value in diagnosis. Functional responsiveness of the ACC has been linked to treatment success, however (Mayberg, et al., 1997; Pizzagalli, 2011). Different treatment regimens target different subregions of the ACC; successful cognitive therapies are associated with increased activation in dorsal ACC, whereas medication based therapies often target ventral and rostral portions of the ACC (Quide,

Witteveen, El-Hage, Veltman, & Olff, 2012; Roiser, Elliott, & Sahakian, 2012). Glutamate cycling, indicating general neural activity, has also been shown to be reduced in the vACC in depression (Horn, Yu, Steiner, Buchmann, Kaufmann, Osoba, et al., 2010), which suggests that tonic levels of activity in the vACC are lower in depression.

Discussion

Anterior cingulate function in depression. Dorsal ACC is generally thought to be associated with cognitive control and conflict resolution. It has also been shown to increase activity for more salient information. For example, a recent fMRI study of fear and phobia revealed that activity in this region parametrically increased as an imaginary tarantula was moved closer to the participant's foot (Mobbs, Yu, Rowe, Eich, FeldmanHall, & Dalgleish, 2010). In addition, another fMRI study of anxiety found that angry faces evoked greater response in the dACC in participants with high social anxiety compared to those with low social anxiety (Duval, Hale, Liberzon, Lepping, Powell, Filion, et al., under review). This fits with earlier findings from Seeley and colleagues, who found that resting state connectivity between the dACC and the anterior insula is positively correlated with anxiety ratings (Seeley, Menon, Schatzberg, Keller, Glover, Kenna, et al., 2007). Hamilton and colleagues have described a neural model for biased responding to negative information in depression using meta-analysis. This model focuses on heightened tonic activity in the pulvinar nucleus, which increases responsivity in the salience network (amygdala, dACC and insula), paired with reduced tonic levels of dopamine in the striatum, leading to lessened coupling between the feed-forward and feedback mechanisms within this circuitry (Hamilton, Etkin, Furman, Lemus, Johnson, & Gotlib, 2012). Collectively, this body of work leads to the conclusion that the dACC is not only involved in cognitive task-switching, but also plays an important role in monitoring for highly

salient information. In this study, depressed participants showed greater activation in this region to mildly emotional sounds, suggesting that for this group, these sounds may have been processed as more salient than they were for ND controls; however, no differences were found in self-reported responsiveness to those stimuli. Additional work is needed to clarify this response.

Implications

The proposed study sought to determine whether emotional musical and nonmusical stimuli were processed in a similar manner by healthy participants. In addition, the study compared the evoked brain responses to those stimuli in people with and without MDD to determine if the pattern of response was affected by MDD. By comparing musical and nonmusical sounds, the current study provides a broader understanding of how individuals with MDD process different types of auditory stimuli. Music is currently used for mood manipulations in clinical and laboratory settings (Clark, 1983; Clark & Teasdale, 1985; Clark, Teasdale, Broadbent, & Martin, 1983; Pignatiello, Camp, & Rasar, 1986; Sutherland, Newman, & Rachman, 1982); therefore, the results may ultimately have significant clinical implications for treating depression, or for the use of music as an affective probe for determining risk of developing the disorder. Additionally, music therapists have been using music to impact mood and depression in terminal illness (Hilliard, 2001) and Alzheimer's disease (Guetin, Soua, Voiriot, Picot, & Herisson, 2009), and are now extending this to mood disorders that are not related to a physical illness, with promising results (Koelsch, Offermanns, & Franzke, 2010; Erkkila, Punkanen, Fachner, Ala-Ruona, Pontio, Tervaniemi, et al., 2011; Maratos, Crawford, & Procter, 2011). The transitory nature of music might make it a useful tool for mood modification; however, the mechanisms by which this may occur are not fully defined. Koelsch and colleagues (2010) argue that music therapy may be useful in treating depression, PTSD, and

other mood disorders by acting on both the NAc-VTA reward processing loop, and by potentially reactivating the anterior hippocampal formation, which has been shown to have a reduced volume in these disorders (Warner-Schmidt & Duman, 2006). The current results suggest that, similar to other forms of treatment, the mechanisms by which music and other forms of emotional auditory stimulation may function in depression could be by reactivating the ACC. Though it is not yet clear whether long-term treatment with music therapy can impact general brain functioning in these areas, continued study of the brain regions activated by music and other sounds using imaging techniques like fMRI will inform theories of depression by helping determine the individual contributions of reward, cognitive rumination, and disordered sensitivity in emotional processing of sound.

Limitations

The current project has some limitations. Specifically, Experiments 1 and 2 were conducted with a small sample size. However, the replication from Experiment 1 to Experiment 2 suggests that this effect is potentially robust. The current stimuli set would, nevertheless, benefit from a larger and more demographically varied sample, particularly given the gender and age effects found in the imaging sample. A second limitation of the stimuli selection process is that the measure used to assess emotional ratings was based on self-report; it did not allow for examination of whether the emotion was experienced or simply recognized. Future studies should include psychophysiological measurements, such as heart rate variability, respiration, and skin conductance, especially in light of the variability in activation to negative sounds found in the dorsal amygdala, a region whose function is to activate autonomic responses. Finally, no musical analysis has yet been performed, and a limited number of examples from Western art music are used in the proposed study. Though these examples were selected empirically to

control for familiarity and linguistic confounds, it is possible that other types of music, such as popular songs or opera, would elicit stronger emotions. A systematic analysis of the musical elements of the current stimuli would allow the stimuli set to be expanded to increase the number and types of musical examples.

Conclusions

In conclusion, the proposed project revealed that in healthy participants, positive auditory stimuli activated reward processing areas of the brain that are known to be affected in depression. Secondly, the present results identified that musical and nonmusical emotional sounds were processed by distinct networks of brain regions that have been proposed to reflect automatic and voluntary appraisal processes. Finally, this set of studies highlighted the anterior cingulate cortex as exhibiting differential responsiveness to these mild emotional stimuli in participants with depression. The present results suggest that participants with depression may be devoting greater cognitive resources to manage their response to emotional sounds, while also showing a general lack of responsiveness in emotion processing regions to positive auditory stimuli. By using fMRI and a standardized music and nonmusical emotion processing probe, the current study has provided insight into finer distinctions of stimulus type, and may have implications for therapeutic interventions or risk assessment.

Chapter 7: Future Directions

Additional Exploratory Analyses with the Current Dataset

While the present analyses are sufficient to address the aims set forth in this dissertation, the data collected for this project could also be used to answer a related set of questions about the role of emotion processing in MDD. As these are not central to the main aims of this project and are potentially underpowered, they have been included here as additional exploratory analyses that may be conducted in the future.

Voxel-Based morphometry. As structural differences have been identified in previous studies, specifically in the ACC and lateral habenular nucleus, potential differences between the brain structure of MDD and control groups in this project may help explain functional differences explored in the main analyses. For this purpose, VBM implemented in SPM 8 (Wellcome Trust Centre for Neuroimaging, London) running under MATLAB (MathWorks, Natick, MA), can be used to assess potential brain structure differences between the two groups. In this procedure, anatomical images (MPRAGE) are aligned to the MNI152 template, and segmented into gray matter, white matter and cerebrospinal fluid masks. Each $1mm^3$ voxel in the image is categorized according to the segmentation masks, correcting for partial volumes. Statistical parametric maps are then generated from group differences at each voxel. Clusters would be considered significant if they survive a threshold of $\alpha < .05$ (corrected).

Mediation analysis. The relationship between brain activation, experience, and self-reported emotional response has not been fully developed. The valence and arousal ratings given in Experiment 4 could potentially be used in a mediation analysis to examine whether brain

activation or inhibition, as measured by BOLD activity, mediates the relationship between negative or positive stimuli and self-reported perceptions of those stimuli.

