Music, Emotion, and the Reward System: Investigations with [11C]raclopride positron emission tomography, functional magnetic resonance imaging, and psychophysiological methods

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Abstract

Music is arguably one of the most potent natural rewards. In this thesis, we examine the brain's response to music through different imaging methods to investigate how musical sounds can be interpreted as pleasurable by a listener. First, we examine the hypothesis that rewarding responses to music are related to emotional arousal. Using self-selected "chill-inducing" music, we measure objectively through psychophysiological measures of emotional arousal autonomic nervous system activity, revealing a robust and direct positive relationship between increases in emotion and self-reported pleasure. Next, we investigate the hypothesis that the intense emotional responses to music may be targeting the brain's reward systems (mesostriatal dopamine circuitry), which have evolved to reinforce highly adaptive behaviours. We use [11C]raclopride positron emission tomography to measure dopamine activity during music listening, and functional magnetic resonance imaging (fMRI) to examine the temporal dynamics of activity in mesostriatal regions. The results provide the first evidence for dopamine release in the ventral striatal regions (specifically, the nucleus accumbens; NAcc) during peak moments of pleasure to music (objectively marked by experience of chills). Furthermore, we demonstrate a temporal distinction in dopaminergic activity as dopamine is released in the dorsal striatal regions in anticipation of the peak pleasure responses, suggesting that expectations and anticipation play an important role in musical pleasure. Finally, in the third study we use fMRI to take a closer look at the dynamic interactions between different brain regions that give rise to musical pleasure when a piece of music is novel, but considered desirable by an individual. The findings of this study reveal that activity in the NAcc during initial listening of music can predict whether that piece of music will be considered rewarding to an individual and subsequently purchased. Moreover, while increased activity in sensory and

valuation areas of the brain does not predict reward value of the music, the connectivity of these regions, namely the auditory cortices, ventromedial and orbitofrontal cortices, and amygdala, with the NAcc predicts whether a piece of music will be subsequently purchased. These findings suggest that musical pleasure is a complex process involving highly integrated connectivity between ancient reward circuits in the brain and more recently evolved cortical areas involved in higher-order cognitive processes.

Résumé

La musique est sans doute l'une des plus puissantes récompenses naturelles qui existe. Dans cette thèse, nous étudions la réponse du cerveau lors de l'écoute de musique en utilisant différentes méthodes d'imagerie pour étudier comment les sons musicaux peuvent être perçus comme étant agréable par un auditeur. Dans un premier temps, nous testons l'hypothèse que le sentiment de récompense suite à l'écoute de la musique pourrait être relié à l'excitation émotionnelle. Nous avons utilisé une musique choisie par chaque participant pour éprouver des frissons en l'écoutant, et nous avons mesuré l'excitation émotionnelle de manière objective avec des mesures psychophysiologiques de l'activité du système nerveux autonome. Ceci a révélé un lien robuste et direct entre une augmentation de l'émotion et du plaisir rapporté par le participant. Ensuite, nous avons testé l'hypothèse que l'intensité des réponses émotionnelles lors de l'écoute de musique pourrait cibler l'ancien circuit de récompense (circuit de dopamine mésostriatal) qui a évolué pour renforcer le comportement hautement adaptif. Nous avons utilisé la tomographie par émission de positons [11C]raclopride pour mesurer l'activité de dopamine pendant l'écoute de musique, ainsi que l'imagerie par résonance magnétique fonctionnelle pour examiner la dynamique temporelle de l'activité des régions mésostriatales. Les résultats montrent pour la première fois la libération de dopamine dans les régions ventrales striatales (nucleus accumbens; NAcc) pendant les moments de pic émotionnel suite à l'écoute de musique (objectivement mesuré par le ressenti de frissons). De plus, nous avons démontré une distinction temporelle dans l'activité dopaminergique pendant que les participants libèrent aussi de la dopamine dans les régions striatales dorsales en anticipation des réponses à un pic de plaisir, ce qui suggère que l'attente et l'anticipation jouent un rôle important dans le plaisir de la musique. Finalement, dans la troisième étude nous prenons une attention particulière aux interactions dynamiques entre les différentes régions cérébrales qui donnent lieu au plaisir musical quand une pièce de musique est nouvelle, mais qui est considérée désirable par l'individu. Les résultats de cette étude montrent que l'activité dans le NAcc, pendant l'écoute initiale de la musique peut prédire si une pièce de musique entraînera un sentiment de récompense par un individu et qui l'achètera par la suite. De plus, alors que l'activité accrue dans des régions sensorielles et évaluatrices ne prédisent le sentiment de récompense lors de l'écoute de la musique, la connectivité de ces régions, i.e. le cortex auditif, les cortex vendromédial et orbitofrontal et l'amygdale ainsi que NAcc semblent prédire si une pièce de musique sera achetée par la suite. Ces résultats suggèrent que le plaisir musical est un processus complexe qui implique une connectivité cérébrale hautement intégrée entre les anciens circuits de récompense et des aires corticales plus récemment évoluées impliquées dans les processus haut niveau.

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Contribution of Authors

I am the primary author of the three manuscripts presented in the thesis. My role included conception and designing of the experiments, data acquisition and analysis, and writing of the manuscript. My thesis supervisor Robert J. Zatorre provided guidance and feedback throughout the entire course of this thesis work. My co-author Alain Dagher provided consultation for design and analysis of the second and third studies, and randy McIntosh provided consultation for analysis of the third study. Gregory Longo assisted with experimental procedures of the first study, Mitchel Benovoy assisted with the experimental procedures of the first and second studies, and Iris van den Bosch assisted with the experimental procedures of the third study. Kevin Larcher assisted with the analysis of the positron emission tomography data for the second study, and Natasa Kovacevic assisted with the connectivity analyses of the third study.

All contents presented in the thesis constitute original scholarship and distinct contributions to knowledge.

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List of Abbreviations

ACC	Anterior cingulate cortex
ANOVA	Analysis of variance
ANS	Autonomic nervous system
BOLD	Blood-oxygen level dependent
BVP	Blood volume pulse
dACC	Dorsal anterior cingulate cortex
DLPFC	Dorsolateral prefrontal cortex
fMRI	Functional magnetic resonance imaging
GSR	Galvanic skin response
HP	High pleasure
НҮРО	Hypothalamus
LP	Low pleasure
NAcc	Nucleus accumbens
NM	Neutral music
OFC	Orbitofrontal cortex
PET	Positron emission tomography
PM	Pleasurable music
THAL	Thalamus
STG	Superior temporal cortex
VMPFC	Ventromedial prefrontal cortex
VTA	Ventral tegmental area
WE	Within-excerpt

Chapter 1: Introduction

Some things can be intensely pleasurable for humans. These "rewarding" experiences can occupy our thoughts, induce cravings, shape desires, and ultimately motivate our actions. For this reason, psychologists and other scientists interested in understanding human behaviour and the underlying influences that shape our decisions have taken a keen interest in better understanding rewarding processes. Conceptually, the term "reward" can have distinct implications for different types of scientists. However, the general consensus is that it refers to the hedonic and pleasurable qualities of a stimulus and often operationalized as the reinforcing qualities of a stimulus or behaviour (see Wise, 2002 for a review). It should be noted different items may be rewarding to different people, and this will largely depend on their desire for a stimulus before consumption or how they perceive the stimulus during and after consumption.

1.1 The Brain's Reward/Reinforcement Systems

1.1.1. Discovery of the dopaminergic pathways. While there exist many different types of rewards, amongst the most fundamental seem to be those relating to food and sex (Cannon & Bseikri, 2004). This is perhaps not a coincidence, as both are biologically relevant and necessary for survival and propagation of the species. It has been widely demonstrated that these stimuli gain their reinforcing quality via the mesostriatal dopamine system in the brain (Figure 1)(Cannon & Bseikri, 2004; Egerton et al., 2009; Leyton, 2010; Wise, 2002), which are circuits that we share with other animals. This system was first discovered serendipitously in 1953 in Montreal, when postdoctoral fellow James Olds and Peter Milner, working in Donald O. Hebb's laboratory, mistakenly placed an electrode in the fibres of the dopaminergic pathways near the ventral

striatum while targeting the ascending reticular activating system of a rat (P. Milner, 1989). They noticed that this rat kept returning to the location where it was first stimulated. They then devised an apparatus that allowed the rat to press a lever to stimulate its own brain, and recognized that the rat will continue this behaviour persistently (Olds & Milner, 1954). Subsequent studies demonstrated that rats would forgo all typically rewarding activities, even to the point of starvation, for electrical stimulation of the bundles extending from the midbrain towards the lateral hypothalamus and ventral striatum or administration of chemicals that stimulate dopamine release in these regions (Fibiger & Phillips, 1979; Olds, 1956; Routtenberg & Lindy, 1965; Wise, 1978). Furthermore, administration of drugs that block dopamine receptors can halt this selfstimulatory behaviour (McBride, Murphy, & Ikemoto, 1999). The classic work of Olds and Milner ignited a large interest amongst the scientific community to better examine the processes that may underly rewarding behaviour, which can help us better understand the essence of motivation. As a result of six decades of research, the dopaminergic pathways involved in reward-related behaviours are now better understood.

1.1.2. Anatomy of the dopaminergic pathways. In the late 1950's, Swedish chemists were also coincidentally investigating midbrain regions that housed the cell bodies of catecholamines, namely dopamine (Falck & Hillarp, 1959). Researchers identified two dense clusters of dopaminergic neuronal cell bodies in the midbrain (mesencephalon), namely the substrantia nigra and the ventral tegmental area (VTA) (Dahlstrom & Fuxe, 1964). The fibre bundles that arose from the dopaminergic cell clusters were named according to their site of origination and termination. The first bundle, known as the nigrostriatal tract, originates in the zona compacta of the substantia nigra and ascends to the dorsal regions of the striatum: the caudate nucleus and dorsal putamen. This pathway is important for voluntary motor function and a primary target for Parkinson's disease (Hornykiewicz, 1966). It is also involved in seeking behaviours and learning (Haber & Knutson, 2010). Two other important tracts arise from the VTA. The first is the mesolimbic dopamine pathway, which extends from the

VTA to the ventral regions of the striatum, namely the nucleus accumbens (NAcc) and ventral putamen. These cells also innervate parts of the limbic system, including the amygdala, hippocampus, septum, and olfactory tubercule (Chinta & Andersen, 2005). It is now recognized that the sites involved in self-stimulation studies of Olds and Milner included these fibre tracts (Bozarth, 1987; Wise & Bozarth, 1984), and it is now well-established that this pathway plays an important role in emotion, motivation, and reward (Chinta & Andersen, 2005). The second set of fibres travel from the VTA towards the cortex, particularly the prefrontal, cingulate, and perirhinal cortices via the mesocortical dopamine pathway. It should be noted that most regions in this system have feedback mechanisms to other parts of the circuit via glutaminergic neurons (Figure 2).



Figure 1. Dopaminergic pathways in the human brain. This simplified figure outlines the main dopaminergic pathways, which originate from dopamine-rich cells of the midbrain. The nigrostriatal (or mesostriatal) pathway originates in the substantia nigra pars compacta and extends to the dorsal striatum, including the caudate and putamen. Another set of dopaminergic neurons arise from the ventral tegmental area (VTA) in the midbrain, and extend out to the ventral striatum (shown) and parts of the limbic system such as the olfactory bulb, amygdala, and the hippocampus (not shown) in the mesolimbic pathways, and further out to the prefrontal cortex and other regions of the cerebral cortex (not shown) in the mesocortical pathways (Haber, Kim, Mailly, & Calzavara, 2006; Nestler, Hyman, & Malenka, 2009).



Figure 2. Dopaminergic and Glutaminergic pathways of the mesocorticolimbic system. (A) This highly schematic figure demonstrates the dopaminergic outputs of the VTA that extend to the NAcc, amygdala, and hippocampus as a part of the mesolimbic system and to the prefrontal cortex as a part of the mesocortical system. Importantly, there is glutaminergic feedback within the system, particularly from the amygdala, hippocampus, and parts of the prefrontal cortex, such as the ventromedial and orbitofrontal cortices and the dorsal anterior cingulate cortex to the NAcc. (B) Additional details about connectivity of the prefrontal cortex, the dorsal and ventral striatum, the thalamus and hypothalamus are simplified in this image. (Haber and Knutson, 2010)

1.1.3. Mesolimbic dopamine and reward in humans. While early investigations of the mesolimbic systems were based on the principles of operant conditioning to assume "rewarding" responses in animal studies, other studies with humans have also provided evidence that comparable electrical brain stimulation (Heath, 1964) and chemical stimulation (Drevets et al., 2001; Laruelle et al., 1995; Martinez et al., 2003; Volkow et al., 1999) in these regions is associated with profoundly pleasurable effects. For example, many substances of abuse that are considered rewarding, reinforcing, or addictive to humans, increase extracellular dopamine in these areas, including cocaine (Cox et al., 2009; Schlaepfer, Pearlson, Wong, Marenco, & Dannals, 1997), alcohol (Boileau et al., 2003), tobacco (S. P. Barrett, Boileau, Okker, Pihl, & Dagher, 2004; Brody et al., 2006; Brody et al., 2004; Dagher et al., 2001), and amphetamines (Boileau et al., 2006; Boileau et al., 2007; Laruelle et al., 1995; Volkow et al., 1994). Importantly, many studies have demonstrated that the degree of self-reported hedonic pleasure, or "high", associated with the drugs was linked to the degree of dopaminergic binding (Abi-Dargham, Kegeles, Martinez, Innis, & Laruelle, 2003; Drevets et al., 2001; Laruelle et al., 1995; Volkow et al., 1997; Volkow et al., 1999). The addictive behaviours demonstrated by humans who are addicted to chemical substances that increase dopamine levels in the mesolimbic systems are perhaps comparable to the repetitive and compulsive self-stimulation behaviours demonstrated by Olds and Milner's experiments.

1.1.4. The role of dopamine under debate. These studies suggest that the degree of dopaminergic binding is related to the pleasurable or hedonic aspects of a reward, or how much it is "liked". However, a distinction has been drawn for "liking" and "wanting" a reward (Berridge, Robinson, & Aldridge, 2009), as other studies have found that dopamine binding was more closely related to desire, craving, or anticipation of the drugs compared with the pleasure experienced after taking them (Evans et al., 2006; Leyton et al., 2002; Volkow et al., 2006; Wong et al., 2006). Some theories suggest that dopamine release is not related to the hedonic aspects of a reward, but rather how desirable or salient it is to the organism at a given moment (Berridge, 2007;

Salamone & Correa, 2002). From this point of view, dopamine release is related to anticipatory or appetitive desire for stimuli. Additional support for this hypothesis comes from brain imaging studies that find increased striatal activity in response to anticipation of monetary gains (Knutson, Adams, Fong, & Hommer, 2001; Knutson, Fong, Adams, Varner, & Hommer, 2001; Knutson, Fong, Bennett, Adams, & Hommer, 2003) and edible rewards (O'Doherty, Deichmann, Critchley, & Dolan, 2002).

The relevance of dopamine in "wanting" a reward extends further when we consider its established role in prediction and expectation (Schultz, 1998, 2007; Schultz, Dayan, & Montague, 1997), and learning associations between rewards and their predictive cues (Gratton & Wise, 1994; Kiyatkin & Gratton, 1994; Wise, 2004). The ability to predict the environment is a crucial skill for survival, affording interactions with the complexities of the environment, dealing with uncertainties, and updating prior schemas. In a series of studies, Schultz and colleagues found increased dopaminergic cell activity in midbrain neurons in response to positive prediction errors (i.e., unexpected rewards) in monkeys (Schultz, 1998, 2007; Schultz et al., 1997). In other words, when an animal makes a prediction about its environment, a prediction error may result depending on the outcome. If this is positive, and the outcome is better than expected, dopaminergic neurons fire faster, but if the outcome is negative or worse than expected, there will be inhibition of the dopaminergic neuron firing (Bayer & Glimcher, 2005; G. Morris, Arkadir, Nevet, Vaadia, & Bergman, 2004). Importantly, it was later verified that it is not only unpredicted rewards, but also cues that predict upcoming reward that cause the release of dopamine from the midbrain neurons to the ventral striatum (Roitman, Stuber, Phillips, Wightman, & Carelli, 2004). The rate of dopaminergic firing has been shown to depend on the uncertainty of the prediction or the probability of the reward, reward magnitude and expected reward value, and motivational state of the organism (Fiorillo, Tobler, & Schultz, 2003; Satoh, Nakai, Sato, & Kimura, 2003). Through these mechanisms the dopamine-containing neurons can tune their range of sensitivity (Tobler, Fiorillo, & Schultz, 2005). Other scientists extend these ideas to learning

and add that that dopamine is involved in "stamping-in" learned associations between predictive cues and goal-attainment (Baldo & Kelley, 2007).