Future Lines of Research

Finally, this project represents the first episode in a program of research. As with any study, while some questions are answered, many more become apparent. The following is an outline of some of the next steps that will be addressed in future studies. First, activation in the ND group in the dorsal amygdala suggested that physiological responses to positive versus negative music may be different. It also suggested that reactions to the mildly negative sounds presented here were highly variable in this non-clinical sample. A psychophysiological study would be an important next step to confirm whether activation in the dorsal amygdala could be related to physiological reactivity. Second, this block design fMRI study gave us the power to detect differences across the broad categories of sound type and valence. This method is not sensitive to differences between individual stimuli, nor can it be used to define relationships between brain activity and self-reported response to individual stimuli. To test the parametric effects of subjective emotional experience, an event-related study would be necessary. In this type of test, participants would be asked to give emotional ratings to each stimulus during fMRI scanning, and analyses would compare neural responses based on those responses, rather than on pre-defined classifications.

In addition to these direct clarification studies, two larger bodies of work are inspired by this project. The first arises from the differences in activation patterns for music versus sounds. These networks seem to map well onto the automatic and voluntary appraisal networks proposed by Phillips and colleagues (2008), suggesting that different appraisal methods are employed when listeners are confronted with these different stimuli types. An investigation into the

appraisal and reappraisal processes for different types of auditory stimuli would be warranted. Finally, the pattern of responsiveness in the ACC among depressed participants in this study raises the question of whether music, and specifically positive music, may be useful in retraining ACC and improving functioning. A longitudinal study with a music-listening intervention would be critical to determine whether activity in ACC is malleable in this population. It is also possible that, as reported by Heller and colleagues (2009), it is not the initial response that is critical, similar to what is tested in this paradigm, but rather the ability to sustain activation that is important for maintaining depression. As so many researchers are dedicated to depression research, the neural mechanisms of this disorder are being clarified at an amazing rate. As information continues to emerge, there is hope that this debilitating disorder will be met with more effective and targeted treatments, and that the numbers of people who suffer from this condition will be reduced, and that the duration of their symptoms may be lessened.

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Tables & Figures

Table 1. Musical pieces identified by Witvliet and Vrana (2007).

Composer	Work	Valence	Arousal
Bizet, Georges	Carmen Suite no. 1: Intermezzo	Positive	Low
Wilson, Ransom	Benjamin. On Fire at Dusk	Positive	Low
Smetana, Bedrich	Ma´ Vlast: Vysehrad	Positive	Low
Bach, Johann S.	Orchestral Suite No. 3 in D major, BWV 1068: Gavote alternativement*Gavotte II	Positive	High
Bach, Johann S.	Orchestral Suite No. 2 in B minor, BWV 1067: Badinerie	Positive	High
Mozart, W.A.	Horn Concerto No. 4 in E flat major, K495: Rondo, Allegro vivace	Positive	High
Stanley, John	Grand Voluntary in D major, Adagio	Negative	Low
Volans, Kevin	White Man Sleeps IV (original, unrevised edition)	Negative	Low
Nancarrow, Conlon	String Quartet: Andante	Negative	Low
Volans, Kevin	White Man Sleeps I (original, unrevised edition)	Negative	High
Riley, Terry	Salome Dances for Peace: Half-Wolf Dances Mad in Moonlight	Negative	High
Hanson, Howard	Symphony No. 4, Op. 34, ‘‘Requiem’’: Lux aeterna	Negative	High

Table 2. Matched IADS subset (Bradley & Lang, 2000).

Sound	Number	Valence
VideoGame	254	Positive
Doorbell	378	Positive
Seagull	150	Positive
SodaFizz	725	Positive
SlotMachine1	716	Positive
Whistling	270	Positive
Kids2	224	Positive
Jet	400	Positive
MaleLaugh	221	Positive
Buzzing	116	Negative
BusySignal	703	Negative
Growl1	106	Negative
Hiccup	245	Negative
ManSobbing	293	Negative
EngineFailure	502	Negative
NoseBlow	251	Negative
Siren2	714	Negative
MaleSnore	252	Negative

Table 3. Descriptive statistics for Never-Depressed Control participants' AIM and MEQ scores.

Score	Minimum	Maximum	Mean	SD
AIM Total	102.00	169.00	135.28	18.32
AIM Positive Affectivity	43.00	72.00	54.50	8.38
AIM Negative Intensity	10.00	25.00	15.67	4.43
AIM Negative Reactivity	14.00	28.00	22.50	3.70
MEQ Commitment to music	1.00	3.00	2.02	0.53
MEQ Innovative musical aptitude	1.00	3.43	1.93	0.84
MEQ Social uplift	2.00	5.00	3.19	0.77
MEQ Affective reactions	3.20	5.00	4.41	0.49
MEQ Positive psychotropic effects	1.38	4.69	3.13	0.86
MEQ Reactive musical behavior	2.33	5.00	3.72	0.80

Table 4. Experiment 3: Areas of greater activation to Positive versus Negative stimuli

Region	Peak X	Peak Y	Peak Z	BA	Max *t*	# Voxels	α
Positive > Negative							
Right Superior Temporal Gyrus (Auditory Cortex)	-54	-4	1	22	5.66	203	< 0.01
Left Inferior Rostral Gyrus (Ventral ACC)	4	36	-9	32	5.32	101	< 0.11
Right Hippocampus	-29	-24	-14	N/A	4.79	97	< 0.13
Negative > Positive							
Right Medial Occipital Gyrus	-16	-91	19	18	-4.50	117	< 0.04
Left Inferior Occipital Gyrus	29	-76	-1	18	-4.94	115	< 0.05

Coordinates refer to Talairach space. BA = Brodmann Area.

Table 5. Experiment 3: Areas of greater activation to Musical versus Nonmusical stimuli

Region	Peak X	Peak Y	Peak Z	BA	Max *t*	# Voxels	α
Music > Sounds							
Right Anterior Cingulate Gyrus (Rostral)	-1	36	14	32	5.34	870	<< 0.01
Left Middle Frontal Gyrus (DLPFC)	21	34	34	9	5.17	151	< 0.01
Right Inferior Temporal Gyrus	-49	-64	-1	19	5.82	713	<< 0.01
Right Central Parietal Lobule	-9	-26	44	5	6.23	2864	<< 0.01
Left Middle Occipital Gyrus	49	-69	9	19	6.64	557	<< 0.01
Sounds > Music							
Left Thalamus	6	-11	11	N/A	-6.78	739	<< 0.01
Left Middle Frontal Gyrus (DLPFC)	39	14	29	9	-6.51	843	<< 0.01
Right Inferior Frontal Gyrus (VLPFC: Broca's Area Homologue)	-44	29	4	45	-6.90	730	<< 0.01
Right Superior Frontal Gyrus (DMPFC)	-1	11	59	6	-5.99	337	<< 0.01
Right Medial Frontal Gyrus (MPFC)	-9	51	41	8	-4.86	171	< 0.01
Left Middle Temporal Gyrus (Auditory Cortex)	59	-49	4	21	-6.29	738	<< 0.01
Right Superior Temporal Gyrus (Auditory Cortex)	-46	-16	6	22	-6.37	1023	<< 0.01
Left Cerebellum	9	-51	-31	N/A	-5.76	163	< 0.01
Right Cerebellum	-21	-64	-29	N/A	-8.38	1524	<< 0.01

Table 6. Experiment 3: Areas of greater activation in the Valence by Type interaction (Positive > Negative; Music > Sounds)

Region	Peak X	Peak Y	Peak Z	BA	Max *t*	# Voxels	α
Left Superior Temporal Gyrus (Auditory Cortex)	59	-16	11	42	7.47	807	<< 0.01
Right Superior Temporal Gyrus (Auditory Cortex)	-46	-14	1	22	6.99	686	<< 0.01

Table 7. Comparisons of Questionnaire Scores between Depressed and Never-Depressed Control participants.