In sum, there is little doubt that mesolimbic dopamine plays an important role in goal-directed reward-related processes, but the precise contributions will continue to be investigated. It is likely that dopamine is involved in recognizing predictive cues and directing attention towards stimuli that may be worth some value to an organism, supporting goal-directed behaviour towards obtaining the reward, noting the actual worth of a craved or desired reward upon reception and strengthening or facilitating learning for future obtention of the reward (see also Leyton, 2010). There is a possibility that different regions of the striatum contribute differently to these different phases of reward processing. Some studies hint at this by suggesting that as reward become more habitual, dopamine activity shifts from ventral to dorsal striatum (e.g., Boileau et al., 2006). Perhaps when a reward is first experienced or unexpected, there is activity in the ventral striatum, particularly the NAcc, and when a desired reward becomes better predictable activity shifts to the dorsal striatum, an integral part of voluntary motor response circuits, to orchestrate movement toward procuring the rewarding stimuli. It is also possible that ventral regions of the striatum, which are parts of the mesolimbic circuit (Figure 1) are more involved in the emotional aspects of a reward, whereas the dorsal regions of the striatum, which are parts of the nigrostriatal circuit (Figure 1) are more involved in the cognitive aspects of reward processing. This claim is supported through the connectivity of dorsal and ventral striatum, where the dorsal regions are better connected to the dorsolateral and ventrolateral prefrontal cortices (Haber & Knutson, 2010; Haber, Kunishio, Mizobuchi, & Lynd-Balta, 1995; Leh, Ptito, Chakravarty, & Strafella, 2007; Selemon & Goldman-Rakic, 1985), typically implicated in advanced cognitive processes such as working memory and executive function (Dagher, Owen, Boecker, & Brooks, 1999; Monchi, Petrides, Petre, Worsley, & Dagher, 2001; Petrides, 2007; Petrides, Alivisatos, & Frey, 2002; Petrides, Alivisatos, Meyer, & Evans, 1993; Stuss & Knight, 2002), whereas the ventral regions are better connected to the ventromedial and orbitofrontal cortices (Haber & Knutson,

2010), both of which are highly connected to the limbic system and involved in integration of sensory and emotional information and valuation (Hampton & O'Doherty, 2007; O'Doherty, 2004; Plassmann, O'Doherty, & Rangel, 2007). These distinctions represent an ongoing theme that we will explore throughout the dissertation, which will be more closely examined in second and third of the experiments of this thesis.

1.2. From Basic to Complex Rewards

In rodents and other animals, mesolimbic dopaminergic systems are thought to reinforce basic adaptive behaviours (Melis & Argiolas, 1995; G. Smith, 1995). For example rodents have been shown to release dopamine in response to food (Carr, 2002; Hernandez & Hoebel, 1988a, 1988b; Kiyatkin & Gratton, 1994), sex (Damsa, Pfaus, Wenkstern, Phillips, & Fibiger, 1992; Lopez & Ettenberg, 2002; Pfaus, Damsma, Wenkstern, & Fibiger, 1995), and mothers demonstrating maternal behaviour towards their pups (Hansen, Bergvall, & Nyiredi, 1993; Wilkins, Logan, & Kehoe, 1997). These are typically behaviours that are adaptive and associated with survival of species.

Humans also show dopamine release in response to basic rewards, such as those that relate to food and sex. For example, one study found dopamine release in response to eating preferred foods after a brief period of starvation (Small, Jones-Gotman, & Dagher, 2003), others found changes in hemodynamic activity in midbrain and striatal dopameringic areas during the anticipation of delivery of a sweet liquid taste reward (O'Doherty et al., 2002; Small, Zatorre, Dagher, Evans, & Jones-Gotman, 2001), viewing attractive faces of the opposite sex (Aharon et al., 2001) or pictures a loved one (Aron et al., 2005; Bartels & Zeki, 2004), and during female orgasm (Komisaruk & Whipple, 2005).

However, a notable difference between reward pathways in humans and other organisms is the connectivity patterns of mesolimbic regions. The complexity of human brain is reflected in the more elaborate connectivity patterns of the mesolimbic regions with other parts of the brain. In more phylogenetically advanced animals these circuits have more elaborate anatomical connectivity

pathways and show more functional integration with higher-order cortical brain regions involved in abstract thought and emotion (Figure 2) (Haber et al., 2006; Haber & Knutson, 2010). These regions include the highly evolved prefrontal cortical areas that underly advanced thinking and reasoning, abstraction, integration of mental processes with emotional responses, and integration of past and present to create expectations and anticipation (Dagher et al., 1999; Ko, Monchi, Ptito, Petrides, & Strafella, 2008; Monchi et al., 2001; Petrides, 2007; Petrides et al., 2002; Petrides et al., 1993; Roth, Randolph, Koven, & Isquith, 2006; Rushworth, Noonan, Boorman, Walton, & Behrens, 2011; Stuss & Knight, 2002).

This anatomical connectivity allows for a pathway whereby organisms may find more complex stimuli reinforcing. For example, humans uniquely obtain pleasure from certain abstract stimuli that do not seem to have a clear survival value, such as music, art, and poetry. These can be considered "aesthetic rewards" (discussed in the next section) and seem to involve some forms of higher-order cognitive analysis. The experience of aesthetic stimuli has long been characterized as pleasurable to not only the senses, but also to the intellect (Dutton, 2009). In support of this concept, a number of studies have demonstrated involvement of the most advanced regions of the brain, namely the prefrontal cortex, when humans process aesthetic stimuli (Cela-Conde et al., 2004; Jacobsen, Schubotz, Hofel, & von Cramon, 2006; Kawabata & Zeki, 2004; Vartanian & Goel, 2004). It is likely that a very intricate connection between intellect and the senses combine to give rise to aesthetic pleasures. One theme that will be investigated and elaborated throughout this thesis is that humans appreciate aesthetics because they have the cognitive architecture linking abstract thought and complex analysis to the reward regions of the brain, allowing them to understand the nuances and non-tangible pleasures of such complex and abstract rewards. These issues will be further explored in the third experiment of this thesis. Here, to unravel this claim we begin by investigating the neural correlates that underly processing of aesthetic stimuli.

1.3. Neural Basis of Aesthetic Rewards

Before examining the neural correlates of aesthetic rewards, it should be noted that the rewarding nature of these stimuli is not universal, and pleasurable responses are often highly individualized. These responses are related to each person's subjective interpretation of the stimulus, which is likely to be related to their social and cultural background, and previous experiences with that particular stimulus or other similar stimuli. This may be contrasted with some basic adaptive rewards. For example, when an individual has been starving for a long period of time, they are likely to find any type of food rewarding (even if it is not their favourite). In contrast, some people may never want to listen to a certain kind of music or poetry regardless of how long it has been since they were exposed to music! This suggests that the appreciation of aesthetic stimuli is much less universal and homogeneous than some other rewards that are necessary for survival. Rather, the responses to aesthetic stimuli and the underlying circuitry for initial consideration of an aesthetic stimulus as potentially rewarding are heterogeneous and show great variability across different people. However, some level of convergence would be expected in the mesolimbic areas as the stimuli are designated as rewarding. As such, while we expect variability amongst individual subjects' brain imaging responses to aesthetic stimuli, we are particularly interested in the similarities in processes involved in constituting a positive response to these stimuli.

With the relatively recent emergence of the field of neuroaesthetics, researchers are examining brain responses to various forms of art to better understand what constitutes aesthetic processes. For example, neuroimaging studies have been conducted with paintings (Kawabata & Zeki, 2004; Vartanian & Goel, 2004), photographs (Cela-Conde et al., 2004), geometrical shapes (Jacobsen et al., 2006), beautiful faces (Winston, O'Doherty, Kilner, Perrett, & Dolan, 2007), desirable cultural objects (Erk, Spitzer, Wunderlich, Galley, & Walter, 2002), and music (Koelsch, 2011; Zald & Zatorre, 2011). It is interesting to note that a number of cortical and subcortical regions appear to stand out as

important for making aesthetic evaluations, regardless of the modality in which the stimulus is presented.

1.3.1. Subcortical regions. Subcortical regions that show patterns of activity in response to aesthetic artworks include various regions of the limbic system (Blood & Zatorre, 2001; Blood, Zatorre, Bermudez, & Evans, 1999; Koelsch, Fritz, Cramon, Muller, & Friederici, 2006; Vartanian & Goel, 2004), including the amygdala, hippocampus, and hypothalamus, as well as parts of the paralimibic or extended limbic system (Blood & Zatorre, 2001; Jacobsen et al., 2006; Koelsch et al., 2006; Vartanian & Goel, 2004) including the insula and anterior cingulate cortex (ACC). These regions have typically been implicated in inducing or experiencing emotional arousal (Bechara & Damasio, 2005; Critchley, 2005). The hypothalamus, insula, and ACC are thought to control various psychophysiological reactions of the body including changes in heart rate, respiration, electrodermal skin response, and other biological symptoms that are indicative of emotional arousal (Cacioppo, Tassinary, & Berntson, 2007; Critchley, 2005), and the amygdala and hippocampus are well know to play a role in emotional arousal and memory formation (Adcock, Thangavel, Whitfield-Gabrieli, Knutson, & Gabrieli, 2006; Adolphs, 1999; Adolphs, Cahill, Schul, & Babinsky, 1997; Moscovitch, Nadel, Winocur, Gilboa, & Rosenbaum, 2006).

Hypothalamus. Many non-voluntary functions in the body are controlled by descending projections from neurons located in the hypothalamus, including automated psychophysiological functions that prepare organisms for emotional responses to stimuli (Nestler et al., 2009; Pyner & Coote, 1999). The hypothalamus consists of the periventricular, medial, and lateral zones. The first two zones control biological rhythms, endocrine and autonomic function, and homeostasis and reproduction, respectively. The lateral zone is specifically involved in controlling arousal and motivated behaviour, by coordinating multiorgan responses to emotional stimuli (Nestler et al., 2009). For example, these may include increases in the force and rate of heart contraction, blood pressure, and blood glucose, dilation of the bronchial tree to increase respiration, and increases in electrodermal response. Importantly, this region projects to (1) the midbrain dopaminergic neurons, which can directly influence dopamine release in the mesolimbic system, and (2) the prefrontal cortex via the dorsal thalamus, which can provide high order cortical centres with information about internal states (Kelley, 2004). It should also be noted that there is a small group of dopaminergic cells in the hypothalamus that terminate in the pituitary gland and regulate prolactin (J. S. Meyer & Quenzer, 2005).

Anterior Cingulate Cortex (ACC). The ACC is a unique part of the frontal cortex, with diverse functions relating to motivation, cognition, and motor control, which integrate to perform functions relating to emotional and rewardrelated processes and goal-directed behaviour. This diversity is reflected in its connections, which stretch across affective, cognitive, and motor areas in the brain (Haber & Knutson, 2010). However, despite the complexity of the connections of this region, the main role of the ACC seems to be integrating and monitoring the diverse set of functions during conflict situations (Botvinick, Nystrom, Fissell, Carter, & Cohen, 1999; Vogt, Vogt, Farber, & Bush, 2005; Walton, Bannerman, Alterescu, & Rshworth, 2003). This is particularly relevant for reward-related processes that involve emotional and cognitive aspects. For example, one of the main functions of this region involves updating cognitive decisions with respect to internal emotional cues (Critchley, 2005). It should further be noted that this region provides one of the main two cortical inputs into the VS (the two others are the ventromedial and orbitofrontal regions of the prefrontal cortex; Haber & Knutson, 2010).

Insula. Anatomically, the ACC has bidirectional connections with the insula, an area responsible for integrating visceral emotional-related and interoceptive information, and together they modulate many physiological functions underlying emotional arousal (Bechara & Damasio, 2005; Critchley, 2005). In addition, the insula has bidirectional connections with the prefrontal regions, amygdala, and NAcc, making it ideally positioned to integrate emotion-related and interoceptive information and feed this information forward to the ACC and prefrontal regions to influence decision making, and further influence amygdala and NAcc (Reynolds & Zahm, 2005). A recent meta-analysis on 93

neuroimaging studies of aesthetic processing found that the insula was the most commonly activated region during processing of aesthetic stimuli across modalities (Brown, Gao, Tisdelle, Eickhoff, & Liotti, 2011). While the insula has traditionally been associated with negatively-valenced emotions, such disgust and pain (Liotti et al., 2000), in the review it was the most concordant area involved in making positively-valenced aesthetic appraisals (Brown et al., 2011). These results suggest that this region may be involved in processing emotional arousal and salience. Indeed, a study by Seeley and colleagues found that the insula was a part of a "salience network", which typically shows activity to any task that requires processing information that is highly arousing or salient (Seeley et al., 2007). This hypothesis may explain why the insula seems to be involved in a diverse set of functions, including those that relate to somatic sensation, visceral sensorimotor, pain, movement, taste, language, and auditory processing (Adolphs, 2002a; Augustine, 1996).

Amygdala. The amygdala plays an important role in emotional valuation, for example the perception of emotion in faces (Adolphs, 1999, 2002b; Critchley, Daly, et al., 2000; Gosselin, Peretz, Johnsen, & Adolphs, 2007; Gosselin et al., 2005) and assigning reward value to various stimuli (O'Doherty, 2004). Importantly, amygdala has also been implicated in the experience of arousal more generally (Sergerie, Chochol, & Armony, 2008). A recent study found that increased heart rate variability during arousing emotional stimuli was associated with increased activity in the amygdala in an fMRI paradigm (Wallentin et al., 2011). While traditionally this regions has been implicated in processing aversive states and negative emotions, such as fear and anxiety (Adolphs, Tranel, Damasio, & Damasio, 1995; LeDoux, 2000), there is now increasing evidence that the amygdala can also respond to positive stimuli and plays a significant role in reward processing (O'Doherty, 2004; Phelps & LeDoux, 2005; Salinas & White, 1998). For example, single cell recording in awake patients has demonstrated that neurons in the amygdala respond to increasing reward value of stimuli (Jenison, Rangel, Oya, Kawasaki, & Howard, 2011). Additional evidence comes from studies that directly compare amygdalar response to both rewarding and aversive

stimuli in the same experiment and reveal no differences (Anderson et al., 2003; Small, Gregory, et al., 2003). These observations have lead researchers to suggest that amygdala may be more involved in marking how arousing a stimulus is, rather than its positive or negative value. This inference is supported by the common observation that amygdala activity habituates rapidly to emotional stimuli (Breiter et al., 1996). For example, one study found that as participants learned to associate cues with rewarding or aversive odours, amygdala response to the rewarding cue diminished over time, whereas NAcc responses increased over time (Gottfried, O'Doherty, & Dolan, 2002). Furthermore, it is believed that the tight connections between the amygdala and ventral striatum are critical for processing stimulus-reward associations (Baxter & Murray, 2002; Cador, Robbins, & Everitt, 1989; Ramirez & Savage, 2007). This connection and its role processing of novel reward stimuli will be better explored in the third experiment of this thesis.

Hippocampus. The hippocampus and amygdala are highly integrated and both are implicated in formation of emotional memories (Adolphs et al., 2003; McGaugh, 2002), perhaps working in concert to do so. Moreover, these regions are intricately connected with the NAcc via glutaminergic neurons (Figure 2), providing a circuit that has recently been associated with facilitation of reward-related memory formation (Adcock et al., 2006; Schott & al., 2006; Schott et al., 2004; Wittman, Schiltz, Boehler, & Duzel, 2008). For example, Adcock and colleagues found that enhanced activity in the VTA, NAcc, and hippocampus during the encoding phase of a memory task corresponded with items that were subsequently better-recalled during a retrieval phase. The hippocampus is also well known to detect novelty (Nadel, 2008). However, in contrast with the amygdala, the hippocampus has more limited connections to the ventral striatum, mostly confined to the NAcc (Friedman, Aggleton, & Saunders, 2002).

1.3.2. Mesolimbic regions. Activity is often found in the mesolimbic reward regions during aesthetic processing, particularly when individuals are viewing paintings (Vartanian & Goel, 2004) or other art images (Lacey et al., 2011), judge the beauty of faces (Aharon et al., 2001; Nakamura et al., 1998;

O'Doherty et al., 2003), or listen to pleasurable music (Blood & Zatorre, 2001; Brown, Martinez, & Parsons, 2004; Koelsch et al., 2006; Menon & Levitin, 2005; Mitterschiffthaler, Fu, Dalton, Andrew, & Williams, 2007; Trost, Ethofer, Zentner, & Vuilleumier, 2011).

Both the dorsal and ventral striatum have been implicated in processing aesthetic stimuli, although the latter (particularly the NAcc has traditionally been more strongly associated with emotion (Breiter et al., 1997; Haber & Knutson, 2010). This is likely due to the NAcc's highly intricate connections with other parts of the limbic system (Figure 2). This anatomical section of the striatum is considered to be a part of the "limbic loop" (Heimer, 1978) based on its connectivity. The NAcc is intricately connected to the amygdala, hippocampus, and hypothalamus (Haber & Knutson, 2010).

It is also interesting to note that a number of studies have not found activity in these regions in response to aesthetic judgements (e.g., Jacobsen et al., 2006). There is a possibility that a certain degree of emotional or pleasurable experiences must be induced before significant activity in these areas is observed. For example, Jacobson and colleagues used tasks that involved of judging the beauty of geometric shapes (Jacobsen et al., 2006), which may be more related to decision-making processes regarding aesthetically pleasing stimuli rather than an intense emotional experience associated with these images. These studies did nonetheless involve activity in cortical regions involved in judgment, as discussed in the next section.

1.3.3. Cortical regions. A number of cortical regions are also involved in processing and appreciating aesthetic stimuli. The most common of these regions appear to be parts of the frontal cortex, including the orbitofrontal cortex (OFC) and ventromedial prefrontal cortex (VMPFC) (Blood & Zatorre, 2001; Blood et al., 1999; Brown et al., 2011; Kawabata & Zeki, 2004; Trost et al., 2011). These regions have typically been associated with detecting the emotional value of novel stimuli (Petrides, 2007), and integrating information from various regions of the brain to assign value to potentially rewarding stimuli (i.e., "valuation") (Chib, Rangel, Shimojo, & O'Doherty, 2009; Fellows, 2011b; Kringelbach, 2005;
O'Doherty, 2004; Wallis, 2007). While other subcortical regions, such as the amygdala and NAcc are also involved in assessing the reward value of stimuli, these cortical regions are believed to perform this task on a more cognitive level, perhaps integrating cortically stored information into the decision-making process (Murray & Wise, 2010).