Score	*t*	df	*p*	$Mean_{DIFF}$	$SE_{MEANDIFF}$
BDI-II	-9.89**	36	< .001	-26.07	2.72
BAI	-6.61**	36	< .001	-16.81	2.54
PASTEP	-12.87**	36	< .001	-96.88	7.53
POMS – Tension	-1.70	36	.10	-4.30	2.53
POMS – Depression	-6.40**	36	< .001	-19.71	3.08
POMS – Anger	-4.48**	36	< .001	-6.56	1.46
POMS – Vigor	3.54**	36	.001	6.53	1.84
POMS – Fatigue	-3.97**	36	< .001	-7.21	1.81
POMS – Confusion	-4.86**	36	< .001	-6.78	1.39
POMS – Total Mood Disturbance	-6.54**	36	< .001	-55.62	8.51
AIM Total	-1.27	36	.21	-8.57	6.74
AIM Positive Affectivity	0.52	36	.60	1.95	3.72
AIM Negative Intensity	-4.06**	36	< .001	-6.98	1.72
AIM Negative Reactivity	-1.63	36	.11	-2.05	1.26
MEQ Commitment to music	-1.49	36	.15	-0.31	0.21
MEQ Innovative musical aptitude	-1.51	36	.14	-0.46	0.31
MEQ Social uplift	0.20	36	.85	0.06	0.29
MEQ Affective reactions	-0.46	36	.65	-0.06	0.13
MEQ Positive psychotropic effects	-2.70**	36	.01	-0.66	0.24
MEQ Reactive musical behavior	-1.04	36	.30	-0.25	0.24

Table 8. Experiment 5: Areas of greater activation in the Group by Valence interaction (Positive > Negative; Never Depressed > Depressed)

Region	Peak X	Peak Y	Peak Z	BA	Max *t*	# Voxels	α
Left Anterior Cingulate Cortex (Rostral)	6	46	4	32	4.81	90	< 0.20

Table 9. Experiment 5: Areas of greater activation in the Group by Type interaction (Music > Sounds; Never Depressed > Depressed)

Region	Peak X	Peak Y	Peak Z	BA	Max *t*	# Voxels	α
Left Anterior Cingulate Cortex (Dorsal)	1	31	14	24	4.30	125	< 0.04

Figure 1. Biaxial emotion rating diagram combining valence and arousal, modified from Russell (1980).

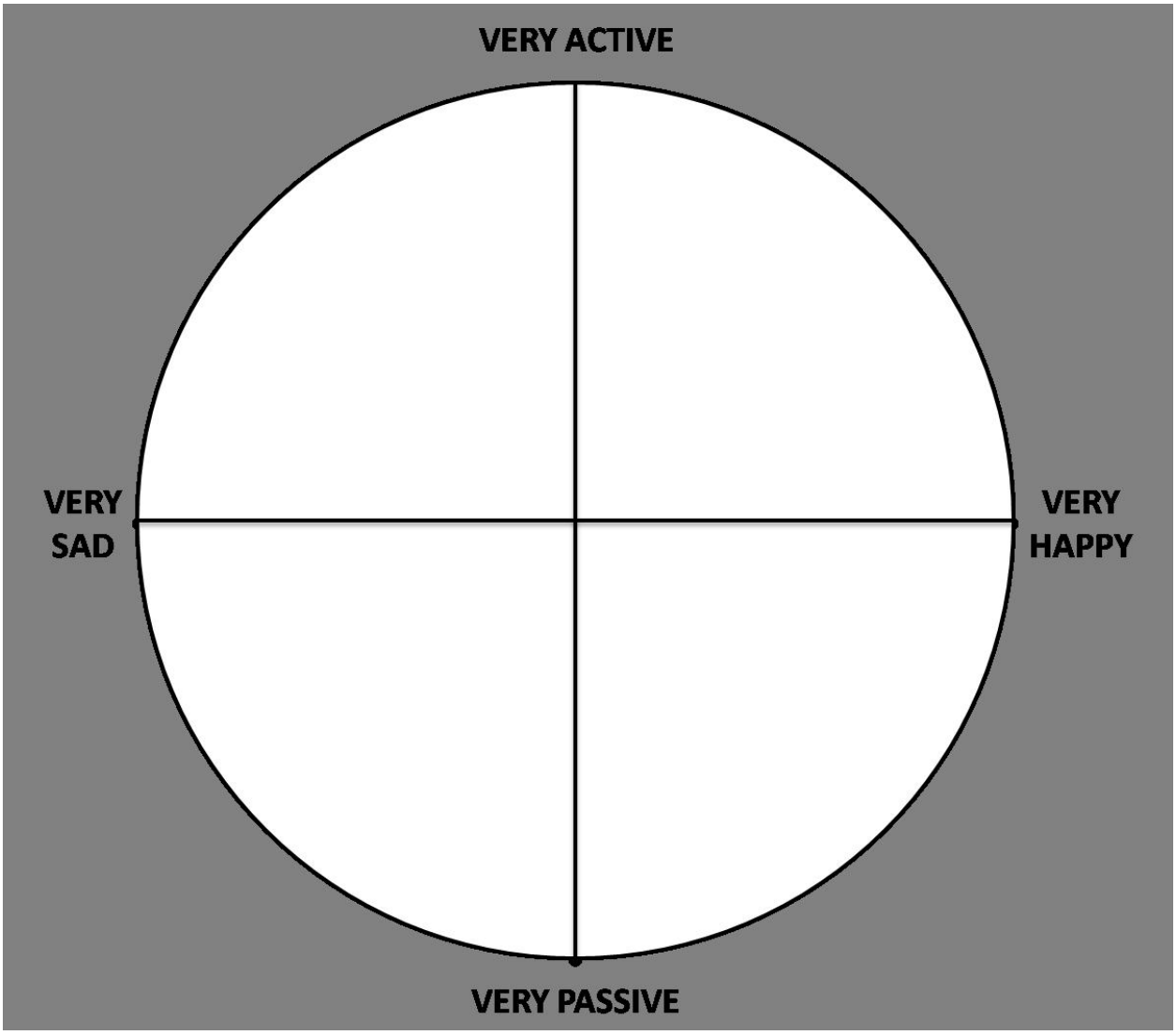


Figure 2. Blocked stimulus paradigm.

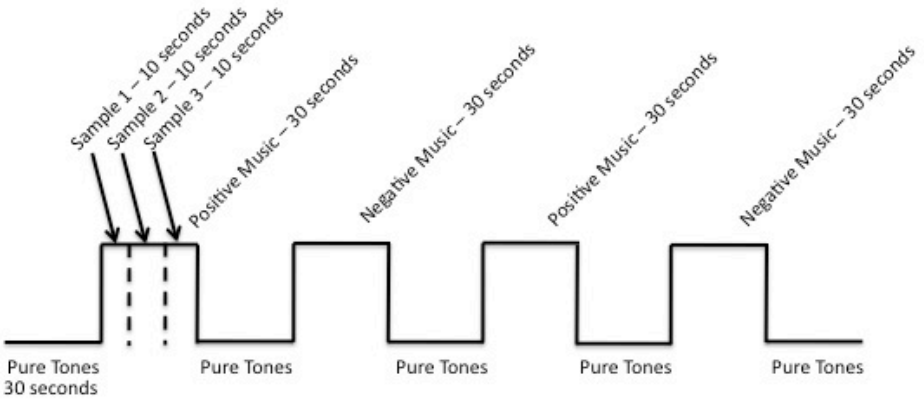


Figure 3. Summary of study procedures.

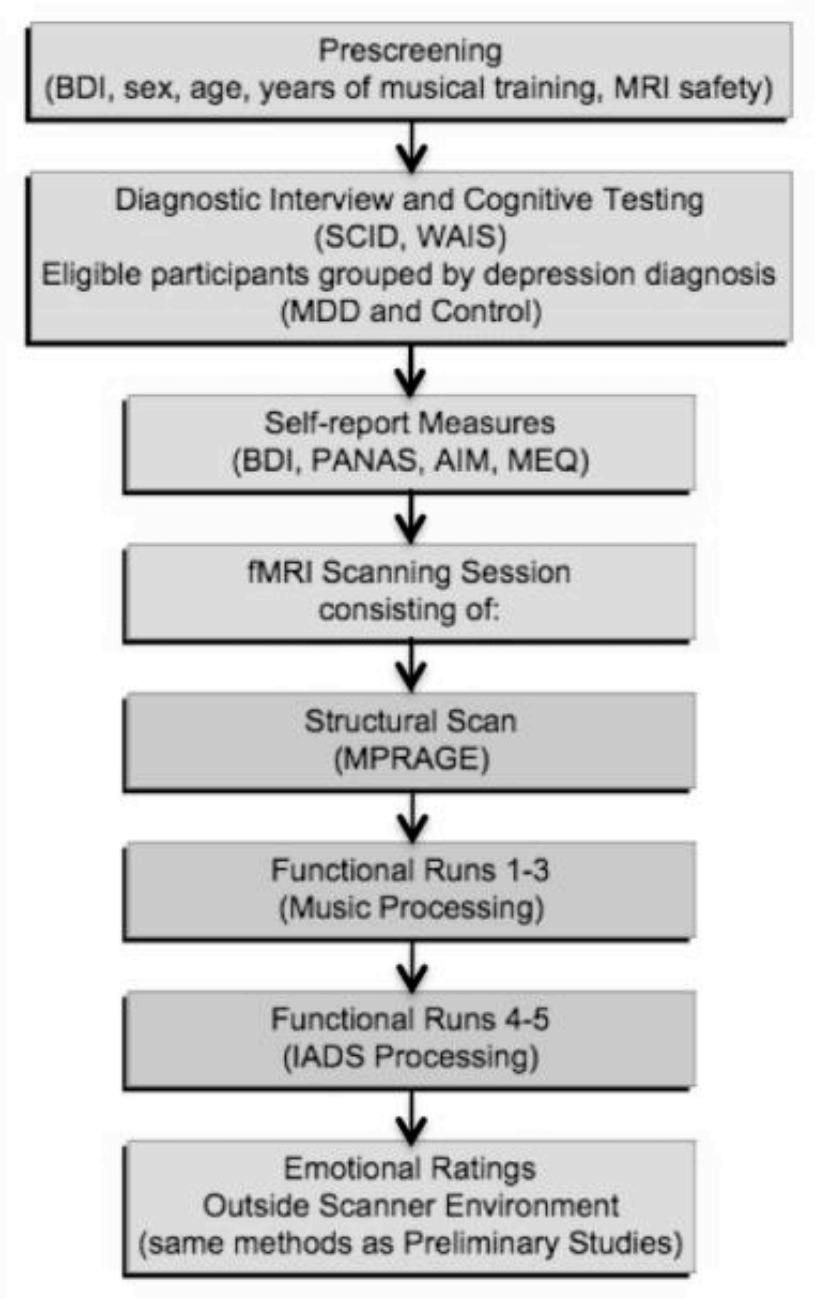
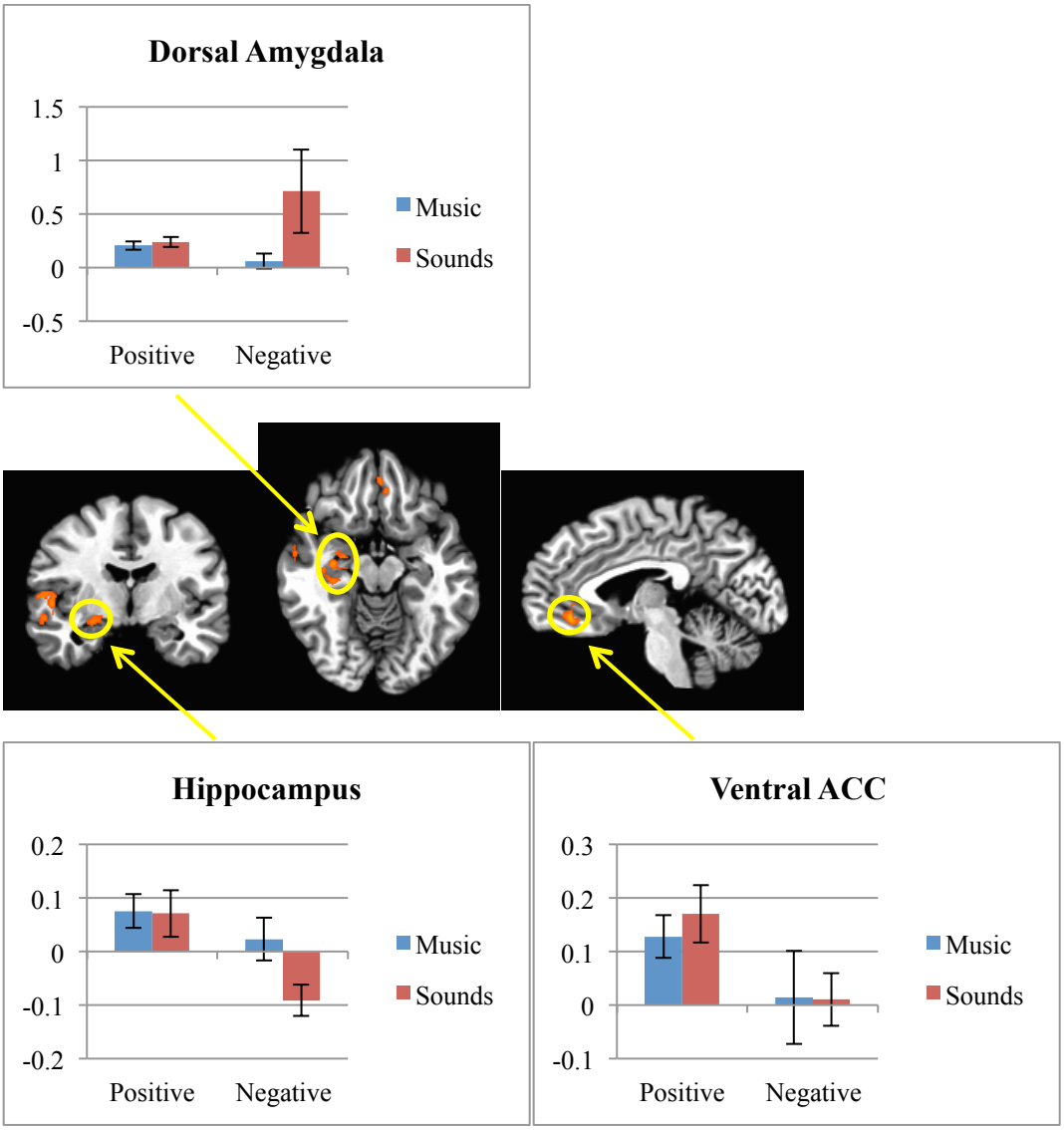
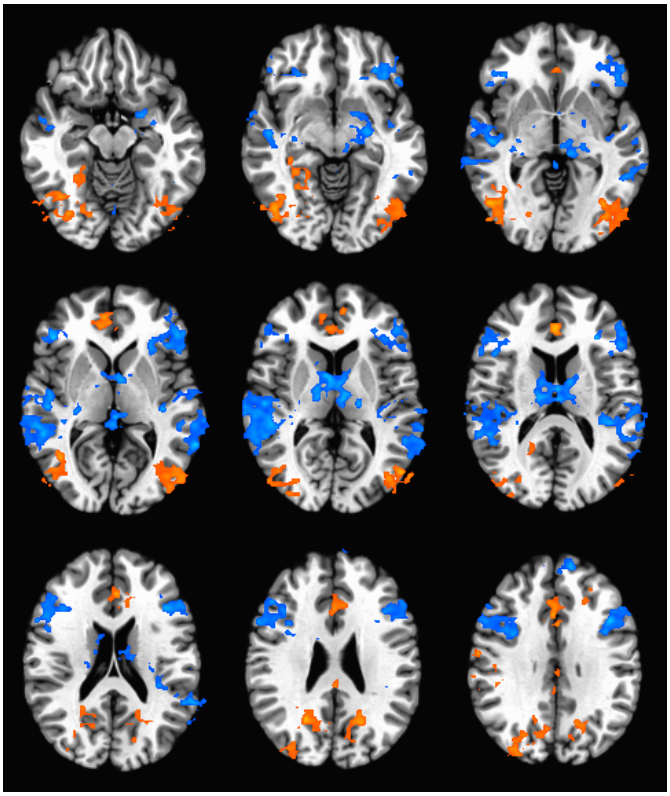