Ventromedial prefrontal cortex (VMPFC). The VMPFC is one of the main cortical regions involved in processing and interpreting emotional arousal, and making strategic decisions based on this information (O'Doherty, 2004). Some of the best evidence for this comes from lesion studies, where individuals with damage to these areas demonstrate abnormalities in emotional behaviour and fail to make appropriate decisions based on emotional or reward cues (Adolphs, Tranel, & Damasio, 1998; Bechara, Damasio, Tranel, & Damasio, 1997; Bechara, Tranel, Damasio, & Damasio, 1996; Damasio, Tranel, & Damasio, 1990; Fellows, 2011b; Henri-Bhargava, Simoni, & Fellows, 2012; Shallice & Burgess, 1991). More recently, the role of VMPFC in economic decision making has been emphasized as this region as been implicated in maintaining reward value prior to the making of a decision, as well as received reward after the outcome of the decision has been revealed (Plassmann et al., 2007; Sescousse, Redoute, & Dreher, 2010; D. V. Smith et al., 2010).

It is important to realize that the value assigned to a stimulus is a product of cognition, rather than a feature intrinsic to the stimulus (Fellows, 2011a). The value of an item will depend largely on the internal, emotional, and motivational state of the organism and other contextual factors, such as the cost of the obtaining the item and other choices available (e.g., Wallis & Miller, 2003). As such, the VMPFC may be responsible for integrating information from various sources to assign value to aesthetic items, and update these when appropriate. This was demonstrated with studies that varied the contextual information presented with two identical stimuli (e.g., price of wine or brand of drink), and found that participants showed different behavioural responses and VMPFC activity in response to marketing manipulations (McClure et al., 2004; Plassmann, O'Doherty, Shiv, & Rangel, 2008). As such, the VMPFC may be responsible for

integrating information from cognitive sources with internal and sensory information to assign value to aesthetic items, and update these when appropriate.

Orbitofrontal cortex (OFC). The OFC is an important junction for highlevel reward processing as it receives inputs from all cortical sensory modalities, including highly processed visual information from the inferior temporal cortex, auditory information from secondary and tertiary auditory areas, secondary somatosensory cortex and parietal areas, and olfactory information from the olfactory nucleus, olfactory bulb, olfactory field of the entorhinal cortex and other primary olfactory areas, and information about taste from the primary gustatory areas (Carmichael & Price, 1995b; Cavada, Company, Tejedor, Cruz-Rizzolo, & Reinoso-Suarez, 2000; Frey & Petrides, 2000; Petrides & Pandya, 2002a; Romanski, Bates, & Goldman-Rakic, 1999). Consistently, in human neuroimaging studies this region has been implicated in tasks that involve encoding details about reward value of stimuli through different sensory modalities, including auditory (Blood & Zatorre, 2001; Blood et al., 1999), visual (Aharon et al., 2001; Jacobsen et al., 2006; Kawabata & Zeki, 2004; O'Doherty et al., 2003), somatosensory (E. T. Rolls, O'Doherty, et al., 2003), gustatory (O'Doherty, Rolls, Francis, Bowtell, & McGione, 2001; Small, Gregory, et al., 2003), and olfaction (Anderson et al., 2003; Gotfried, Deichmann, Winston, & Dolan, 2002; E. T. Rolls, Kringelbach, & De Araujo, 2003).

However, similar to the VMPFC, the OFC is not merely involved in processing sensory information intrinsic to a stimulus. Electrophysiology studies with monkeys have demonstrated that neurons in the OFC encode the value of a stimulus to the organism at a specific time (Padoa-Schioppa & Assad, 2006). Similarly, a number of studies have reported OFC activity in response to food stimuli pre-satiety, but not post-satiety, suggesting that these regions are specifically involved in processing the reward value of the items to the individual at a give moment rather than sensory aspects of the stimuli (Kringelbach, O'Doherty, Rolls, & Andrews, 2003; O'Doherty et al., 2000; B. J. Rolls, Rolls, Rowe, & Sweeney, 1981; Small et al., 2001). It is believed that the OFC is specifically involved in detection of novel sensory stimuli and formation of memories (Frey & Petrides, 2000; Petrides, 2007), and thereby linking sensory information to reward value (Wallis, 2007). In support of this, in addition to the sensory connections, the OFC has additional links to areas implicated in reward processing, including the dorsal and ventral striatum (Haber & Knutson, 2010), and linked to emotions through extensive connections to the limbic system, including the amygdala, ACC, and hippocampus (Carmichael & Price, 1995a; Morecraft, Geula, & Mesulam, 1992; Petrides & Pandya, 2002a). Finally, the OFC is also in a position to influence emotional arousal through connections with hypothalamus and other brainstem structures (Ongur, An, & Price, 1998; Rempel-Clower & Barbas, 1998).

1.3.4. Integration of brain regions. The brain imaging studies presented here provide biological evidence that at least three processes are involved in aesthetic reward processing: valuation and appraisal, emotional responses, and reward-related responses. These processes are likely to be highly dependent on one another in a way that provides feedback and ongoing updating for each component of the process. Support for integration comes from studies of anatomical and functional connectivity. For example, the results of tracer injection studies (reviewed in Haber & Knutson, 2010) that provide information about structural connectivity pathways of various brain regions, reveal three patterns relevant to understanding how valuation, emotional responses, and reward responses can integrate to process an aesthetic experience:

(1) The OFC and VMPFC (along with the dorsal portion of the ACC; dACC), areas involved in integration of high-level processed sensory information and valuation of stimuli, constitute the main cortical input to the NAcc. This provides a direct cortical pathway for influencing mesolimbic regions.

(2) The amygdala, involved in emotional experience and appraisal, has direct input to all three regions OFC, VMPFC, and NAcc.

(3) The NAcc projects to the nucleus basalis in the basal forebrain, which in turn projects to the cerebral cortex and the amygdala, providing a mechanism through which NAcc activity can impact these regions.

These connectivity patterns suggest that these areas are likely to be working in concert to give rise to the emotional, cognitive, and rewarding experiences associated with processing aesthetic stimuli. We examine these interactions and how they may play a role in processing rewards in Chapter 4.

1.4. The Pleasurable Aspects of Music

One aesthetic stimulus that has been extensively studied is music. Listening to or producing music seems to be a part of human nature for a number of reasons. First, music is ubiquitous in human society and has been around in every culture for at least as long as history has been recorded (Conard, Malina, & Munzel, 2009; McDermott & Hauser, 2005; Wallin, Merker, & Brown, 2000). It is likely that some form of music has existed long before that, as anthropologists continue to discover older remnants of various musical instruments. Currently, the oldest musical instruments discovered are flutes made of vulture bones and mammoth ivory vulture bones, found in a cave in southern Germany, carbon dated to be around 42,000 years old (Higham et al., 2012). A second relevant point is that music was not created in one place and passed on, but appears to have developed independently in each culture (Wallin et al., 2000) suggesting that it may be innate to some form of human behaviour. Third, relating to the innate nature of music, humans are able to make sophisticated perceptual decisions about musical sounds at an early age (Trehub, 2001), and without formal training (J. J. Bharucha, 1984; Bigand, 2003; Bigand & Poulin-Charronnat, 2006; Koelsch, Gunter, Friederici, & Schroger, 2000).

Yet if music does not have a clear and direct survival value (Darwin, 1871), why has it been ubiquitous throughout history and how has it lasted this long? What has made music so reinforcing for humans? These are questions that will be explored throughout this thesis, particularly in the second experiment. The next section will review a series of experiments intended to examine why music is considered so rewarding from a neurobiological perspective.

1.5. Music and Emotion

Music is merely a sequence of tones arranged over time. Each of these sound events in isolation may not be considered particularly rewarding; yet somehow their temporal dynamics can induce some of the most intensely pleasurable responses known to man, creating "highs" that have been famously described as similar to those of powerfully addictive drugs. How can the temporal arrangement of otherwise neutral sound events lead to such a potent response?

1.5.1. Why do people listen to music? When individuals are asked why they listen to music, responses range from changing a mood to matching a mood, relaxing, feeling nostalgic, getting cheered up or energized (Behne, 1997; Juslin & Laukka, 2004; Sloboda & O'Neill, 2001; Zillman & Gan, 1997). What all the responses seem to have in common is that emotions of the listener are somehow being influenced. Indeed, the most prominent researchers in the field of music and psychology have linked music and emotion (e.g., Gabrielsson, 2001; Grewe, Nagel, Kopiez, & Altenmuller, 2007a; Huron, 2006; Juslin & Sloboda, 2010; Juslin & Vastfall, 2008; Koelsch, 2010; Koelsch, Fritz, & Schlaug, 2008; Konecni, 2005; Krumhansl, 1997; Lerdahl & Jackenodoff, 1977; L. B. Meyer, 1956; Panksepp & Bernatzky, 2002; Peretz, Gagnon, & Bouchard, 1998; Sloboda, 1992; Zald & Zatorre, 2011; Zentner, Grandjean, & Scherer, 2008). The idea that music enhances emotions has been around for centuries, dating at least as far back as ancient Greece (Budd, 2000). Music is richly integrated with human culture, and has played an important role in social gatherings, ranging from weddings to funerals to tribal ceremonies, amongst others. There is little doubt that music plays a role in sharing and uniting emotional responses in social groups, parts of which may overlap with music's well-established role in movement and dance (Wallin et al., 2000; Zatorre, Chen, & Penhune, 2007). The link between music and emotion is further supported through its popular use in other situations that may benefit from emotional induction, such as films (Cohen, 2001) and marketing (Bruner, 1990).

1.5.2. How does music induce emotions? There are a number of factors that may give rise to emotional responses to music. For example, Juslin and Vastfall have identified six mechanisms through which music can induce emotions: brain stem reflex, evaluative conditioning, emotional contagion, visual imagery, episodic memory, and musical expectancy (Juslin & Vastfall, 2008). Brain stem reflex refers to the way in which acoustical characteristics of the music may signal a potentially important event. For example, loud or dissonant sounds may signal feelings of unpleasantness (Berlyne, 1971; Foss, Ison, Torre, & Wansack, 1989; D. Halpern, Blake, & Hillenbrand, 1986). Evaluative conditioning refers to the induction of emotions as a result of repeated pairing of a piece of music with a particular emotion in the past. For example, certain music may have always been associated with positive events (e.g., weddings), and can induce positive emotions through this conditioning. Emotional contagion involves "mimicking" the emotional expressions that are perceived in the music. For example, listening to cheerful tunes may make an individual feel happy. Visual imagery involves conjuring visual images (e.g., a beautiful landscape) during music listening that can then induce emotions associated with the images. Episodic memory involves triggering specific emotional memories through music listening. A large body of research has demonstrated that this is a powerful method for triggering emotions (F. S. Barrett et al., 2010a; H. Baumgartner, 1992; Davies, 1978; Gabrielsson, 2001; Janata, 2009; Janata, Tomic, & Rakowski, 2007; Sloboda, 1992). Finally, musical expectancy involves a process whereby features of the music violate, delay, or confirm the listener's expectations, which can then lead to emotional arousal. This thesis will focus largely on this final factor, which has gained significant interest since Leonard Meyer's systematic studies of music and emotion presented in Emotion and Meaning in Music (1956). Meyer's theory states that emotional responses to music depend on temporal expectancies involved in processing of sequential information over time and the violation of expectancies in music. This is of particular interest as it suggests that complex mechanisms that are uniquely human may be involved in this form of processing, and an exploration of these issues can aid in our understanding how

temporal pattern recognition can lead to abstract forms of pleasure and reward for humans. We will return to these ideas later in subsequent sections, and they will be further explored in each experiment of the thesis, particularly the first and third experiments. For now, it is sufficient to say that these ideas generated a surge of systematic research on music and emotion (for reviews, see Gabrielsson, 2001; Hodges, 2010; Huron, 2006; Juslin & Sloboda, 2010; Juslin & Vastfall, 2008; Koelsch, 2010, 2012; Sloboda, 1992; Vuust & Frith, 2008; Zald & Zatorre, 2011).

1.5.3. Are musical emotions "real" emotions? The ability and desire to feel emotions may be considered a fundamental quality that makes us human. Emotions are defined by having a valence and an arousal component (Russell, 1980). Positively valenced emotions are generally most sought after, since negative emotions are typically preceded or followed by negative consequences (e.g., sadness or fear). However, it appears that humans may nonetheless desire to experience these negatively valenced emotions when the consequences do not impact them directly, as evidenced by the popularity of sad or scary stories, poetry, music, or films. Perhaps it is the intensity of the emotional arousal that we crave. Furthermore, some emotions experienced to music are more complex, such as nostalgia, which is generally considered pleasurable although it combines elements of dysphoria (F. S. Barrett et al., 2010b). It therefore follows that emotional valence of music is not specific enough to assess rewarding responses, as both positively and negatively valenced (e.g., "happy" and "sad") pieces of music can be considered pleasurable. The "arousal" dimension of emotion in response to music, or the intensity by which emotions are felt may be a better indicator of pleasurable responses (Rickard, 2004). It should also be noted that more intricate models have been proposed to account for the complexity of emotions experienced in response to music. A recent example is that of Zentner and colleagues, who report a nine-factor model based on confirmatory factor analysis of mood ratings, which include Joy, Sadness, Tension, Wonder, Peaceful, Transcendence, Tenderness, Nostalgia, and Power (Zentner et al., 2008), demonstrating the richness of emotions that may be experienced in response to music. However, in a factor analysis, they found that the nine dimensions could

be parsimoniously explained by three factors they called sublimity, vitality, and unease, which largely map on to arousal and valence (Trost et al., 2011).

1.5.4. Assessment of emotions induced by music. Emotional arousal is a subjective experience and difficult to compare across individuals. For example, one subject's response to how emotional they feel on a scale of 1 to 10 may not be comparable with another's. One reliable method of assessing emotional arousal is to objectively target the biological source of arousal, and assess autonomic nervous system (ANS) activity. The ANS is a division of the nervous system that innervates virtually every organ in the body, and is responsible for maintaining homeostasis of the internal milieu by controlling the body's automated and physiological functions and arousal via two branches: the sympathetic and parasympathetic nervous system (Cacioppo et al., 2007; Nestler et al., 2009). Generally, the balance of activity within these two subdivisions achieves homeostatis. The parasympathetic branch is considered "vegetative", and involved when an organism is ready for digestion or relaxation. The sympathetic nervous system, involves physiological functions that facilitate motor action and prepare an organism for "fight or flight", such as increased electrodermal skin response, heart rate, respiration, and blood flow to the body core as well as corresponding decrease in blood volume and temperature in the extremities (Bloom, Lazerson, & Hofstadter, 1985; LeDoux, 1986). Sympathetic activity is closely related to emotional arousal (Cacioppo et al., 2007; Martin & Venables, 1980).

Separating valence and arousal. Many physiological responses of the ANS, such as cardiovascular, respiratory, temperature, electrodermal, and muscle movements can be measured directly on a millisecond basis, providing objective cues for assessing emotional arousal (Bechara & Damasio, 2005; Bradley & Lang, 2000; Cacioppo et al., 2007). Early published studies of psychophysiological changes in response to music date back to the 19th century when Warthin reported changes in heart rate when hypnotized patients listened to music (Warthin, 1894). Since then, the literature has expanded considerably. It is important to know that the type of emotion experienced is extremely difficult to assess via such measures,

as many different emotions will have similar arousal profiles. For example, extreme anger or extreme happiness are very different emotions, yet they both involve increases in heart rate, respiration, electrodermal response, and other indicators of increased SNS function. To illustrate this, one study found increases in skin conductance in response to both "joyful" (Jupiter from the Planets, by Holst) and "horrific" (Threnody for the Victims of Hiroshima, by Penderecki) amongst college students (Vanderark & Ely, 1992, 1993). As such, distinguishing amongst different valences using psychophysiological measures alone has been challenging due to similarities in the degree of arousal experienced with various emotions (Khalfa, Peretz, Blondin, & Manon, 2002; Krumhansl, 1997). However, assessment of the intensity of emotional experiences with measures of psychophysiological arousal has been more successful (Rickard, 2004).

Separating bottom-up and top-down influences. An important consideration to take into account when designing music studies is that music can have different effects on different people. Despite over a hundred studies examining psychophysiology changes in response to music (Hodges, 2010), few studies have accounted for individual preferences while examining the link between ANS arousal and music listening. That is, many researchers use experimenter-selected music, under the assumption that all participants will have the same experience in response to the music. For example, while some studies have found that "stimulant" music causes changes in heart rate, respiration, electrodermal skin response, and blood pressure (see Hodges, 2010 for a review) others have found the same ANS effects with "sedative" music (Ellis & Brighouse, 1952; Krumhansl, 1997; Rickard, 2004; Shatin, 1957; Weld, 1912). These findings suggest that the "sedative" music may have been arousing for some individuals. These inconsistencies make it difficult to draw conclusions about whether certain types of music reliably induce a pattern of psychophysiological responses in all individuals, and outline the importance of considering a top-down approach in studies using musical stimuli. There is evidence that on average, certain features such as tempo or loudness are associated with arousal and others such as consonance are associated with valence (Gomez & Danuser, 2007; Hodges, 2010). However, the complexities of topdown interaction with auditory input suggest that individual differences should be taken into account.