Figure 4. Experiment 3 Main Effect of Valence



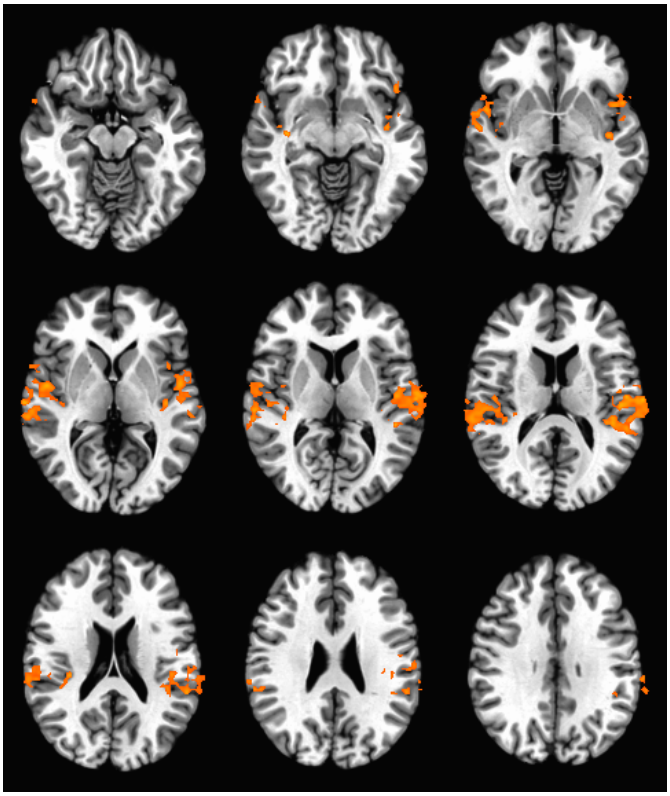
All Positive > All Negative

Figure 5. Experiment 3 Main Effect of Stimulus Type



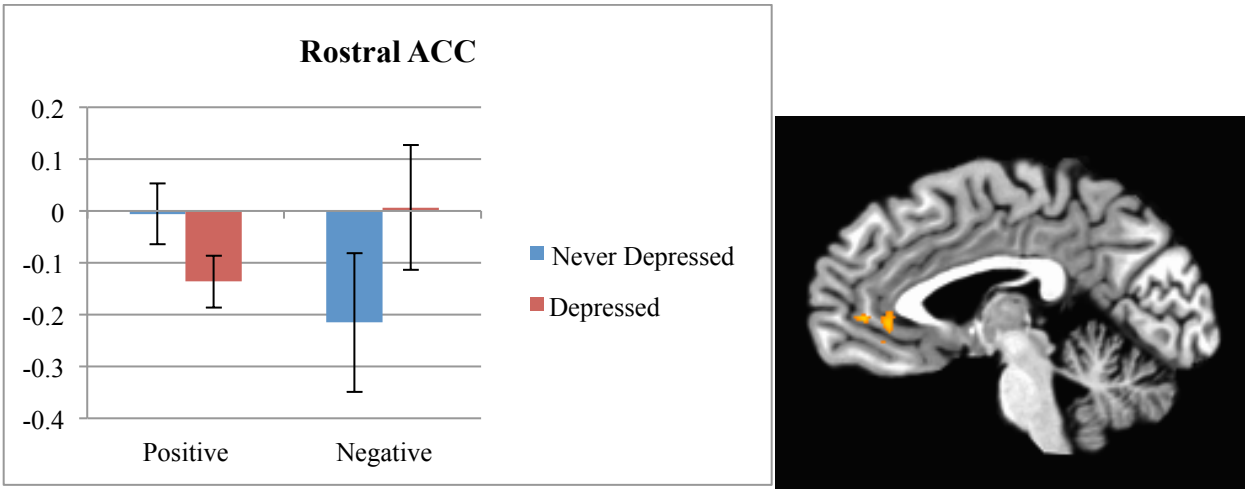
All Music > All IADS

Figure 6. Experiment 3 Full Interaction



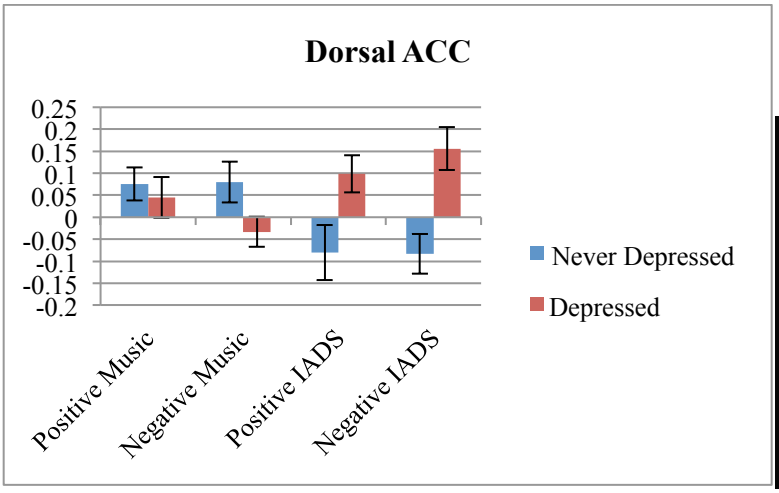
Music > IADS; Positive > Negative

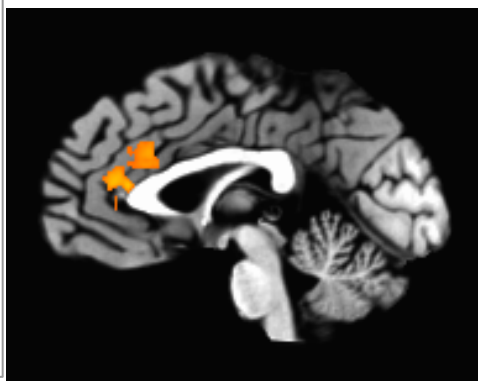
Figure 7. Experiment 5 Interaction of Group by Valence



All Positive > All Negative; Controls > Depressed

Figure 8. Experiment 5 Interaction of Group by Type





All Music > All IADS; Controls > Depressed

Appendices

Appendix A

Stimuli Development and Validation: Human Subjects Committee Approval and Consent Letter

KUMC HSC# 12071; KU-L HSC# 18448

The University of Kansas Medical Center

Human Research Protection Program

January 5, 2010

Project Number:	12071
Project Title:	Pilot Study of Emotional Audio Stimuli Validation
Sponsor:	None
Protocol Number:	N/A
Primary Investigator:	Cary Savage, Ph.D.
Department:	HBIC
Meeting Date:	12/15/2009
HSC Approval Date:	12/31/2009
HSC Expiration Date:	12/30/2010
Type of Approval:	Expedited f (7)

Dear Investigator:

This is to certify that your research proposal involving human subject participants has been reviewed and **approved** by the KUMC Human Subjects Committee (HSC). This approval is based upon the assurance that you will protect the rights and welfare of the research participants, employ approved methods of securing informed consent from these individuals, and not involve undue risk to the human subjects in light of potential benefits that can be derived from participation.

Approval of this research is contingent upon your agreement to:

(1) Adhere to all KUMC Policies and Procedures Relating to Human Subjects, as written in accordance with the Code of Federal Regulations (45 CFR 46).

(2) Maintain copies of all pertinent information related to the research study including, but not limited to, video and audio tapes, instruments, copies of written informed consent agreements, and any other supportive documents in accordance with the KUMC Research Records Retention Policy.

(3) Report unanticipated problems to the HSC by completing the Internal or External HSC Unanticipated Problem/Adverse Event reporting form, as applicable.

(4) Submit deviations from previously approved research activities which were necessary to eliminate apparent and immediate dangers to the subjects by using the KUMC Protocol Deviation Report.

(5) Submit Amendments to the HSC for any proposed changes from the previously approved project using the Request for Amendment form. Changes may not be initiated without prior HSC review and approval, unless a delay in implementation would place subjects at risk.

(6) Submit Continuing Review Form (CR Form) to the KUMC HSC before the expiration date. Federal regulations and HSC policies require continuing review of research at intervals appropriate to the degree of risk, but not less than once per year.

If you have any questions regarding the human subject protection process, please do not hesitate to contact our office.

Very truly yours,

Daniel J. Voss, M.S., J.D.
IRB Administrator

Dear Participant,

We are interested in having you participate in a brief research study. We are studying how people respond to different musical and non-musical sounds. Our research involves having participants listen to short clips of music or other sounds and asking them to rate the sounds on familiarity, pleasantness, and excitement. We will also ask you to fill out a brief questionnaire about yourself, your medical history, and your music training and listening habits. This study is being conducted through the University of Kansas Medical Center with Cary Savage, Ph.D. as the primary investigator.

The purpose of this research study is to develop a set of sound files to use in a future neuroimaging study. Musical and non-musical sounds have been shown by other research studies to affect a person's emotional experience. We want to find out how people experience the sounds we have chosen. We currently have a large set of sounds that have not been rated, and we will use the ratings you give in this study to choose which sound files are most relevant for our neuroimaging study.

If you agree to be in the study, you may be asked to spend about two hours at Hoglund Brain Imaging Center. You will be asked to listen to and rate approximately 500 short sound clips, so you may become tired during your participation. If you do not want to continue you may stop participating at any time. There is also a risk of a possible breach of confidentiality; however, the study team has procedures in place to keep your information confidential. Your health information is protected by government laws on privacy. We are required to get your permission to use your information for the study. We will save your ratings, your answers to the questionnaire, and your name, age, education, musical training, and whether or not you have ever had a psychiatric illness. We will keep this information at KUMC until we finish our study and write our report.

You have the right to cancel permission to use your information at any time. If you cancel your permission, your information will not be used in the report. Only people doing the study, or people who oversee research, will be able to look at the study information. When we publish the results of our study, we will not share anything that identifies you, so the privacy of the information will stay protected.

You will not directly benefit from this research. We hope the information from the research will help us learn more about how people respond to different types of music and other sounds.

Being in a research study is completely voluntary. You are free to choose whether or not you want to participate. Deciding not to participate will in no way affect any current or future care or services

HSC # 12071
HSC Approval Date 12/31/09- 12/30/10
Assurance #FWA 00003411

you may receive at KUMC. If you are a student, deciding not to participate will not affect your status or grades at KU or KUMC.

If you have any questions about the research, or if you want to cancel your permission to use your information, please feel free to contact Dr. Cary Savage at (913)588-9078. You can also write Dr. Cary Savage at KUMC, MS 1052, 3901 Rainbow Blvd, Kansas City, KS 66160. If you have questions about your rights as a research participant, or if you think you have been harmed by the research, you can call the KUMC Human Subjects Committee at (913)588-1240.

Thank you for considering participation in this research study. If you agree to participate, please sign the form below. You will get a signed copy of this letter for your records.

I agree to participate in this research study.

Print Name of Participant	Time	Date
Signature of Participant		
Print Name of Person Obtaining Consent	Time	Date
Signature of Person Obtaining Consent		

HSC # 12071
HSC Approval Date 12/31/09 - 12/30/10
Assurance #FWA 00003411

Appendix B

Musical Training Questionnaire

Subject ID: _____

Questionnaire

Please answer the following questions as accurately as possible:

Age _____ Male ___ Female ___ Date _____

Highest Level of Education Completed _____

How much musical training have you had (in school, private lessons, self-taught, etc.)

none ___ 1-3 years ___ 4-6 years ___ 7-10 years ___ more than 10 years ___

Have you ever participated in any musical activities?

Solo___ Choir ___ Band___ Orchestra___ Small ensemble ___ Write music ___
Other(s) _____

Do you currently participate in any musical activities?

Solo___ Choir ___ Band___ Orchestra___ Small ensemble ___ Write music ___
Other(s) _____

Have you ever had any dance training?

Jazz___ Tap ___ Ballet___ Ballroom___ Square Dance ___ Other(s)_____

If so, how many years of dance training have you had (in school, private lessons, self-taught, etc.)

none ___ 1-3 years ___ 4-6 years ___ 7-10 years ___ more than 10 years ___

Have you ever been diagnosed with a psychiatric disorder?

Depression ___ Anxiety___ ADD/ADHD/Learning disorder___ Schizophrenia ___
Other(s) _____

How many days per week do you listen to music?

0 _____ 1 _____ 2 _____ 3_____ 4_____ 5_____ 6_____ 7_____

When you listen to music, how many minutes on average?

0-15 minutes ___ 15-30 minutes ___ 30-45 minutes ___ 45-60 minutes ___ 60 minutes + ___

Where do you listen to music?

Home ___ Car___ Work___ Bar/Restaurant ___ Concert___ While exercising ___ While sleeping___
Other(s) _____

How many days per week do you listen to music without words (lyrics)?

0 _____ 1 _____ 2 _____ 3_____ 4_____ 5_____ 6_____ 7_____

Which genres of music do you like?

Rock/Pop ___ Country___ Rap/Hip-hop___ Jazz___ Blues___ Heavy metal ___ Classical___
Other(s) _____

Which genres of music do you dislike?