Experimenter-selected versus self-selected music: individual preferences and inducing ecologically valid emotional intensities in a laboratory setting. A second related issue to consider is the extent of emotional arousal that is induced in a laboratory setting. Rickard (1994) argues that to see clear differences in psychophysiological responses, musical selections that induce intense emotional responses must be used, rather than music that induces more mild pleasurable states. When experimenter-selected musical selections are used for experimentation, it is likely that they could result in only mild pleasurable states since music preferences are highly individualized. For example, Rickard (1994) asked participants to select their own "emotionally powerful" music and found wide diversity amongst the selections, ranging from dance music to opera, and a range of tempi, forms, and complexities. This study found that electrodermal changes were most extreme to self-selected musical pieces, compared to experimenter-selected "arousing" and "relaxing" music. Additionally, other studies found that when participants listen to other individual's emotionally powerful music, they do not show the same responses as the individual who selected the music (Blood & Zatorre, 2001; Panksepp, 1995). These studies provide empirical evidence that emotional arousal to music is a highly individualized response, and may depend on factors such as previous experience with music, personality differences, and cultural influences (Gabrielsson, 2001; Grewe, Nagel, Kopiez, & Altenmuller, 2007b; Rentfrow & Gosling, 2003; Schafer, Tipandjan, & Sedimeier, 2012; Tervaniemi, Tupala, & Brattico, 2012; Thaut & Davis, 1993). A good example of cultural differences in appreciating different types of music comes from the contrast between Pansksepp et al. (1995) and Grewe et al.'s (2007) studies, where American students demonstrated highly emotional responses to a pop song popular in the United States in the 1980's ("Making Love out of Nothing at All") in Panksepp et al.'s study, while the German students in Grewe et al's study not being familiar with this music did not

show such responses. It is likely that some "bottom-up" features inherent in the music are likely to induce specific responses for many individuals. However, the response of the individual will ultimately depend on an interaction of "top-down" processes based the factors outlined above and the specific features in the music.

In addition to differences in the types of music that induce emotional responses for different individuals, there is also some variability in the likelihood that individuals will experience intense emotion. This is thought to rely partly on personality differences (Kopacz, 2005; Vuoskoski & Eerola, 2011) and sensitivity to reward (Mas-Herrero, Marco-Pallares, Lorenzo-Seva, Zatorre, & Rodriguez-Fornells, In Press). For example, some studies have found that individuals who experience more intense emotions are those who score high on the personality dimension Neuroticism (F. S. Barrett et al., 2010a; Chamorro-Premuzic & Furnham, 2007) and Openness on the Big Five Inventory (Nusbaum & Silvia, 2010). The combination of personality factors, sociocultural influences, and individual needs creates complex interactions that must be taken into consideration when examining why and how people listen to and appreciate music.

Physiological manifestations of intense emotional responses to music. To assess intense emotional responses, a number of studies have taken advantage of the observable physiological responses that individuals display in response to highly emotion-producing music, such as tears, laughter, or "chills" (Gabrielsson, 2001; Sloboda, 1991). Musical "chills", also known as "goosebumps", "frissons", or "shivers-down-the-spine", has been a particularly well-studied physiological manifestation of emotional responses to music (Blood & Zatorre, 2001; A. Goldstein, 1980; Grewe, Katzur, Kopiez, & Altenmuller, 2008; Grewe, Kopiez, & Altenmuller, 2009; Grewe, Nagel, Kopiez, & Altenmuller, 2005; Grewe, Nagel, et al., 2007a; Huron & Hellmuth Margulis, 2009; Konecni, Wanic, & Brown, 2007; Panksepp, 1995; Panksepp & Bernatzky, 2002; Rickard, 2004; Sutherland et al., 2009). In 1980, Goldstein observed that this physiological experience to music was experienced by approximately half of the individuals surveyed. Other studies have found even higher prevalence (Panksepp, 1995). Importantly, Goldstein found that the chills response diminished in some individuals by injection of a pharmacological substance that blocks opiate receptors in the brain (naloxone), suggesting that neurotransmitters that bind to opiate receptors in the brain (e.g., endorphins) (A. Goldstein, 1976), may be somehow involved in this process. This was a small effect, demonstrated only in 3 out of 10 individuals who experienced chills, but nonetheless suggested that an emotional response involving the ANS might be mediated by neurotransmitters involved in pleasurable responses (A. Goldstein, 1976; A. Goldstein, 1980). The chills response will be further explored in the second and third chapters of the dissertation.

1.6. Music, Emotion, and Pleasure

The next question we address is how can emotional arousal link to pleasure. To answer this question, a more in-depth look at physiological responses is required, and for this we turn to the brain.

1.6.1. Brain imaging findings linking music, emotion, and pleasure. Advances in neuroimaging over the past two decades have allowed for examinations of how music impacts the brain. The first study of this kind was conducted in 1999 on a positron emission tomography (PET) scanner (Blood et al., 1999), which can be used to provide a measure of changes in regional cerebral blood flow (rCBF). Blood and colleagues examined changes in neural activity of ten participants in response to six versions of a piece of music with systematically varying degrees of dissonance. A parametric analysis revealed that increases in consonance and experienced pleasantness were associated with rCBF changes in the OFC and increases in dissonance and experienced unpleasantness were associated with rCBF changes in parahippocampal cortical regions. This study provided the first evidence that listening to music recruits emotionally-relevant brain regions. But it also showed involvement of distributed circuits in cortical areas, implying that quite complex cognitive systems might also be at play, together with the more fundamental reward-related system. As discussed in Section 1.3.3, the OFC is a multifunctional region of the brain that has also been

implicated in processing many other types of aesthetic stimuli, largely involved in tasks that require reflection and decision-making based on internal states with inputs from the five major sensory pathways to appraise the quality of objects by integrating various sources of sensory and cognitive information.

Additional evidence for the role of OFC in processing pleasurable music came from a second study from Zatorre's lab, which was the first study to examine neural activity in response to pleasant music (Blood & Zatorre, 2001). Using PET imaging, Blood and Zatorre found that activity in the OFC, along with other regions, was elicited by listening to highly emotional (chill-inducing) selfselected music, contrasted against other participants' music. More importantly, this study was the first to demonstrate activity in the mesolimbic reward regions of the brain, specifically in the NAcc, during emotional responses to music. As outlined in Figure 1, this area of the mesolimbic striatum is a major site for dopaminergic output from the VTA. Dopaminergic activity in this site has been linked to highly addictive psychoactive chemical substances, such as cocaine (Cox et al., 2009), amphetamines (Leyton et al., 2002), alcohol (Boileau et al., 2003), and nicotine (Di Chiara & Imperato, 1988), as well as to highly emotional rewards, such as winning money unexpectedly (Pappata et al., 2002) or through videogames (Koepp et al., 1998). Some argue that this is the "emotional" part of the striatum (Breiter et al., 1997; Haber & Knutson, 2010). As outlined in Section 1.3.2, the NAcc's is known as the "emotional" part of the striatum and has intricate connections with other parts of the limbic system (Figure 2), including the amygdala, hippocampus, and hypothalamus (Haber & Knutson, 2010).

Subsequent studies of processing pleasant music confirmed activity in the NAcc when individuals listened to pleasant music compared with silence (Brown et al., 2004), scrambled music (Menon & Levitin, 2005), dissonant music (Koelsch et al., 2006), and "neutral" music (Mitterschiffthaler et al., 2007). A recent study examining more complex emotions with fMRI also revealed NAcc activity in correspondence with parametric increases in ratings of pleasant emotion categories, such as Joy and Wonder (Trost et al., 2011).

With additional studies on music and emotion, more patterns in brain activity were revealed. Koelsch et al. (2006) manipulated the consonance of a piece of music, and asking participants to rate how they were feeling after hearing each piece of music. This paradigm was similar to Blood et al's (1999) study, but using fMRI, which has higher spatial resolution as compared to PET. fMRI estimates involvement of neural regions by examining changes in blood oxygenation level while participants are performing a task compared to control conditions (Huettel, Song, & McCarthy, 2009). Koelsch and colleagues contrasted neural activity associated with listening to classical music excerpts with their dissonant counterparts, otherwise maintaining the structure of the pieces. Their results revealed increases in blood-oxygen level dependent (BOLD) signal in the ventral striatum (including the NAcc) and anterior insula when participants listened to pleasant music and BOLD increases in the amygdala, hippocampus, and parahippocampal gyrus, and temporal poles while participants listened to dissonant pieces. This study supported Blood et al.'s finding of amygdala and parahippocampal activity in response to unpleasant music. Additional support for parahippocampal involvement with unpleasant music comes from lesion studies which reveal that when patients have damage to this region and surrounding temporal areas they demonstrate diminished emotional sensitivity to dissonant music (Gosselin et al., 2006; Khalfa, Guye, et al., 2008). Koelsch suggests that these regions may be involved in processing acoustic roughness and decoding affective content of vocal signals (Koelsch, 2010). However, it should be noted that another study by Mitterschiffthaler and colleagues has found activity in this region during processing of happy music (Mitterschiffthaler et al., 2007).

The finding that amygdala was involved in processing unpleasant music is also notable as this region also showed increased activity in response to sad states induced by music (Mitterschiffthaler et al., 2007), and conversely revealed decreased activity in response to pleasant music in Blood and Zatorre's study (2001). Similarly, a study by Baumgartner et al.(2006) found that activity in the amygdala was enhanced when photographs were paired with fearful and sad

music, and Lerner et al. (2009) found increases amygdala activity when participants listened to fearful music with their eyes closed. Lesion studies examining emotional recognition of patients with amygdala damage also found impaired recognition of scary, fearful, and sad music (Gosselin et al., 2007; Gosselin et al., 2005). The amygdala has been demonstrated to be involved in a number of other non-musical studies involving unpleasant emotional stimuli (Lang, Davis, & Ohman, 2000; J. S. Morris et al., 1996), and implicated in mood, anxiety, and post-traumatic stress disorders (Drevets et al., 2002; Stein, Simmons, Feinstein, & Paulus, 2007), making it tempting to conclude that it may be involved in processing negative emotions. However, as outlined in Section 1.3.1, this region has also been implicated in experiencing positive emotions (Canli, Sivers, Whitfeld, Gotlib, & Gabrieli, 2002; Sergerie et al., 2008). Indeed, a study similar to Baumgartner's found amygdala activity increases in response to joyful music presented along with neutral film clips (Eldar, Ganor, Admon, Bleich, & Hendler, 2007). Two other studies, using gustatory and olfactory stimuli, demonstrated that the amygdala showed increased activity to both positive and negative tastes and smells, and activity in this region was much more sensitive to the intensity of stimuli over their valence (Anderson et al., 2003; Small, Gregory, et al., 2003). As the amygdala is composed of several different nuclei, it is also possible that anatomically distinct subregions may play different roles under different circumstances via differential functional connectivity to various regions in the brain (Ball et al., 2007; Koelsch, 2010). The amygdala may therefore contribute to different emotional networks.

Three other regions that tend to show up consistently in music processing are the hypothalamus (Menon & Levitin, 2005), insula (Blood & Zatorre, 2001; Brown et al., 2004; Koelsch et al., 2006; Menon & Levitin, 2005; Mitterschiffthaler et al., 2007; Trost et al., 2011), and the ACC (Blood & Zatorre, 2001; Brown et al., 2004; Mitterschiffthaler et al., 2007). All three regions have been implicated in controlling ANS arousal (Cacioppo et al., 2007; Critchley, 2005; Critchley, Corfield, Chandler, Mathias, & Dolan, 2000) and have direct connections to the mesolimbic reward areas of the brain (Haber & Knutson, 2010). This connectivity is particularly relevant for music listening, which is thought to be rewarding due to its ability to enhance emotional arousal. Indeed, at least one study has reported evidence for functional connectivity between the NAcc and hypothalamus when individuals listen to music (Menon & Levitin, 2005).

Another region that consistently shows increased activity in response to music is the hippocampus. It is well established that this region plays a role in formation and retrieval of memories (Henke, 2010; B. Milner, 1972; B. Milner, Squire, & Kandel, 1998; Penfield & Milner, 1958; Szapiro et al., 2002). Thus, hippocampal activity in response to music should not be surprising, as music has privileged access to memory. People often experience a rush of emotional memories while listening to a piece of music from their past (F. S. Barrett et al., 2010a; Janata, 2009; Janata et al., 2007; Jancke, 2008). However, understanding its precise contributions to emotional responses may provide a more difficult challenge. For example, it may be challenging to find musical stimuli with which all participants are equally familiar, which could result in differential hippocampal activity. Nonetheless, there is little question that the hippocampus plays a pivotal role in music processing.

Finally, the precise role of the nearby temporal poles in processing music is not entirely clear. Koelsch et al. (2006) found increased activity in this region in response to unpleasant music and Baumgartner et al. (2006) found activity in this region during presentation of fearful and sad music in combination with similarly valenced photographs, and Brown et al., (2004) found activity in this region in response to listening to pleasant music compared with rest.

1.6.2. Challenges associated with brain imaging and music. It is important to note that many of the regions listed above are not specific to processing emotional music, and are involved in a number of processes that may be tangential to experiencing emotions in music. For example, while insula activity is widely observed in music studies, activity in this region has been demonstrated when there are physiological increases in heart rate and blood pressure (Critchley, 2005; Critchley, Corfield, et al., 2000), making it difficult to

determine whether this activity in this region is directly involved in music processing or merely a byproduct of emotional arousal. As such, there are a number of important issues to consider when evaluating brain imaging studies with musical stimuli.

Isolating emotional responses. First, listening to music involves many different processes, ranging from detecting changes in beat, pitch, rhythm, and music structure, to the experience of emotional responses, visual imagery, and previous memories associated with music. Therefore, it is not always possible to claim that observed brain activity is in response to "emotion" per se, and not one of the other processes involved. This consideration applies in particular to studies that compare neural activity induced by music with nonspecific control conditions (Brown et al., 2004; Menon & Levitin, 2005).

Individual preferences and emotion induction. A second issue relates to individual differences in music preferences. As previously discussed, it is challenging to reliably induce a feeling in all participants using experimenter-selected music. In order to make inferences about neural correlates of specific emotions or pleasurable responses, it is important to ensure that participants did indeed experience the intended emotion. Menon and Levitin (2005) compared neural activity associated with listening to musical selections with their less-recognizable scrambled counterparts. While it is likely that participants found the scrambled stimuli "unpleasant" to listen to, there was no direct measure to assess whether individuals found the unscrambled counterparts "pleasant", making it difficult to draw conclusions about how rewarding the pleasant music was to the participants. Other studies took this issue into consideration by asking participants to rate how they were feeling either during or immediately after hearing each piece of music (Koelsch et al., 2006; Mitterschiffthaler et al., 2007).

Objective measures of emotion. A third issue to consider is the degree to which participants can accurately rate their subjective emotional states. For example, some participants may rate their mood as "happy" because they recognize that the music they listen to is joyful-sounding and intended to make them feel that way. The abstract and subjective nature of emotional responses

proposes a challenge in measuring and comparing responses across individuals (for a review, see Gabrielsson, 2001; Juslin & Sloboda, 2010; Juslin & Vastfall, 2008; Zentner et al., 2008). One method to improve objective detection of emotional arousal is to incorporate psychophysiological measures of ANS activity during music listening (see, for example, Blood & Zatorre, 2001). As described above, psychophysiological measures cannot reliably distinguish various emotional states, but have demonstrated to be effective in detecting emotional arousal (Cacioppo et al., 2007).

Despite the challenges associated with examining responses to music, the studies on music and brain imaging collectively demonstrate that emotional regions in the brain are involved in processing music that individuals find pleasurable, further strengthening the link between emotion and pleasure in response to music. Moreover, these studies suggest that cortical processes are also involved, suggesting that there are higher-order cognitive mechanisms are implicated in appreciating music. The interaction of higher-order cortical regions and subcortical regions may be what is giving rise to pleasurable responses to music. Importantly, nearly all studies on pleasurable music also showed some degree of activity in the dopaminergic mesolimbic striatal regions, particularly the NAcc, suggesting that a dopaminergic response may play a critical role in mediating the positive responses to music. Nonetheless, the fMRI and PET methods used in these studies rely on hemodynamic activity and do not allow us to draw conclusions about whether dopamine is involved in these processes, and precisely how emotions can be linked to pleasure.

1.7. The missing links: Neural interactions that give rise to musical pleasure

Collectively, the results presented in the previous section support a relationship between music and emotional arousal, and suggest involvement of the brain's reinforcement circuitry. However, a number of questions remain. For example, how do emotional responses to sound events begin to form? How do emotional responses link to pleasure? Is dopamine really involved and if so where does it exert its impact and what role does it play in rewarding responses to

music? Why do different people have different emotional responses to music and why do they find different types of music rewarding?

In this dissertation, I will present a series of studies designed to examine these questions and further investigate the physiological and neurological mechanisms and interactions that are involved processing the rewarding qualities of music. The goals of these studies and the dissertation were to integrate previous theoretical hypotheses and empirical findings into a model and elaborate it by investigating the missing links.

The proposed model is predicated on the following concepts: Rewarding responses related to music listening represent an abstract form of pleasure that involves integration of sensory, affective, and cognitive processes in the brain, some of which involve neural circuitry that may be unique to humans. Subjectively reported pleasurable responses to music are related to enhanced emotional arousal, reinforced by acting on the dopaminergic circuitry. These emotional responses result from complex interactions between sensory processing and highly-evolved cortical regions of the brain involved in abstract-level processing of information, such as sequencing, predicting, and pattern identification. There is a prominent role in top-down influence that interacts with bottom-up processing of auditory information, to give rise to the vast differences in individual preferences and responses to music.

Therefore, our theory can be separated into specific hypotheses to address the three broader issues:

1.7.1. Issue 1: Link between Pleasure and Emotional Arousal

Question: Is music rewarding because it enhances emotions?

Hypothesis 1.1. As outlined in section 1.5, the most researchers in the field of music psychology link music to emotions, and there is ample evidence that pleasurable music targets emotion centres in the brain (Koelsch, 2010; Zald & Zatorre, 2011). Yet, there is no demonstration that there is a clear and direct relationship between pleasurable responses to music and emotional arousal. If there is a direct correlation between emotion and pleasure we expect that subjective reports of increasing pleasure during music listening should be

accompanied by corresponding increases in emotional arousal. Importantly, as outlined in section 1.5.3, subjective reports of emotional arousal may not be reliable. Therefore, we predicted that increases in pleasure should be associated with automated physiological manifestations of emotional arousal that can be objectively measured. The verification of this hypothesis would set the groundwork for further research on how music enhances emotional arousal and how this can lead to highly pleasurable responses.

Hypothesis 1.2. As outlined in sections 1.3, 1.5, and 1.6.2, there is large variability in individual preferences for music. We predict that emotional responses will mirror preferences and individuals with different levels of liking for a piece of music will display different physiological manifestations of emotional arousal in response to the same music. If this prediction is accurate, there is evidence for top-down interactions with incoming auditory information that interact with any effects that may be observed through bottom-up responses to psychoacoustical features of the music.

Hypothesis 1.3. Section 1.5 describes the musical chills phenomenon (A. Goldstein, 1980; Grewe et al., 2008; Grewe et al., 2009; Grewe et al., 2005; Panksepp, 1995; Sloboda, 1991, 1992), thought to be physiological manifestations of peak responses to music. Based on this, we aim to validate this and predict that those individuals who are prone to experiencing them will experience chills during peak emotional and pleasurable responses to music.

1.7.2. Issue 2: Link between Emotional Arousal and Dopamine Release

Questions: Can positive emotional arousal elicited by music lead to dopamine release in the brain? If dopamine is released, which regions are involved, and is it involved with the anticipation or with the experience of the peak pleasure or emotional moments in music?

Hypothesis 2.1. We hypothesize that listening to music may be targeting the brain's mesolimbic reward systems. This hypothesis is based on three observations:

(1) Music has persisted as far back as prehistory throughout all cultures, despite any clearly demonstrated survival value (see Section 1.4). Stimuli that persist for such long periods are typically those that are biologically adaptive (see Section 1.1), and behaviours related to them are reinforced through the mesolimbic reward circuits. If music were somehow targeting this system, there would be some explanation of why it continues to be ubiquitous in societies worldwide, despite not a having a direct adaptive purpose.

(2) Listening to music can lead to intensely pleasurable responses, some of which have been described as similar to those of powerful drugs of abuse. The fact that many of these drugs target the mesolimbic dopamine system further suggests that there may be a connection between music and this circuitry.

(3) As outlined in Section 1.6, there is a growing literature showing increased hemodynamic activity in mesolimbic regions of the brain during music listening. It should be noted that the techniques used in previous studies have measured differences in blood-oxygenation levels and metabolic activity, which does not provide information about the neurotransmitters involved. As there are a number of different neurotransmitters that play important roles in mediating mesolimbic activity (Nestler et al., 2009), these techniques do not have the specificity to identify dopamine release during music listening in these regions. Therefore, a procedure with sufficient sensitivity to detect dopamine activity in the brain would need to be used to examine dopamine release associated with music listening.

Hypothesis 2.2. Based on the recent literature that dopamine is involved in anticipatory and predictive cues that signal a reward (see Section 1.1.6), we hypothesized that if dopamine is released during music listening, it would be while individuals are listening to predictive cues in the music that signal a desirable passage. In other words, activity in dopaminergic regions would be observed prior to peak pleasure moments in the passages when maximum emotional arousal is reached. This would also be consistent with prominent musical theories, which claim that emotional responses to music are a result of anticipations created through music listening (see Section 1.5).

Hypothesis 2.3. Based on the anatomical connectivity on the NAcc (ventral striatum) with the systems in the brain that underly emotional arousal (see Section 1.1.2), we predicted that if there is dopamine release during music listening, it would be associated with this region. We further predicted that there may be dopamine release in the dorsal striatum, as this area is largely involved in detecting predictive cues in habitual reward-related circumstances (Section 1.1.2).

1.7.3. Issue 3: Interactions that give rise to Rewarding Responses

Questions: How does a piece of music gain initial reward value? How do brain systems interact to make this happen? Why do different people have different emotional responses to music and why do they find different types of music rewarding?

Hypothesis 3.1. Based on the structural and functional interconnectivity of the mesolimbic, nigrostriatal, and mesocortical dopaminergic circuits (see Sections 1.1.2 and 1.3), we hypothesized that there would be intricate interplay between various regions in the circuits during musical reward processing. We further hypothesized that the phylogenetically older subcortical circuits interact with more recently evolved cortical systems, such as those involved in higherorder, sensory, perceptual, and cognitive processing to give rise to the pleasures that we experience in response to an abstract reward, such as music. In other words, complex top-down interactions (i.e., cortical influences) with affective and sensory regions of the brain would be involved in giving rise to pleasurable responses associated with music, and critical mesolimbic dopaminergic sites, such as the NAcc would play a central role in this interaction. Finally, we hypothesized that these connectivity patterns would best be revealed with multivariate analysis techniques, which allow the investigation of a number of brain regions simultaneously, since brain regions work in concert as dynamically integrated networks give rise to various cognitive and emotional functions.

1.8. The present investigation

To investigate these issues, we designed three experiments, each of which examined one of the hypotheses and will be discussed in chapters 2, 3, and 4, respectively. The first experiment set the foundation for our model by testing the hypothesis that there is a direct link between subjectively reported pleasure and emotional arousal. We followed a number of procedural guidelines to appropriately deal with critical issues raised in the review of previous literature above. First, we used psychophysiological measures of ANS arousal to obtain an objective assessment of emotional arousal, avoiding pitfalls of unreliability that can accompany subjective ratings of emotional arousal (see Sections 1.5 and 1.6.2). Next, to ensure that individuals experience intense emotional arousal in the laboratory, we asked participants to bring in self-selected music which they find intensely pleasurable, rather than using experimenter-selected music that could result in only mild enhancements of mood (see Section 1.6.2). We further asked participants to select music to which they experience "chills", which is an unmistakable physiological response to emotionally evocative musical stimuli (Section 1.5). The purpose of this experiment was to examine real-time relationships between self-reported ongoing pleasure ratings and objectively assessed emotional arousal, as individuals listened to their emotionally evocative music. This experiment is discussed in Chapter 2.

Following this experiment, a second study was designed to examine whether listening to music can lead to dopamine release. We took advantage of the specificity afforded by ligand-based PET imaging to determine whether intense emotional responses to music are directly targeting dopamine in the mesolimbic or mesostriatal circuitry. If there was any dopamine release we were also interested in examining the dynamic nature of this activity, which is not possible with ligand-based PET due to low temporal sensitivity. As such, we also implemented fMRI scanning, which provided a mechanism to examine hemodynamic activity in any areas that show dopamine release. This combined procedure would allow one procedure to compensate for the limitations of the

other. Furthermore, we maintained the psychophysiological measurements to validate emotional responses. This experiment is discussed in Chapter 3.

The third experiment in my dissertation was designed answer questions raised by the first two experiments and to integrate the findings of the second experiment with the larger hypothesis that rewarding responses to music involved complex interactions between sensory, affective, and cognitive areas of the brain. In this experiment, we implemented a procedure from economics (the Becker-Degroot-Marschak auction paradigm) to help us objectively assess reward value of a musical excerpt. The excerpts were novel and unfamiliar to the participants to allow us to examine how a new piece of music gains reward value. Multivariate connectivity analyses were applied to examine the various sensory, perceptual, emotional, and cognitive mechanisms that give rise to reward-related processes that make a piece of music rewarding to an individual. This experiment is discussed in Chapter 4.

Chapter 2: The Link between Emotion and Pleasure in Music

2.1. Preface

This chapter describes an experiment conducted to examine the links between pleasure and emotional arousal. Music is commonly believed to impact emotional arousal (Section 1.5). Therefore, as a first step in determining how music exerts pleasurable influences, we tested the hypothesis that increases in emotional arousal underly increased pleasurable responses to music. The manuscript was published in a 2009 issue of PloS-ONE (Salimpoor, V. N., Benovoy, M., Longo, G., Cooperstock, J., Zatorre, R. (2009) The Rewarding Aspects of Music Listening are Related to Degree of Emotional Arousal. PLoS-ONE, 4(10) e7487).

2.2. Abstract

Listening to music is amongst the most rewarding experiences for humans. Music has no functional resemblance to other rewarding stimuli, and has no demonstrated biological value, yet individuals continue listening to music for pleasure. It has been suggested that the pleasurable aspects of music listening are related to a change in emotional arousal, although this link has not been directly investigated. In this study, using methods of high temporal sensitivity we investigated whether there is a systematic relationship between dynamic increases in pleasure states and physiological indicators of emotional arousal, including changes in heart rate, respiration, electrodermal activity, body temperature, and blood volume pulse. Twenty-six participants listened to self-selected intensely pleasurable music and "neutral" music that was individually selected for them based on low pleasure ratings they provided on other participants' music. The "chills" phenomenon was used to index intensely pleasurable responses to music. During music listening, continuous real-time recordings of subjective pleasure states and simultaneous recordings of sympathetic nervous system activity, an objective measure of emotional arousal, were obtained. Results revealed a strong positive correlation between ratings of pleasure and emotional arousal. Importantly, a dissociation was revealed as individuals who did not experience pleasure also showed no significant increases in emotional arousal. These results have broader implications by demonstrating that strongly felt emotions could be rewarding in themselves in the absence of a physically tangible reward or a specific functional goal.

2.3. Introduction

Why is music pleasurable? It is simply a sequence of tones. Yet music has been present in every known human culture as far back as history dates. Although there are various theories as to why music may have developed (for a review see W. T. Fitch, 2005), the intense degree of pleasure associated with listening to music remains a mystery. The conundrum lies in the fact that there are no direct functional similarities between music and other pleasure-producing stimuli: it has no clearly established biological value (cf., food, love, and sex), no tangible basis (cf., pharmacological drugs and monetary rewards), and no known addictive properties (cf., gambling and nicotine). Despite this, music is consistently ranked amongst the top ten things that individuals find highly pleasurable (Dube & Lebel, 2003), and it plays a ubiquitous and important role in most people's lives.

One prominent theory is that music asserts its effects through influencing emotions (Huron, 2006; Juslin & Sloboda, 2010; L. B. Meyer, 1956). It follows from this that music may evoke or enhance emotions, and that emotion in itself could be rewarding. Empirical evidence linking music and emotional arousal comes from subjective reports that "modifying emotions" is reported as the top reason why people listen to music (Sloboda & O'Neill, 2001), as well as through objective measures of physiological changes in the body in a direction indicative of emotional arousal during music listening (Harrer & Harrer, 1977; Khalfa et al.,

2002; Krumhansl, 1997; Rickard, 2004; Zimny & Weidenfeller, 1963). Emotion, by definition, involves a physiological component (Damasio, 1999; James, 1884; Schacter & Singer, 1962). More specifically, emotional arousal is physiologically marked by increased activity of the sympathetic branch of the ANS, without voluntary control. The connection between emotional arousal and sympathetic nervous system activity has been well-established (Damasio, 1994; Ekman, Levenson, & Friesen, 1983; LeDoux, 1996). This connection has also been substantiated with music stimuli (Grewe, Nagel, et al., 2007a; Rickard, 2004). It should be noted, however, that while physiological arousal is a reliable indicator of the "arousal" component of emotions, it is more controversial with respect to detecting the "valence" dimension of emotions. This concern does not present a problem here, as we are only interested in emotions with positive valence.

Despite the established link between music listening and emotional arousal, it is not clear whether this arousal underlies the pleasurable aspects of music, and there is little empirical evidence to suggest that emotional arousal is directly related to music's rewarding properties. The aim of our study was to test this theory by systematically examining the relationship between emotional arousal and pleasure during music listening. Pleasure is a construct that refers to a subjective state, and implies that the associated behaviour is rewarding and likely to be repeated. The broader implication of this experiment is to understand why humans feel pleasure from listening to music, and why this behaviour continues to be repeated despite any apparent functional significance. One way to examine this question would be to manipulate the degree of pleasure experienced in response to music listening on a continuum, and examine the underlying changes in emotional arousal. This represents a challenge as the range of such a manipulation would have to be large enough to produce sufficient variability for reliable results. In other words, a mild change in mood would not suffice; participants would have to experience "no pleasure" on one end of the spectrum and "extreme pleasure" on the other (also see Rickard, Toukhsati, & Field, 2005). Since musical preferences vary widely (Carter, Wilson, Lawson, & Bulik, 1995; Harrer & Harrer, 1977; Thaut & Davis, 1993), this would be an extremely

difficult task to achieve with a single set of experimenter-selected musical samples. Thus, we used participant-selected music. However, this, in turn, implies that different stimuli would be used for different individuals, not allowing one to accurately conclude whether any observed changes in physiology are specific to acoustical parameters of the music (e.g., changes in tempo, pitch, harmony, etc.), or to a change in subjective state. For example, some studies suggest that changes in tempo lead to corresponding changes in respiration rate (Etzel, Johnsen, Dickerson, Tranel, & Adolphs, 2006; Khalfa, Roy, Rainville, Dalla Bella, & Peretz, 2008). If it is also the case that a participant begins to enjoy a piece of music more as its tempo increases, one would not be able to conclude whether any corresponding changes in respiration rate are attributable to increases in pleasure states, or a bottom-up physiological reaction to psychoacoustical features of the music. As such, it is necessary to distinguish between any changes in physiology that may be caused by the stimulus more generally from those that are reflective of individualized emotional response to that stimulus. Here, we developed a paradigm that separates these two processes. First, participants were asked to provide self-selected musical pieces to which they experience intense pleasure. To index the presence of an intensely pleasurable state, we used the "musical chills" response. Chills, or "shiversdown-the spine", are well-established physiological phenomena that are experienced in response to music listening (Blood & Zatorre, 2001; A. Goldstein, 1980; Grewe, Nagel, et al., 2007a; Panksepp, 1995; Rickard, 2004; Sloboda, 1991). Musical chills are not experienced by everyone, but those who do experience them tend to do so consistently during moments of peak pleasure. Importantly, chills involve stereotypical changes in physiological arousal (Blood & Zatorre, 2001; Grewe et al., 2008; Grewe et al., 2005; Grewe, Nagel, et al., 2007a) that can be objectively indexed to verify their occurrence. Finally, each individual was asked to listen to all other participants' "chills music" selections, and rate how much pleasure they felt as a result of listening to it, from none to intense pleasure. Using this technique, each musical excerpt was matched with two individuals, one who experienced intense pleasure to it, and one who

experienced no pleasure to it. This method allowed for a direct comparison of changes in physiological responses to the music, allowing us to isolate any stimulus-driven changes that might be observed in both participants versus response-driven changes that are individualized.

We also needed a reliable indicator of emotional arousal. Traditionally, this has been obtained by asking people to evaluate their emotional state after listening to each excerpt (Iwanaga, Kobayashi, & Kawasaki, 2005; Johnsen, Tranel, Lutgendorf, & Adolphs, 2009; Khalfa, Roy, et al., 2008; Krumhansl, 1997; Roy, Mailhot, Gosselin, Paquette, & Peretz, 2009). However, there are two problems with this method, particularly for the purposes of our study. First, subjective ratings of emotional arousal may be too arbitrary for comparisons across different participants since one person may consider a major change in arousal as a one point increase on the scale, whereas another participant may consider only a minor change sufficient for this increase. To account for this, we implemented a more objective method by recording the physiological signals mediated by the ANS that are highly sensitive to emotional arousal, including changes in electrodermal activity, heart rate, blood volume pulse (BVP) amplitude, respiration rate, and body temperature (Bradley & Lang, 2000; Rickard, 2004). The second problem is that music is a dynamically changing stimulus. That is, any associated emotions and intensely pleasurable responses (such as those marked by chills) develop over time. Thus, a single value averaged over the entire stimulus would not fully capture the second-by-second changes in subjective and physiological states. To correct for this problem, our paradigm involved continuous real-time millisecond recordings of both pleasure and physiological arousal, which allowed us to capture the dynamic relationships between the two with high temporal sensitivity.

In summary, to overcome previous limitations, simultaneous recording of subjective pleasure states and objective indicators of emotional arousal recorded in real-time were used to capture any systematic relationships between the two. We tested the hypothesis that if the rewarding aspects of music listening are indeed a result of the emotional states produced, there would be a positive

correlation between emotional arousal and pleasure states. It further follows that a lack of pleasurable responses should also be accompanied by low emotional arousal.

2.4. Methods

2.4.1. Participants. Two hundred and seventeen participants responded to advertisements posted around the university campus and sent to various university and community email lists. The advertisement recruited individuals who experience "chills" as an intensely pleasurable response to music. Three rounds of screening were implemented (email, telephone, in-person interview) to assess whether participants met the following criteria: (1) experienced chills consistently to a piece of instrumental music, and (2) chills were pleasurable (i.e., not experienced because the individual was cold, surprised, or frightened) and did not diminish greatly with multiple listening. In addition, the chill-inducing music could not contain any lyrics or be associated with a specific memory (see Stimuli section). Individuals who met all the above criteria were selected for the study. A sample of over 200 chill-inducing music selection submitted through the first round of recruitment can be found in supplementary files online (Supplementary Table 1: Appendix 2). Participants who met all the exclusion criteria and were selected for the study included 17 women and 15 men, between the ages of 18 to 36 (M = 22, +/- 3.8 years), with a broad range of musical experience (no training to 18 years of experience). All individuals were healthy and free from any neurological or psychological disorders, assessed through a prescreening interview, and gave written informed consent before participating in the study. Ethical consent for the study was approved by the Montreal Neurological Institute Internal Review Board (Appendix 3).