Rock/Pop ___ Country___ Rap/Hip-hop___ Jazz___ Blues___ Heavy metal ___ Classical___
Other(s) _____

Appendix C

fMRI Experiments: Human Subjects Committee Approval and Consent Form

KUMC HSC# 11997; KU-L HSC# 18620

The University of Kansas Medical Center

Human Research Protection Program

December 1, 2010

Project Number:	11997
Project Title:	Neural Processing of Emotion in Music Among Individuals with Major Depressive Disorder
Primary Investigator:	Cary Savage, Ph.D.
Department:	Hoglund Brain Imaging Center
Sponsor:	None
Protocol Number:	N/A
Meeting Date:	11/23/2010
HSC Approval Date:	12/01/2010
HSC Expiration Date:	11/30/2011
Type of Review:	**Continuing Review** -- Expedited Review under §46.110 f (8)

Dear Investigator:

Your Continuing Review Form (CR Form) was reviewed, and the KUMC HSC has determined that you are **APPROVED TO CONTINUE** to conduct human subject research on the above-referenced project. HSC approval will expire one (1) year from the date of approval unless otherwise indicated above. Before the one (1) year expiration date, you must submit a Continuing Review Form to the HSC. If applicable to your study, you will find attached a copy of the recertified stamped consent form that supersedes any previous consent form. A copy of it needs to be kept with all other documentation pertaining to the above study. Only a copy of this most current approved stamped consent form may be used to consent subjects.

Approval of this research is contingent upon your agreement to:

(1) Adhere to all KUMC Policies and Procedures Relating to Human Subjects, as written in accordance with the Code of Federal Regulations (45 CFR 46).

(2) Maintain copies of all pertinent information related to the research study including, but not limited to, video and audio tapes, instruments, copies of written informed consent agreements, and any other supportive documents in accordance with the KUMC Research Records Retention Policy.

(3) Report problems that require prompt reporting to the HSC by completing the Internal or External HSC Problem/Adverse Event reporting form, as applicable.

(4) Submit deviations from previously approved research activities which were necessary to eliminate apparent and immediate dangers to the subjects by using the KUMC Protocol Deviation Report.

(5) Submit Amendments to the HSC for any proposed changes from the previously approved project using the Request for Amendment form. Changes may not be initiated without prior HSC review and approval, unless a delay in implementation would place subjects at risk.

(6) Submit Continuing Review Form to the KUMC HSC before the expiration date. Federal regulations and HSC policies require continuing review of research at intervals appropriate to the degree of risk, but not less than once per year.

If you have any questions regarding the human subject protection process, please do not hesitate to contact our office.

Very truly yours,

Daniel J. Voss, M.S., J.D.
IRB Administrator

Mail-Stop 1032, 3901 Rainbow Blvd., Kansas City, KS 66160
Phone: (913) 588-1240 Fax: (913) 588-5771 humansubjects@kumc.edu

RESEARCH CONSENT FORM
NEURAL PROCESSING OF EMOTION IN MUSIC
Protocol # 11997

You are being asked to join a research study. You are being asked to take part in this study because you have been diagnosed with depression, or you have no history of psychiatric illness. You do not have to participate in this research study. The main purpose of research is to create new knowledge for the benefit of future patients and society in general. Research studies may or may not benefit the people who participate.

Research is voluntary, and you may change your mind at any time. There will be no penalty to you if you decide not to participate, or if you start the study and decide to stop early. Either way, you can still get medical care and services at the University of Kansas Medical Center (KUMC).

This consent form explains what you have to do if you are in the study. It also describes the possible risks and benefits. Please read the form carefully and ask as many questions as you need to, before deciding about this research.

You can ask questions now or anytime during the study. The researchers will tell you if they receive any new information that might cause you to change your mind about participating.

This research study will take place at the University of Kansas – Lawrence campus (KU-L), and the University of Kansas Medical Center (KUMC) with Cary R. Savage, Ph.D. as the researcher. About 40 people will be in the study at KU-L and KUMC.

BACKGROUND
Depression is a mood disorder with symptoms of low overall mood and loss of interest or pleasure in things one used to enjoy. One possible explanation for the causes of these symptoms is that people with depression may be more sensitive to negative information around them. Research studies tell us that this may be the case for emotionally charged words and pictures. We do not know if depression affects how a person responds to emotional music.

Many people find listening to music rewarding. Even music that may call up negative emotions, such as sadness or fear, can still be enjoyable. Previous research has shown that when people listen to emotional music, certain areas of the brain are active. These same brain areas may be affected by depression.

PURPOSE
By doing this study, researchers hope to learn if emotion expressed through music is processed differently by people who have depression.

HSC #: 11997
Approval Date: 12/01/10 to 11/30/11
Assurance #: FWA00003411

PROCEDURES

If you are eligible and decide to participate in this study, your participation will last a total of five hours. You will have an initial appointment lasting approximately two hours at KU-Lawrence or Hoglund Brain Imaging Center (HBIC) at KUMC, whichever is most convenient for you, and a second appointment lasting approximately three hours at HBIC. Your participation will involve a psychological interview at KU-Lawrence or HBIC, followed by one MRI scanning session, questionnaires and cognitive testing at HBIC.

Psychological Interview:

The psychological interview will last approximately two hours. The psychological interview is for research purposes only, and will be used by the researchers to determine if you fit the criteria for the depression group or for the non-depressed group. During this interview, a researcher will ask you questions about your emotions, and about how you handle emotional situations. You might be embarrassed by some of the questions the researchers ask you. You are free not to answer any questions. The interview will be kept confidential.

Though the purpose of this interview is not to diagnose psychological illness, the interview may reveal previously undiagnosed problems. If this occurs, you will be referred to the KU Psychological Clinic or Counseling and Psychological Services for follow-up.

Magnetic Resonance Imaging (MRI) visit:

Following the psychological interview, you will have one MRI appointment at Hoglund Brain Imaging Center. This visit will last approximately three hours. Participants in both groups will have a single one-hour scanning session, and two hours of questionnaires and cognitive testing. For safety reasons, all female participants will have a urine pregnancy test before scanning.

The investigators will collect and analyze data from a brain imaging method called Magnetic Resonance Imaging (MRI). MRI examines how water molecules in the brain behave in a strong magnetic field. MRI gives a detailed picture of what the brain looks like, and can also provide information on blood flow, metabolism, and function of the brain. This method is considered to be non-invasive and is commonly used in routine tests of brain structure and function.

During testing, you will lay on a table that "slides" into the scanner. Your head will be positioned within the scanning coil. This coil will come close to your face and partly restrict you from moving your head. During the scanning session, you will hear a series of short segments of music. You will be asked to press a button after each segment is finished. After the scan, you will be asked to give your opinion of the music you hear during the scanning session. The MRI evaluation takes less than one hour to complete.

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You will also have additional questionnaires and cognitive testing that will take approximately 120 minutes to complete. All testing is for research purposes only. The questionnaires are pencil and paper tests that measure mood, self-image, and behaviors related to musical activities, as well as feelings and coping responses. During part of the cognitive testing, a member of the study team will ask you to answer questions, define words, and complete pictures. You might be embarrassed by some of the questions the researchers ask you. You are free not to answer any questions.

RISKS

Psychological Interview: You may feel uncomfortable answering some of the questions during the interview. You are free not to answer any questions.

MRI: During the MRI, you will be by yourself in the scan room, although a technologist or an investigator can stay with you if you wish. MRI scanning in general is not associated with any health risks, but it is important that you complete the metal screening form accurately. If you have a pacemaker, blood vessel clips, or other internal metal, you may not be allowed to participate in this study. If you have a pacemaker or vascular clip and accidentally enter the MRI suite, a life-threatening situation can develop. Some subjects get a feeling of mild claustrophobia during MRI. To help reduce this, the MRI unit has a mirror so that you can see outside of the scanner. Also, the MRI unit makes loud noises during the examination. You will be listening to the musical segments through earbud headphones, which are surrounded by foam earplugs that fit into your ears. You will also be given earphones to wear over the earbuds to block the noise, and minimize any possible discomfort.