2.4.2. Stimuli. Participants were instructed to provide 3-5 pieces of intensely pleasurable instrumental music to which they experience chills. Prescreening interview questionnaires were implemented to ensure that chills are experienced consistently each time the participant listens to the music and experienced at moments of intense pleasure, rather than when the participant is

surprised or scared. An important exclusion criterion was that the selected music could not be specifically or generally associated with an episodic memory. That is, the music could not be associated with a specific life event (e.g., prom, a memorable concert, etc.) or a period of time (e.g., summer of 2004, high-school, etc.). Movie soundtracks were acceptable as long as the individuals had not seen the movie. These criteria were implemented to decrease extra-musical associations (L. B. Meyer, 1956), and ensure that the music was pleasurable in itself and not acting as a trigger for emotional memories.

There were no restrictions to the genre of music that could be provided. This was done to increase the ecological validity of our findings and to ensure that any observed effects were not due to a specific genre of music. We obtained music from various genres, including classical, folk, jazz, electronica, rock, punk, techno, and tango (see Table 1 for a sample list of excerpts used in study), with a wide range of psychoacoustical parameters. The modal genre was classical music. Musical clips were cut down to three-minute clips to ensure consistency. Time-frame guidelines to cut the clips were selected by participants to represent the most pleasurable section of each musical excerpt.

Title	Composer/	Genre	Considered	Considered
	Artist		Pleasurable	Neutral
Canon in D	Pachelbel	Classical	P1	P10
Clair de Lune	Debussy	Classical	P2	P22
Adagio for Strings	Barber	Classical	P3	P5
Adagio for Strings	Barber	Classical	P4	P17
Requiem – Lacrimosa	Mozart	Classical	P5	P3
Second Symphony	Beethoven	Classical	P6	P24
New World Symphony	Dvorak	Classical	P7	P18
Moonlight Sonata	Beethoven	Classical	P8	P4
Swan Lake	Tchaikovsky	Classical	Р9	P1
Romeo and Juliet	Prokofiev	Classical	P10	P6
Piano Concerto 2	Shostakovich	Classical	P11	P14
Fifth Symphony	Shostakovich	Classical	P12	P15
Symphonie Fantastique	Berlioz	Classical	P13	P20
Pines of Rome	Respighi	Classical	P14	P11
Second Symphony	Mahler	Classical	P15	P23
Rhapsody Paganini	Rachmaninoff	Classical	P16	P19
Morceaux de Fantasies	Rachmaninoff	Classical	P17	P26
Elegy	Elgar	Classical	P18	P7
Claressence	Holland	Jazz	P19	P8
Shine on You Crazy	Pink Floyd	Rock	P20	P21
Nyana	Tiesto	House	P21	P16
Hardstyle Disco	Biomehanika	Trance	P22	P13
Horns of a Rabbit	Do Make Say	Post-Rock	P23	Р9
Lincolnshire Posy	Grainger	Folk	P24	P25
Jamedaran	Alizadeh	International	P25	P12
Vicious Delicious	Infected Mushroom	Trance	P26	P2

Table 1. Self-Selected Musical Excerpts. Excerpts used in the study, includingtitle, composer, and genre, are presented in Table 1. To account forpsychoacoustical differences between self-selected chill-inducing stimuli, eachexcerpt was used once as an experimental and once as a control stimulus. In otherwords, each excerpt was matched with one participant who considered it

pleasurable and one who considered it neutral, as indicated in the last two columns.

2.4.3. Procedures. Participants were tested individually over one session. During the first half of the session, each individual listened to one-minute clips of all musical pieces provided by other participants and rated each piece on a subjectively experienced pleasure scale of 1 - 10 (1 = neutral, 10 = extremely pleasurable). Musical clips represented the most pleasurable minute of each excerpt, as previously selected by participants, and included the point at which chills are experienced. Participants were then asked to choose the most familiar pieces amongst those that they had rated the lowest on pleasure. This step was taken to decrease differences in familiarity across their self-selected pleasurable and "neutral" music. Individuals often selected pieces that they knew well but found "boring". If participants were not familiar with any of their low rated pieces, they were played the selections up to two more times to increase familiarity. Thus, the most familiar pieces rated low on pleasure were then selected as control stimuli for each person. Individuals were also asked to identify any musical pieces that were unpleasant. These excerpts were not used as control stimuli because they are not representative of a relatively "neutral" state, but rather may contribute to arousal indicative of annoyance or displeasure.

During the second half of the session, participants were fitted with psychophysiological equipment to record heart rate, BVP amplitude, respiration rate, electrodermal activity or galvanic skin response (GSR), and body temperature. These sensors consisted of 11mm Ag/AgCl dry electrodes placed on the ring and middle fingers for recording electrodermal activity and secured with Velcro straps, a photoplethysmyograph sensor placed on the middle finger for recording heart rate and BVP amplitude also secured with Velcro straps, and a digital thermometer inserted inside the BVP attachment strap on the index finger for recording peripheral skin surface temperature (Figure 3). A Hall effect respiration sensor was placed around the diaphragm to record respiratory rate. Physiological data were collected with the Procom Infinity biofeedback system by Thought Technology.



Figure 3. Assessment of Pleasure and Emotional Arousal. Emotional arousal was assessed through psychophysiological measurements of galvanic skin response (GSR), temperature, heart rate, blood volume pulse (BVP) amplitude, and respiration rate. Pleasure states were continuously obtained through subjective ratings of "neutral", "low pleasure", and "high pleasure" using a button box. Chills were also indicated through button presses. Psychophysiological correlates of each pleasure state were analyzed to determine systematic relationships between increases in pleasure and emotional arousal.

When measuring psychophysiological data, it is important to consider baseline differences in physiological activity amongst participants. Since we were interested in relative differences in ANS activity that can be attributed to music listening, rather than absolute differences amongst participants, it would not be valid to directly compare differences amongst participants. Rather, to account for inter-individual differences in physiological activity, recordings during music listening were compared with baseline physiological data that were collected over a 5-minute silent relaxation period for each participant. Subtracting this baseline data provides a difference score indicating the changes in physiological responses that were due to music listening.

All participants were tested in a sound proof laboratory at the Centre for Interdisciplinary Research in Music Media and Technology (CIRMMT). Individuals were asked to position themselves comfortably on a couch in a dimly lit laboratory and all distractions were minimized. Music was played through Sennheiser hd 595 high fidelity headphones and volume was adjusted to a comfortable listening level before beginning the session. After baseline physiological data were collected, six musical excerpts, three "chills" and three "neutral" pieces, were played in a randomized order. While participants were listening to music, they rated the degree of pleasure they were experiencing to the music in real-time (1 = neutral, 2 = low-pleasure, 3 = high-pleasure) using three separate buttons on a game-type input device held in the dominant hand (Figure 1). They were required to hold down the appropriate button as long as they were experiencing the respective degree of pleasure, and press a fourth button when they were experiencing a chill. We tested whether button presses alone could elicit a significant physiological response, which may contaminate the data. Consistent with previous studies, this was not the case (Guhn, Hamm, & Zenter, 2007; Rickard, 2004).

To investigate the degree to which the number and intensity of intensely pleasurable events (marked by chills) contribute to the overall pleasure experienced by a musical excerpt, after hearing each musical selection participants were asked (1) how many chills they experienced; (2) to rate the intensity of each chill (1 = low intensity, 10 = high intensity); and (3) rate the overall degree of pleasure they felt in response to the musical excerpt (1 = not at all pleasurable, 10 = extremely pleasurable). Musical pieces that were still rated as "neutral" on the pleasure dimension (but not described as "annoying" or "unpleasant") after hearing the entire excerpt were selected to be used for comparison against that same piece played for a participant who rated it extremely high on pleasure. To examine differences between felt and perceived emotions, participants were also asked to rate the valence (1 = sad, 10 = happy) and arousal (1 = not at all aroused, 2 = highly aroused) they felt in response to the musical excerpt, as well as the valence and arousal they believed the composer was

intending to convey. This was then followed by another one-minute "rest" condition to ensure that the biosignals have returned to a relaxed resting condition and minimize cross-contamination of psychophysiological effects between subsequent excerpts.

2.4.5. Data analysis. During music listening, any changes in subjective evaluations of pleasure states as indicated by participants were recorded continuously. It is important to consider that individuals have different response times; the exact moment at which participants press the button to indicate an increase in pleasure may vary by 1-2 seconds. To avoid miscategorizing pleasurable events, we accounted for reaction time differences between participants by segmenting the data into three-second epochs, during which the highest pleasure rating of that epoch was recorded. Thus, each 3:00 minute clip was divided into 60 three-second epochs, each of which was categorized as "within-excerpt neutral" (WE-neutral), "within-excerpt low pleasure" (WE-LP), "within-excerpt high pleasure" (WE-HP), or "within-excerpt chills" (WE-chills) according to button presses (Fig. 1). In addition, the first two epochs (first six-seconds) of recording for each excerpt was discarded in order to remove data related to any possible startle response associated with music onset.

To prepare physiological data for analysis, signal filtering was performed to remove noise and artifacts. The raw respiration and BVP signals are highly susceptible to noise caused by torso and hand movement, respectively. These artifacts are usually characterized by brief (< 100 ms), high frequency and large amplitude spike events or non-linear DC offsets. A third-order Butterworth lowpass filter was convolved with the raw signals to remove the high-frequency contaminants without loss of physiologically-related information. A detrending function using a polynomial regressor was applied to cancel out the DC shifts. The GSR sensor's output exhibits a slow downwards drift over long recording times on some subjects. This is due to charge accumulation at the electrode-skin junction, which causes a linear decrease of conductance. The raw GSR signal was thus detrended using a piecewise linear regression model when this drift was
noticed through visual inspection. No filtering was required for the temperature signal as this was outputted clean from the Procom unit.

Despite using individual baseline levels of physiological activity, the data revealed large variability between changes in physiology amongst participants. For example, a participant may have extreme changes in GSR in response to musical stimuli, although this response would remain extreme during all rating conditions (WE-neutral, WE-LP, WE-HP, and WE-chills) and maintain a relative difference between the conditions. As such, if outliers were removed from the data as a group, all data from this participant may be removed, despite their validity. To correct for this problem, outliers beyond four standard deviations from the mean of each rating category (WE-neutral, WE-LP, WE-HP, and WEchills) were removed for each excerpt and for each participant individually. These outliers are most likely caused by intermittent events unrelated to the music, such as coughing, sneezing, a sudden deep breath, or any other type of a distraction, despite great care taken to minimize distractions as much as possible. Approximately 2-5% of the datapoints were removed for each of the psychophysiological measures: GSR, heart rate, respiration, temperature, and BVP amplitude.

To examine whether within-excerpt changes in psychophysiology are due to individualized emotional reactions to the excerpt or related to the changes in acoustical features of each musical excerpt, we matched each excerpt with one individual who considered it pleasurable and one individual who considered it neutral. Although it was not possible to find a perfect match for all the musical selections, we were able to match 26 excerpts in this way, such that two excerpts were used for each person: one that they considered pleasurable and one that they considered neutral (see Table 1). Thus, the analyses presented here are limited to data collected from these excerpts.

A 2 x 4 mixed analysis of variance (ANOVA) was performed with Excerpt Type as the repeated measure with two levels (Considered Pleasurable and Considered Neutral), where data were collected on the same excerpt under two conditions, and Within-Excerpt Rating as the second variable with four levels

(WE-neutral, WE-LP, WE-HP, and WE-chills). Each psychophysiological measure (GSR, heart rate, respiration, temperature, and BVP amplitude) was separately analyzed as a dependent variable. The values of the Rating condition were determined in the following way: Excerpts were divided into three-second epochs and each epoch was labeled with a rating (i.e., WE-neutral, WE-LP, WE-HP, and WE-chills), based on the button-presses of the individual who found the pieces pleasurable. Once each epoch had an associated Rating condition, the physiological response that corresponded with each epoch was compared between the individual who considered the excerpt pleasurable with the individual who considered it neutral. As such, if physiological responses were significantly different between a WE-LP and a WE-chills epoch, but only for the individual who considered the excerpt pleasurable, we can assume that this increase is really related to increasing pleasure, and not to only to some physical feature of that portion of the excerpt. However, if the increase in physiological response were also observed in the individual who did not consider the excerpt pleasurable, then this change may be due to a specific psychoacoustical parameter of the musical piece (e.g., a sudden increase in tempo). Thus, we examined whether there were significant differences on each psychophysiological measure between the four rating conditions on the excerpts when they were considered pleasurable as compared with when they were considered neutral.

2.5. Results

2.5.1. Pleasure and emotional arousal. Our data revealed a strong positive association between subjective ratings of pleasure and ANS arousal. Figure 4 demonstrates increases in electrodermal activity, heart rate and respiration rate, as well as decreases in temperature and BVP amplitude, as participants report experiencing more pleasure to the musical excerpts; each of these will be discussed individually. Importantly, participants who reported no increases in pleasure in response to the same epochs of the same excerpts did not show any significant increases in ANS activity on any of the physiological measures.



Figure 4. Relationship between Pleasure and Emotional Arousal. Data showed significant positive correlations between subjectively reported pleasure states and objectively measured increases in ANS activity for all physiological measures. Participants who reported "no pleasure" on the same epochs of the same musical excerpts revealed no significant changes in physiological activity.

Electrodermal activity. The two-way mixed ANOVA revealed a significant main effect of Excerpt Type [F(1,1398) = 2384.32, p < .001], indicating that GSR was significantly higher when an excerpt was considered pleasurable than when the same excerpt was considered neutral. More importantly, there was also a main effect of Within-Excerpt Rating [F(3,1398) = 14.99, p < .001], providing evidence for physiological changes in GSR within excerpts that corresponded to real-time subjective reports of increasing pleasure. Importantly, a significant interaction [F(3,1395) = 20.60, p < .001] revealed that within-excerpt changes in GSR were only significant for the Considered Pleasurable group, but not the individual in the Considered Neutral group, suggesting that the changes in

GSR were not due to psychoacoustical parameters, but specific to individualized emotional reaction to the same excerpts. For individuals who considered the excerpts pleasurable, GSR increased by 0.072 uS (σ =0.53) or 10% of its increase from baseline as pleasure ratings progressed from WE-neutral to WE-LP, but this increase was not significant. However, GSR became significantly different from baseline during WE-HP, where it increased by 0.078 uS (σ =0.55) or 22% (p<.01). The largest change was observed during the chills response, where GSR demonstrated a large increase of 0.21 uS (σ =0.81) or 53% (p<.001). There were no significant differences in GSR on the ratings for the Considered Neutral group. Furthermore, post-hoc tests revealed that GSR was higher for the Considered Pleasurable group compared to the Considered Neutral group during all ratings: WE-neutral, WE-LP, WE-HP, and WE-chills (p<.001; Figure 4).

Heart Rate. Heart rate revealed a highly significant main effect for Excerpt Type [F(1,1371) = 428.32, p < .001] and Within-Excerpt Rating [F(3, p)](1371) = 39.43, p < .001, as well as a significant interaction [F(3,1371) = 31.03, p < .001]. Thus, similar to GSR, psychoacoustical parameters of the music could not account for changes in HR since only participants in the Considered Pleasurable group demonstrated significant changes. For the Considered Pleasurable group, heart rate increased as participants experienced heightened pleasure states an average of 5.5 beats per minute (BPM; $\sigma = 9.4$) or 340% of its increase from baseline as pleasure ratings increased from WE-neutral to WE-LP (p < .001). Heart rate continued to increase with increases in pleasure ratings, and although the changes between WE-LP, WE-HP, and WE-chills were not significantly different from each other, they were all significantly different from WE-neutral (p < .001). Heart rate increased 6.41 BPM ($\sigma = 11.6$) or 398% from WE-neutral to WE-HP, and 8.1 BPM (σ =8.9) or 500% to WE-chills. There were no significant differences in heart rate on the ratings for the Considered Neutral group, and post-hoc tests confirmed significantly higher heart rate for the Considered Pleasurable group compared to the Considered Neutral group during ratings of WE-neutral (p < .01), WE-LP (p < .001), WE-HP (p < .001), and WEchills (p < .001; Figure 4).

Respiration rate. Respiration rate did not reveal a significant main effect for Excerpt Type, however, there was a significant main effect for Within-Excerpt Rating [F(1,1340) = 23.42, p < .001], as well as a significant interaction [F(3,1340)]= 28.09, p < .001]. For the Considered Pleasure group, respiration rate increased significantly with increases in pleasure ratings. Mean respiration rate increased 6.2 breaths per minute (BtPM; $\sigma = 10.4$) or 76% from baseline as pleasure ratings increased from WE-neutral to WE-LP (p < .001). Respiration rate increased 7.8 BtPM(σ =12.9) or 94% from baseline during WE-HP, which was not significantly different from WE-LP, but still a significant increase from WEneutral. There was another significant increase of 11.18 BtPM (σ =16.4) or 139% from baseline to WE-chills (p < .05). There were no significant differences in respiration on the ratings for the Considered Neutral group. Post-hoc tests revealed that compared to the Considered Neutral group, respiration rates of the Considered Pleasurable group were lower during WE-neutral (p < .001), not significantly different during WE-LP and WE-HP, but significantly higher during WE-chills (p < .001; Figure 4).

Body temperature. Changes in peripheral skin temperature did not demonstrate a main effect of Excerpt Type, however, there was a significant main effect of Within Excerpt Rating [F(3,1395) = 8.84, p < .001], suggesting that changes corresponded with pleasure ratings within-excerpts; and a significant interaction [F(3,1395) = 6.74, p < .001], suggesting that within-excerpt changes were not generalizeable to everyone, but only those who found the pieces highly pleasurable. For individuals who experienced pleasure, peripheral skin surface temperature demonstrated a general decrease as participants experienced heightened pleasure states. Temperature decreased 0.087 °C (σ =0.248) or 138% from baseline as pleasure ratings increased from WE-neutral to WE-LP (p < .01), 0.079 °C (σ =0.184) or 124% to WE-HP (n.s.), 0.137 °C (σ = 0.144) or 217% to WE-chills (p < .05). There were no significant differences in temperature on the ratings for the Considered Neutral group. Post-hoc tests revealed that compared to the Considered Neutral group, respiration rates of the Considered Pleasurable group were higher during WE-neutral (p < .001), not significantly different during WE-LP and WE-HP, but significantly lower during WE-chills (p < .05; Figure 4).