Questionnaires and Cognitive Testing: You may become tired during the testing session. You may take breaks as needed.

PREGNANCY RISKS

Although no negative effects for MRI have been demonstrated, MRI does impart a small amount of energy to the body. Therefore, imaging should not be done with pregnant women. If you think you might be pregnant, tell the investigators before you begin the testing. In addition, all female participants will have a urine pregnancy test at the beginning of the MRI visit. There may be pregnancy risks that are not known yet. For this reason, you must tell the researcher right away if you are pregnant during the study.
There may be other risks of the study that are not yet known.

NEW FINDINGS STATEMENT

You will be told about anything new that might change your decision to be in this study. You may be asked to sign a new consent form if this occurs.

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BENEFITS
You will not benefit from this study. Researchers hope that the information from this research study may be useful in the treatment of patients with depression.

ALTERNATIVES
Participation in this study is voluntary. Deciding not to participate will have no effect on the care or services you receive at the University of Kansas Medical Center.

COSTS
There is no cost for being in the study.

PAYMENT TO SUBJECTS
You will be paid $50 for your participation in this study. Additionally, students recruited through the SONA system at KU-L may receive course credit for participating. The KUMC Research Institute will be given your name, address, social security number, and the title of this study to allow them to write checks for your study payments. Study payments are taxable income. A Form 1099 will be sent to you and to the Internal Revenue Service if your payments are $600 or more in a calendar year.

IN THE EVENT OF INJURY
If you have a serious side effect or other problem during this study, you should immediately contact Dr. Savage at 913-588-9078. If it is after 5:00 p.m., a holiday or a weekend, you should go to the emergency room or call 911.

If you have a bodily injury as a result of participating in this study, treatment will be provided for you at the usual charge. Treatment may include first aid, emergency care and follow-up care, as needed. Claims will be submitted to your health insurance policy, your government program, or other third party, but you will be billed for the costs that are not covered by the insurance. You do not give up any legal rights by signing this form.

INSTITUTIONAL DISCLAIMER STATEMENT
If you think you have been harmed as a result of participating in research at the University of Kansas Medical Center (KUMC), you should contact the Director, Human Research Protection Program, Mail Stop #1032, University of Kansas Medical Center, 3901 Rainbow Blvd., Kansas City, KS 66160. Under certain conditions, Kansas state law or the Kansas Tort Claims Act may allow for payment to persons who are injured in research at KUMC.

CONFIDENTIALITY AND PRIVACY AUTHORIZATION
The researchers will protect your information, as required by law. Absolute confidentiality cannot be guaranteed because persons outside the study team may need to look at your study records. The researchers may publish the results of the study. If they do, they will only discuss group results. Your name will not be used in

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any publication or presentation about the study.

Your health information is protected by a federal privacy law called HIPAA. By signing this consent form, you are giving permission for KUMC to use and share your health information. If you decide not to sign the form, you cannot be in the study.

The researchers will only use and share information that is needed for the study. To do the study, they will collect health information from the study activities. You may be identified by information such as name, address, phone, date of birth, social security number, or other identifiers. Your health information will be used at KU Medical Center by Dr. Savage, members of the research team, the KUMC Research Institute, the KUMC Human Subjects Committee and other committees and offices that review and monitor research studies. Study records might be reviewed by government officials who oversee research, if a regulatory review takes place.

All study information that is sent outside KU Medical Center will have your name and other identifying characteristics removed, so that your identity will not be known. Because identifiers will be removed, your health information will not be re-disclosed by outside persons or groups and will not lose its federal privacy protection.

Your permission to use and share your health information remains in effect until the study is complete and the results are analyzed. After that time, researchers will remove personal information from study records.

QUESTIONS

Before you sign this form, Dr. Savage or other members of the study team should answer all your questions. You can talk to the researchers if you have any more questions, suggestions, concerns or complaints after signing this form. If you have any questions about your rights as a research subject, or if you want to talk with someone who is not involved in the study, you may call the Human Subjects Committee at (913) 588-1240. You may also write the Human Subjects Committee at Mail Stop #1032, University of Kansas Medical Center, 3901 Rainbow Blvd., Kansas City, KS 66160.

SUBJECT RIGHTS AND WITHDRAWAL FROM THE STUDY

You may stop being in the study at any time. Your decision to stop will not prevent you from getting treatment or services at KUMC. The entire study may be discontinued for any reason without your consent by the investigator conducting the study.

You have the right to cancel your permission for researchers to use your health information. If you want to cancel your permission, please write to Dr. Savage. The mailing address is Cary Savage, Ph.D., University of Kansas Medical Center, 3901 Rainbow Boulevard, Kansas City, KS 66160. If you cancel permission to use your health information, you will be withdrawn from the study. The research team will stop collecting any additional information about you. The research team may use and share information that was gathered before they received your cancellation.

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CONSENT

Dr. Savage or the research team has given you information about this research study. They have explained what will be done and how long it will take. They explained any inconvenience, discomfort or risks that may be experienced during this study.

By signing this form, you say that you freely and voluntarily consent to participate in this research study. You have read the information and had your questions answered.
You will be given a signed copy of the consent form to keep for your records.

_____
Print Participant's Name

_____ _____ _____
Signature of Participant Time Date

_____
Print Name of Person Obtaining Consent

_____ _____
Signature of Person Obtaining Consent Date

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NEURAL PROCESSING OF EMOTION IN MUSIC
Research Database Addenda (Optional)

In addition to the main study, you are also being asked to participate in an optional separate study involving the creation of a research database. You can participate in the main study without needing to agree to participate in this optional database.

You will not directly benefit from participating in the database.

If you agree to participate in the database, information collected during today's testing, including the images of your brain, will be copied and stored in the research database. This information will be saved indefinitely. It will be used now by Dr. Savage and members of the research team. It may be used in the future by researchers both at KUMC and outside KUMC to help answer questions about memory, thinking, and aging. It will not be used for any other research purposes.

If your information is shared with other researchers, it will be sent using a code number, your date of birth, and the date the information was collected. It will not include your name or identify you in any other way. By limiting the information, we will protect your privacy and lessen the risk of your identity being re-disclosed to outside individuals. If study records are inspected, only authorized persons will have access to your information.

Even if you agree to participate in the database now, you have a right to change your mind later. You may cancel your permission to use your information in the future by sending a request to Dr. Cary Savage, University of Kansas Medical Center, 3901 Rainbow Boulevard, Mail Stop 1052, Kansas City, KS 66160. The research team may use and share information that was gathered before they received your cancellation.

Allowing us to store your information is completely voluntary. If you decide not to sign this consent addendum, then we will not store your information in the research database. If you have any questions about the research, you may call Dr. Savage at (913)588-9078.

Permission to be included in the MRI Database

_____ I agree to allow my data from this study to be stored indefinitely in the KU Structural MRI database for future research use.

_____ I do not agree to allow my data from this study to be stored indefinitely in the KU Structural MRI database for future research use, but it may be used for purposes of this study only.

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In the future, researchers at KUMC will be conducting additional studies from data included in the MRI database, which may require additional information. Please check the appropriate line to indicate whether or not you are willing to have us contact you when such future studies come up:

_____ Yes, I am willing to be contacted about future studies for which I might be eligible.

_____ No, I do not want to be contacted about future studies for which I might be eligible.

A separate consent would be obtained at the time of your participation in any additional studies.

You will be given a signed copy of this consent form to keep for your records.

_____
Type/Print Subject's Name

_____ _____ _____
Signature of Subject Time Date

_____
Type/Print Name of Person Obtaining Consent

_____ _____
Signature of Person Obtaining Consent Date

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