Blood volume pulse amplitude. Results of the BVP analysis, which reveals peripheral blood vessel vasoconstriction, revealed a significant negative correlation with pleasure ratings. A significant main effect for Excerpt Type [F(1,1392) = 107.66, p < .001] and Within-Excerpt Rating [F(3,1392) = 14.70, p < .001] were found, as well as a significant interaction [F(3,1392) = 15.38, p < .001]. For the Considered Pleasurable group BVP amplitude demonstrated an average decrease of 0.43 ($\sigma = 1.20$) or 34% of its decrease from baseline as pleasure ratings increased from WE-neutral to WE-LP (p < .01), 0.52 ($\sigma = 1.20$) or 41% to WE-HP (n.s.), and 1.02 ($\sigma = 1.73$) or 81% during WE-chills (p < .01). There were no significant differences in temperature on the ratings for the Considered Neutral group, and post-hoc tests confirmed significantly lower BVP amplitude for the Considered Pleasurable group compared to the Considered Neutral group during ratings of WE-LP (p < .001), WE-HP (p < .001), and WEchills (p < .001; Figure 4).

2.5.2. The "chills" response. Data from real-time button presses revealed that out of a total of 310 chills experienced by all participants, 250 were experienced during self-appraised states of highest pleasure (binomial p < .0001). In other words, over 80% of chills occurred at the highest moments of pleasure. This confirmed that chills are not random phenomena, but correspond with peak pleasure responses. To examine the nature of the relationship between increases in pleasure ratings and chills onset, ratings were plotted against the time-course of the excerpt. Each excerpt was first divided into 15 second epochs and a one-way ANOVA demonstrated that the only significant change in pleasure ratings involved the 15 second epoch prior to the onset of chills (F(10,3780)=521, p < .001; Figure 5). Post-hoc Games-Howell tests revealed that ratings become significantly higher than the mean of ratings for the entire excerpt six seconds before a chill is experienced (mean difference = +.19, p < .001), and show another significant increase three seconds before the chill onset (mean difference = +.34, p < .001). The peak of the pleasure ratings coincided with the chills response, and

decreased significantly thereafter (mean difference = -0.9, p < .001). To ensure that the changes in pleasure ratings were due to individualized emotional reactions to the excerpt and not specific to the changes in acoustical features, data for each excerpt was matched with the same piece listened to by a participant who had rated that piece as "neutral". There were no significant increases in real-time pleasure rating during or prior to the epochs at which chills were experienced for participants who considered the excerpts neutral (Figure 5).



Figure 5. Relationship between Pleasure and the Chills Response. Real-time pleasure ratings plotted against the time-course of the chills response reveal that chills are experienced at the peak of pleasure ratings. Individuals who experienced no pleasure to the same excerpts showed no increases in pleasure during the epochs that chills were experienced in individuals who found the music highly pleasurable.

To examine the time course of sympathetic nervous system activity leading up to chills, the mean of physiological responses during epochs immediately preceding chills were plotted over time. Figure 6 reveals that all physiological signals tend to show increasing ANS arousal during the prechills epochs and peak during the chills response. These trends are not observed in physiological signals of individuals who consider the excerpts neutral, suggesting that they are due to individualized emotional reactions to the excerpt and not specific to changes in acoustical features (Figure 6).



Figure 6. Time-Course of the Chills Response. Real-time physiological recordings plotted against the time-course of the chills response reveal that chills are experienced during the peak of sympathetic nervous system activity. Individuals who experienced no pleasure to the same excerpts did not show significant changes in psychophysiological responses during the epochs that chills were experienced in individuals who found the music highly pleasurable.

Finally, after listening to each musical excerpt, participants responded to questions about the number and intensity of chills experienced, and rated the degree of pleasure they experienced in response to the entire excerpt. These results revealed that the reported intensity of the chills was highly correlated with the overall pleasure experienced in response to a piece of music (r = .74, p < .001) and the number of chills experienced during a music excerpt was moderately correlated with this measure (r = .29, p < .001).

2.5.3. The relationship between felt and perceived emotional responses. After listening to each musical excerpt, participants rated the degree of valence and arousal they (1) felt in response to the excerpt, and (2) believed the excerpt was intended to convey. To investigate the hypothesis that individuals do not always feel the emotions that an excerpt is intended to convey, we analyzed differences between these two ratings. Paired-sampled t-tests confirmed significant differences between the emotions that participants felt in response to an excerpt with that which they believed the music was intended to convey, with respect to both valence (t(235) = 2.46, p < .01), and arousal (t(235) = 11.96, p < .001).

We had further hypothesized that emotions would be more genuinely felt in response to some musical excerpts, namely the self-selected pieces, more so than experimenter-selected pieces. Thus, we examined self-selected and experimenter-selected musical excerpts separately. Experimenter-selected pieces were those that were not provided by the participant, but brought in by other participants as their self-selected pieces. As such, even the experimenter-selected pieces were considered high on emotionality by some individuals. A two-way fixed-factorial ANOVA was conducted with self-selected versus experimenterselected as one factor and felt versus perceived as the other. Results revealed a significant interaction for both valence and arousal [F(1, 232) = 7.51, p < .01; F(1, 232) = 27.15, p < .001), respectively], suggesting that similarities between felt and perceived ratings depend on whether excerpts are self-selected or experimenter selected.

For self-selected pieces, there were no significant differences between the valence (i.e., degree of happiness or sadness) that participants thought a piece of music was intended to convey, compared to what they felt in response to listening to that excerpt (M=2.28 versus M=1.87 deviation from "neutral", respectively; S.E.=.30, .29, respectively; Figure 7). Rather, there was a positive correlation between felt and perceived valence with self-selected music (r=0.52, p<.001) showing that the two were highly associated. However, for the experimenterselected pieces, significant differences existed between perceived and felt valence (M=0.21 versus M=1.03 deviation from "neutral", respectively; S.E.=.23, .33, respectively; Figure 7). In other words, there was no significant correlation between the emotion that the participant felt and what they believed the music was intended to convey (r=0.11, n.s.). Additionally, with experimenter-selected music, participants felt more neutral than what they thought the excerpt was intended to convey, despite whether it was a happy or a sad piece. For these excerpts, participants also reported significantly less felt arousal than what they perceived in the excerpts (M=5.02, S.E.=.23 versus M=7.37, S.E.=.19, respectively; Figure 7). Interestingly, the degree of pleasure experienced from an excerpt was most strongly correlated with felt arousal (r = .53, p < .001), followed by felt valence (r = .39, p < .001). Importantly, perceived valence demonstrated no significant relationships (r = -.043, n.s.) with subjective pleasure ratings, suggesting that participants experienced pleasure from excerpts that they believed was intended to convey sadness just as much as that which was intended to convey happiness.



Figure 7. Perceived versus Felt Emotions. Post-listening ratings of valence and arousal revealed significant differences amongst the self-selected and experimenter-selected musical pieces. Self-selected excerpts revealed higher correlations between perceived and felt valence and arousal than experimenterselected pieces. Furthermore, participants generally reported lower arousal and a more "neutral" valence on experimenter-selected pieces than self-selected pieces.

2.6. Discussion

The results of this experiment provide clear evidence for a direct link between emotions and the rewarding aspects of music listening by demonstrating a robust dynamic relationship between increases in emotional arousal and reported increases in pleasure. These findings are also novel insofar as they demonstrate dissociation between physiological responses of individuals who find a given piece of music pleasurable from those who do not, solidifying the predicted connection between emotional arousal and pleasure. Participants who did not report pleasurable states in response to a particular excerpt did not show any significant changes in psychophysiological arousal, whereas others who found those same excerpts pleasurable showed a distinct profile of increasing sympathetic nervous system activity as pleasure increased. These findings provide strong support for the theory that musical emotions underlie the pleasurable aspects of music listening.

Amongst the measures used in the study, electrodermal activity (EDA) is generally considered to be the best predictor of emotional arousal, as it is not under voluntary control, is highly sensitive to ANS changes, and is widely used by music and emotion researchers (Grewe et al., 2005; Grewe, Nagel, et al., 2007a; Khalfa et al., 2002; Krumhansl, 1997; Rickard, 2004; Sequeira, Hot, Silvert, & S., 2009). This measure revealed the best correlation with increases in pleasure ratings, demonstrating a robust increase as subjective reports progressed from low-pleasure to high-pleasure to chills. Even at the lowest pleasure ratings (WE-neutral), participants demonstrated significantly higher EDA on excerpts that they considered pleasurable versus those that were considered neutral. In other words, even listening to the least-pleasurable moments of a musical piece that an individual likes leads to higher EDA than listening to an entire excerpt that the individual finds neutral.

As within-excerpt ratings progressed from neutral to low pleasure, we observed significant increases in heart rate and respiration, and decreases in temperature and BVP amplitude, but only for those who considered the music pleasurable. Interestingly, although all WE-HP states were significantly different

from WE-neutral, most measures did not distinguish between WE-LP and WE-HP. One reason for this might be that these measures may not be as sensitive to smaller changes in ANS arousal as EDA. However, it is of particular relevance to note that significant differences in mean respiration, temperature, and BVP amplitude were observed during the chills response, not only in relation to WE-neutral, but also in relation to WE-LP and WE-HP. Furthermore, there were significant differences in these variables when comparing across excerpts as well (Fig 6). This suggests that even the potentially less sensitive measures reveal significant changes during the chills response, alluding to the potency of its affects on the nervous system. The lack of main effect on respiration may be due to the likelihood that rapid respiration rates are often preceded by compensatory periods of deeper and slower breathing. In this case, mean respiration rate for the entire excerpt would not be expected to be very different between the two different excerpt types, but changes in respiration within the excerpts would be expected to differ; this was indeed the case.

It is important to clarify that our findings are not intended to suggest that all increases of sympathetic nervous system activity will necessarily lead to increasing pleasurable states. There are other highly aroused states that are not pleasurable (e.g., fear or anxiety). However, these responses can be ruled out in our study, as we focused exclusively on pleasurable stimuli; music clips that aroused unpleasant feelings were omitted as potential stimuli as they do not relate directly to our hypothesis. Thus, the link between pleasure and emotions is unidirectional: an increase in emotional arousal does not necessarily imply pleasurable states, however, pleasurable states are accompanied by emotional arousal.

A second clarification involves the differential contributions of bottom-up and top-down processes to physiological indicators of emotional arousal. Etzel and colleagues (2006) have found that physiological responses, particularly respiration, synchronize with the tempo of a musical excerpt after listening for some time, referred to as tempo entrainment. This process suggests a bottom-up process is leading to changes in physiological activity. However, our results show

that two people can have strikingly different physiological responses to a given musical excerpt depending on how pleasurable they find this piece, suggesting a top-down process. Although these findings seem to contradict each other, this is not necessarily the case. There may have been tempo entrainment in our study as well; however, this was accounted for by presenting the same excerpts to both groups. As such, tempo entrainment would be experienced by all and relatively tonic throughout the excerpt. The phasic increases in physiological activity that are more representative of emotional arousal were not observed in all listeners, but only those who reported increases in pleasure, suggesting that they are over and above tempo entrainment.

In a similar vein, other researchers have found that specific psychoacoustical events in music can lead to changes in subjectively reported emotional arousal and psychophysiological indicators of this arousal (Grewe et al., 2005; Sloboda, 1991; Steinbeis, Koelsch, & Sloboda, 2006), emphasizing the stimulus-driven properties of musical stimuli in inducing temporary physiological changes. We took this into account by defining events based on subjective ratings of those who found the music pleasurable, which do not necessarily coincide with changes in psychoacoustical parameters. In other words, a sudden change in loudness or an unexpected harmony may lead to transient stimulus-driven changes in psychophysiology across all listeners, but these nuances will be masked since the epochs during which those who experienced pleasure enjoyed the music are relatively longer and may not necessarily contain these psychoacoustical features. Thus, although it is quite likely that specific psychoacoustical parameters resulted in some psychophysiological changes, these would be expected across all participants, and the differential autonomic activation that was observed across groups is over and above exclusively bottom-up processes. It is likely that a combination of highly individualized top-down processes (e.g., expectancies) that are tightly connected to the pleasurable aspects of a given piece of music (Huron, 2006) and bottom-up processes (e.g., fulfillment of those expectancies) interact to result in the intense sympathetic nervous system arousal observed over and above exclusively bottom-up processes that are experienced similarly for everyone.

Numerous studies have examined the autonomic activation patterns elicited by different musical emotions, such as happy sad, and fearful (T. Baumgartner et al., 2006; Johnsen et al., 2009; Khalfa et al., 2002; Khalfa, Roy, et al., 2008; Khalfa, Schon, Anton, & Liegeois-Chauvel, 2005; Krumhansl, 1997; Nater, Abbruzzese, Krebs, & Ehlert, 2006; Nyclicek, Thayer, & Van Doornen, 1997; Sammler, Grigutsch, Fritz, & Koelsch, 2007; Vanderark & Ely, 1992, 1993; Witvliet & Vrana, 2007; Zimny & Weidenfeller, 1963). However, a number of these studies have found inconsistent results (see Bartlett, 1996; Roy et al., 2009 for a review), and specific patterns of psychophysiological activity have not been established for the experience of different emotions induced by music. These inconsistencies challenge the emotivist perspective, as one would expect greater consistency in the experience of musical emotions if they were experienced in a similar manner to basic emotions. Our results provide some clarification for the reasons behind the inconsistencies. The first points to a methodological concern involving the difference between felt and perceived emotions (also see Gabrielsson, 2001; Sloboda, 1991). Our findings demonstrate that the emotions felt in response to a musical piece are not necessarily the same as those that the music is intended to convey. In our study, participants were asked to rate separately the emotion and degree of arousal that they perceived in the music (i.e., thought it was intended to convey), with that which they felt in response to listening to it. The results demonstrated highly significant differences, suggesting that individuals can acknowledge that a piece of music may intend to invoke a particular emotion that is different from the emotion that they are feeling. For example, it was not uncommon for people to rate an excerpt high on valence and arousal when asked "What do you think this excerpt is intended to convey?", but also low on valence and arousal when asked "How did you feel when listening to this excerpt?". This finding reveals a major flaw in current paradigms of research with music and emotions, with compulsory implications for future studies.

Although it seems intuitive that felt emotions are different than perceived emotions, this distinction has not been acknowledged in the majority of previous studies (see Gabrielsson, 2002). If perceived and felt emotions are not explicitly

differentiated for subjects in a study, they may be assumed to be similar by that individual, and lead to a demand characteristic (e.g., "This is a happy piece of music, therefore, I should say that I'm happy."). However, what is essentially being examined in these situations will involve emotion recognition, rather than the subjective experience of the emotion, which may explain some of the inconsistencies in findings. A second reason for inconsistencies is the finding that an individual may experience pleasure to music that is intended to convey sadness. Although this seems counterintuitive, our results demonstrate that intense pleasure can be experienced in response to both happy and sad music, but importantly, the degree of pleasure experienced in response to the music mediates emotional arousal, regardless of whether happiness or sadness was conveyed by the music. Thus, these findings suggest that identifying specific patterns of psychophysiological activity associated with musical emotions is complicated by highly individualized top-down processes involving the degree of pleasure experienced in response to a piece of music. Further, since it has been wellestablished (and further confirmed in our study) that musical preferences vary widely, it is likely that inconsistencies in previous studies are arising from more complex phenomenon relating to interpersonal differences. Musical emotions are unique from other emotions in that they are based on aesthetic stimuli, and unlike other basic emotions do not have an obvious adaptive or survival value (Pinker, 1997). For this reason, it would be expected that the experience of them would not be universally similar, but highly individualized depending on personal preferences and previous experiences. Our data support this hypothesis, and provide new avenues for future research. More specifically, it remains to be determined how interpersonal factors, such as personal preferences, familiarity, and expectations contribute to emotional responses to musical stimuli (also see Huron, 2006).

One might argue that factors such as familiarity or associations may act as confounding variables when using self-selected musical stimuli. That is, it may be difficult to parse out the extent to which the observed results are due to differences between listening to familiar versus novel music. We accounted for

this issue in several ways. First, we made several attempts to decrease any differences in degree of familiarity between pleasurable and neutral excerpts. After participants selected the excerpts to which they felt most "neutral", they were asked to choose amongst those that they were most familiar with; these pieces were then selected as that participant's control. This was possible as many of the pieces were popular and well-known classical pieces. In the case that participants were not sufficiently familiar with any of their selected "neutral" excerpts, the pieces were replayed for them two more times to increase familiarity. Thus, for the most part, we tried to minimize differences in familiarity across conditions as much as possible. Although broadly speaking, music that is familiar can be more pleasing, this is not always the case. For example, many familiar pieces of music may be considered "boring". Similarly, some pieces that may be pleasing at some point become less so with repetition (e.g., TV commercials, popular songs, etc.). This was indeed the case in our study where some participants reported selecting a familiar piece as "neutral" because they were "bored" with it (e.g., Pachelbel's Canon, Barber's Adagio for Strings, Moonlight Sonata, Clair de Lune, etc.). Since familiarity with a musical excerpt is a subjective phenomenon, it would be unreasonable for us to assume that we can control for it entirely, unless all the selections were novel. However, as another way to deal with the issue we also took advantage of the within-excerpt design. It can be safely assumed that participants are familiar with an entire piece of music, and not just the brief parts that they find most highly pleasurable. Since the results showed significant changes in psychophysiological responses within the excerpts, and these correlated with self-reported increases in pleasure, we can rule out the possibility that changes in psychophysiological responses were entirely due to familiarity rather than increases in pleasure.

A second related confounding variable involves associations of music with autobiographical memories. It is difficult to assess the extent to which music may be triggering pleasurable memories, and it is likely impossible to rule out all associations to memory with self-selected stimuli, as some may be unconscious. However, we took steps to rule out any obvious associations with memory. For

this reason, participants were asked if the music was associated with (1) a specific memory (e.g., prom, a memorable concert, etc.), or (2) a period of their lives (e.g., summer of 2004, high-school, etc.). This was indeed the case for a number of individuals amongst the initial pool of 217 potential participants, who were then excluded from participating in the study. Once again, however, it is important to note the within-excerpt changes in physiology in response to the pleasurable pieces, which decrease the possibility that the effects were entirely due to recalling autobiographical events, since these would be relatively consistent throughout the piece.

The findings of this study can be differentiated into two main categories: those that involve increases in pleasure, and those that are specifically associated with the chills response. The latter can only be generalized to individuals who do experience chills to music. Although this limits the generalizeability of this part of the findings, one purpose of the study was to specifically examine these intense events. The first category relating to pleasure, however, can be generalized more widely. Those results showed that even without the experience of chills, selfreported increases in pleasure (subjective) are directly associated with increases in psychophysiological arousal (objective). This point is best demonstrated by the finding that participants often experienced "high pleasure" that did not give them chills, but nonetheless demonstrated significant increases in psychophysiology during these periods. This suggests that physiological arousal and pleasure show a direct correspondence when assessed in "real-time", even without the experience of chills. The chills phenomenon is of interest because when they are experienced, there are extreme increases in ANS arousal that are much more significant that those relating to "high pleasure". Previous studies had demonstrated that chills are subjectively described as pleasurable (Blood & Zatorre, 2001; Grewe, Nagel, et al., 2007a; Panksepp, 1995), and their occurrence generally corresponds with increases in heart rate and electrodermal activity (Grewe et al., 2008; Grewe et al., 2005; Grewe, Nagel, et al., 2007a; Rickard, 2004). Our study corroborated these findings with methods involving higher temporal resolution, which allowed us to examine the time-course of

physiological activity leading up to the chills response. Results revealed that chills represent peak ANS arousal, demonstrating extreme sympathetic nervous system activity. Physiological measures of heart rate, respiration rate, electrodermal activity, skin temperature, and BVP amplitude display a gradual change preceding the chills response and highly significant arousal was observed immediately prior to, and during, the chills response. Subjectively, the chills response is preceded by increases in pleasure ratings that reach a maximum when chills are experienced, and decreases significantly post-chills, further confirming that chills are experienced at the climax of the pleasurable responses. It may be the case that chills are a physiological byproduct of a sudden or intense increase in ANS activity. These findings provide strong evidence for Blood and Zatorre's (2001) hypothesis that the chills response is a physical manifestation of the most rewarding experiences to music listening. Additional support comes from our finding that the number and intensity of chills contribute significantly to the overall pleasure experienced from the musical excerpt, with the latter being a stronger predictor. This is consistent with Blood and Zatorre's results that the intensity of the chills ratings is positively correlated with the degree of blood flow to the ventral striatum, an area implicated in processing pleasurable experiences in response to reward (Camara, Rodriguez-Fornells, & Munte, 2008; Koepp et al., 1998; Schott et al., 2008). These results provide evidence that individuals can experience intensely emotional and rewarding responses to self-selected music, which in turn can lead to chills that act as distinct physiological markers of extreme ANS arousal experienced during the climax of pleasure responses to music. It is also of particular significance that Blood and Zatorre (2001), found neural activity in regions of the brain typically involved in emotional processing, namely the amygdala, insula, orbitofrontal cortex, and ventral medial prefrontal cortex while participants were listening to chills-inducing music. This finding further supports the link between emotion and pleasure. The causal link between emotional arousal and reward has long been speculated (North & Hargreaves, 1997; E. T. Rolls, 1975) but difficult to test empirically, since pleasure is a highly subjective phenomena.

In summary, the results of our study provide clear evidence for a relationship between pleasure and emotional arousal. It may be argued that individuals often enjoy music that "relaxes" them, which seems contradictory to our results. However, although moderate enjoyment of music is not necessarily accompanied by major changes in emotional arousal, as pleasure intensifies so do physiological signs of emotional arousal. Individuals listen to music for a variety of reasons, and a wide spectrum of changes in emotional states or pleasurable responses may be experienced in response to music. At the lower end of the pleasure spectrum are mild changes in mood, and at the highest end of the spectrum are intensely rewarding experiences, such as those that induce chills as a physiological response. The latter is of particular significance since such intense pleasure states are rarely caused by stimuli that have no pragmatic, instrumental, or apparent survival value. The intensity of pleasure experienced from music listening has lead some researchers to suggest that it may act upon the dopamine reward system of the brain (Panksepp & Bernatzky, 2002), which is implicated in processing highly rewarding stimuli such as cocaine and amphetamines (Leyton et al., 2002; Schlaepfer et al., 1997), food (Small, Jones-Gotman, et al., 2003), and playing videogames (Koepp et al., 1998). The assumption that music may also involve this system is largely based on brain imaging findings that have found increasing blood flow or oxygenation to striatal regions of the brain that are implicated in reward, particularly the ventral striatum, or NAcc (Blood & Zatorre, 2001; Brown et al., 2004; Koelsch et al., 2006; Menon & Levitin, 2005). These imaging studies have also found neural activity in surrounding limbic regions, indicative of emotional arousal. Whether or not dopamine is actually involved remains to be determined, but the present findings suggest that musical pleasure is associated with physiological markers which are consistent with the experience of reward.

Assessment of emotional responses to music, particularly the ability for music to induce highly pleasurable feelings, has become a topic of interest to music researchers with practical implications for music composition, therapy, and marketing. The present data provide a direct link between emotions and pleasure

in music listening, and reveal new avenues for research to examine whether strongly felt emotions can be rewarding in themselves in the absence of a physically tangible reward or a specific functional goal.

Chapter 3: The Link between Emotion, Pleasure, and Dopamine Release in the Brain during Music Listening

3.1. Preface

This chapter describes an experiment conducted to follow-up the results of the first experiment by linking them more directly to reward systems in the brain. While the first experiment demonstrated that intense emotional arousal could lead to highly pleasurable responses, there is no neural model that translates between the two. Due to previous demonstrations of hemodynamic activity in dopaminerich mesolimbic regions of the brain during music listening (Section 1.6), we investigated whether intense emotional responses to music can lead to dopamine release in the brain by taking advantage of ligand-based PET imaging. As we were interested in examining the temporal nature of reward processing in response to music, we also ran fMRI on the same participants to gain temporal sensitivity of activity changes in mesolimbic regions during music listening. We continued to use psychophysiological measures to profile emotional states. Finally, as we confirmed that the musical chills response may be a valid and reliable measure of peak emotional responses to music, we continued to used self-selected chillinducing music to have an objectively identifiable marker of peak pleasure states.

The manuscript presented in this chapter was published in a 2011 issue of Nature Neuroscience (Salimpoor, V. N., Benovoy, M., Larcher, K., Dagher, A., Zatorre, R., (2011) Anatomically Distinct Dopamine release During Anticipation and Experience of Peak Emotion to Music. Nature Neuroscience, 14(2), 257-262).

3.2. Abstract

Music, an abstract stimulus, can arouse feelings of euphoria and craving, similar to tangible rewards that involve the striatal dopaminergic system. Using the neurochemical specificity of [¹¹C]raclopride PET scanning, combined with

psychophysiological measures of ANS activity, we provide direct evidence for endogenous dopamine release in the striatum at peak emotional arousal during music listening. To examine the timecourse of dopamine release we used fMRI with the same stimuli and listeners, and found a functional dissociation: the caudate is more involved during the anticipation, and the NAcc during the experience of peak emotional responses to music. These results provide clear evidence that intense pleasure in response to music can lead to dopamine release in the striatal system. Importantly, the anticipation of an abstract reward can result in dopamine release within an anatomical pathway distinct from that associated with the peak pleasure itself. These findings help to explain why music is of such high value across all human societies.

3.3. Introduction

Humans experience intense pleasure to certain stimuli, such as food, psychoactive drugs, and money; these rewards are largely mediated by dopaminergic activity in the mesolimbic system, implicated in reinforcement and motivation (see Egerton et al., 2009 for a review). These rewarding stimuli are either biological reinforcers necessary for survival, synthetic chemicals that directly promote dopaminergic neurotransmission, or tangible items that are secondary rewards. However, humans uniquely have the ability to obtain pleasure from more abstract stimuli, such as music and art, which are not directly essential for survival, nor can they be considered as secondary or conditioned reinforcers. Yet, they have persisted through cultures and generations, and play a pre-eminent role in most people's lives. Importantly, the experience of pleasure to these abstract stimuli is highly specific to cultural and personal preferences, which can vary tremendously across individuals.

Most people agree that music is an especially potent pleasurable stimulus (Dube & Lebel, 2003) that is frequently used to impact emotional states. It has been empirically demonstrated that music can effectively elicit highly pleasurable emotional responses (Sloboda & Juslin, 2001), and previous neuroimaging studies have implicated emotion and reward circuits of the brain during pleasurable music listening (Blood & Zatorre, 2001; Koelsch et al., 2006; Menon & Levitin, 2005;

Mitterschifthaler et al., 2007), particularly the ventral striatum (Blood & Zatorre, 2001; Koelsch et al., 2006; Menon & Levitin, 2005), suggesting the possible involvement of dopaminergic mechanisms (Knutson & Gibbs, 2007). Yet, the role of dopamine has never been directly tested. Here, we took advantage of ligand-based PET scanning to estimate dopamine release specifically within the striatum based on the competition between endogenous dopamine and $[^{11}C]$ raclopride for binding to dopamine D₂ receptors (Laruelle, 2000). Pleasure is a subjective phenomenon that is difficult to assess objectively. However, physiological changes occur during moments of extreme pleasure, which can thus be used to index pleasurable states in response to music. Here, we used the "chills" or "musical frisson" (Huron & Hellmuth Margulis, 2009) response, a well-established marker of peak emotional responses to music (Blood & Zatorre, 2001; Grewe, Nagel, et al., 2007a; Panksepp, 1995; Sloboda, 1991). Chills involve a clear and discrete pattern of ANS arousal (Salimpoor, Benovoy, Longo, Cooperstock, & Zatorre, 2009), which allows for objective verification through psychophysiological measurements. Therefore, the chills response can be used to objectively index pleasure, a subjective phenomenon, which would otherwise be difficult to operationalize, and it also allows us to pinpoint the precise time of maximal pleasure.

Previous studies have typically used experimenter-selected musical stimuli (Koelsch et al., 2006; Menon & Levitin, 2005; Mitterschiffthaler et al., 2007). However, musical preferences are highly individualized; thus, to ensure maximal emotional responses, participants were asked to select their own highly pleasurable music. After extensive screening (see Methods), we recruited a group of people who consistently experience objectively verifiable chills during their peak emotional responses, so that we could quantify both the occurrence and the timing of the most intense pleasurable responses. We also collected psychophysiological measurements (heart rate, respiration rate, electrodermal skin conductance, blood volume pulse amplitude, and peripheral temperature) during the PET scans to verify ANS differences between conditions. To account for psychoacoustical differences across self-selected stimuli, musical excerpts were matched per a previously established paradigm (Blood & Zatorre, 2001), such that participants listened to one another's choices which served as either pleasurable or neutral stimuli. We predicted that if the rewarding aspects of music listening are mediated by dopamine, significant [¹¹C]raclopride binding potential differences would be found between neutral and pleasurable conditions in mesolimbic regions.

The second aim of our study was to explore the temporal dynamics of any dopaminergic activity, since distinct anatomical circuits are thought to underly specific phases of reward responses (O'Doherty et al., 2002; Schultz et al., 1997). That is, if there is dopamine release, we wanted to examine whether it is associated with the experience of the reward, or its anticipation (Wise, 2004). Music provides an innovative means of assessing this distinction because the temporal unveiling of tonal arrangements elicits anticipatory responses, based on cognitive expectations and prediction cues (Huron, 2006; Huron & Hellmuth Margulis, 2009; L. B. Meyer, 1956) that can be examined to isolate the functional components that precede peak pleasurable responses. Since PET does not afford the temporal resolution required to examine this distinction, we combined the temporal specificity of fMRI with the neurochemical specificity of PET. We therefore acquired fMRI scans with the same participants and stimuli to examine the temporal profile of blood-oxygenation-level dependent (BOLD) response specifically in those regions that also showed dopamine release with PET. Striatal dopamine release and BOLD responses are known to be correlated, although the relationship is complex (Knutson & Gibbs, 2007; Schott et al., 2008). We predicted that regions revealing dopamine activity in the PET data would show the largest increases in hemodynamic response during peak emotional experiences. We separately analyzed the BOLD data from epochs of peak pleasure, and the time immediately preceding these responses (i.e., "anticipation"), based on participants' real-time behavioural responses of when "chills" were experienced. Spatial conjunction analyses were used to confine the analysis only to those striatal voxels showing both dopamine release from PET and increased BOLD during fMRI, to ensure that we would be measuring the

hemodynamic signal only from regions known to release dopamine in response to the same stimuli. This multimodal procedure revealed a temporally-mediated distinction in dopamine release to anticipatory and consummatory responses in the dorsal and ventral striatum, respectively.

3.4. Methods

3.4.1. Participant screening and stimulus selection. Two hundred and seventeen individuals responded to advertisements requesting people who experience chills to music; after five rounds of screening the final group included eight participants. First, individuals provided ten pieces of instrumental music to which they experience intense pleasure and "chills" without restrictions to the genre of music, which included classical, folk, jazz, electronica, rock, punk, techno, and tango (see http://www.zlab.mcgill.ca/home.html Supplements for samples). Next, an email questionnaire was completed to determine if their chills are experienced (1) at times of extreme pleasure, (2) consistently at the same point in the music without diminishing upon multiple listening, (3) in different environments, and (4) the selected music is not specifically or generally associated with an episodic memory. Forty-five individuals continued to the third screening session, where a history of medical, psychiatric illness, or substance abuse was ruled out. Forty participants continued to the fourth screening session, where control stimuli were selected for each individual using a paradigm where one individual's pleasurable music is used as another person's neutral music (Blood & Zatorre, 2001; Salimpoor et al., 2009). This way, group-averaged data analysis involves comparison of similar sets of stimuli. Although we were not able to match perfectly between the control and pleasurable pieces used for all participants, efforts were made to ensure that pieces were as evenly distributed as possible. Each individual rated other participants' music on a scale of 1 - 10("neutral" to "extremely pleasurable"). From the pieces rated neutral, the ones that were most familiar to that subject were selected to minimize differences in familiarity between pleasurable music (PM) and neutral music (NM) conditions. Individuals whose music was found to be "neutral" by at least one other participant were asked to continue. Participants were asked not to listen to those

pieces anymore during the course of the study to ensure maximal responses during testing. Twenty-eight individuals participated in the final screening session to verify the chills response at prespecified times through subjective and physiological responses. Participants listened to their chills-inducing music while providing subjective ratings of pleasure through button presses, and indicating when they experienced a chill. Additional details on procedures and results of psychophysiological testing can be found in Salimpoor et al. (Salimpoor et al., 2009). Ten participants (5 female, 5 male) who most reliably experienced chills during their peak pleasure responses to music accompanied by clear increases in ANS activity were selected for the study. The final group of participants was between the ages of 19 and 24 (M = 20.8, +/- 1.9 years) and had a wide range of musical experiences from no training to 15 years of experience.

3.4.2. Procedures. Ethical approval for the study was granted by the Montreal Neurological Institute (MNI) Research Ethics Board. All individuals gave written informed consent before participating in the study. Testing took place over three sessions. The first two sessions involved PET scanning (Fig. 8) and psychophysiological recording (Fig. 9), and the third session involved fMRI scanning (Fig. 10).

3.4.3. Statistical analysis

Psychophysiology. Signal filtering was performed to remove noise and artifacts (see Salimpoor et al., 2009 for additional details). Data were down-sampled to 1-second epochs and compared across NM and PM conditions. To account for unequal variances across conditions, Welch's t-test was used. A second analysis examined the relationship between the intensity of chills experienced and psychophysiological responses. Outliers beyond four standard deviations from the mean were removed for each excerpt and for each participant individually (2–5% of the data points). Subjective ratings for one individual were not recorded and BVP amplitude data for one participant demonstrated excessive artifacts, thus these data were not included in the analysis. Z-score values of each biosignal were calculated for each excerpt and plotted against subjective ratings of chills intensity that subjects reported after hearing each excerpt (Fig 11).

Correlation coefficients were calculated for the intensity of chills and changes in each of the psychophysiological measures (see Table 2 of the Results section).



Figure 8: Acquisition of PET scans over two sessions. Each subject participated in two [11C]raclopride PET scans over two days, at approximately the same time of day to control for diurnal variations in dopamine function. Women completed the PET scan between the 10th and14th days of their menstrual cycles to ensure consistency in hormonal levels across participants. Physiological measurements were obtained continuously throughout both PET scanning sessions. PET scans were obtained with a CTI/ Siemens ECAT-HR+ tomograph (CTI PET Systems, Inc., Knoxville, TN), with lead septa removed, operated in three- dimensional mode. Subjects listened to their pleasurable music during one scan and neutral music during the other scan. The scan order was counterbalanced between participants. A catheter was inserted into the antecubital vein for tracer injection. At this point, participants listened to 15 minutes of music to allow for release of dopamine before the radioligand was injected. A transmission scan was acquired using a 68Ge source for the purpose of attenuation correction. After 15 minutes, approximately 10 mCi of [11C]raclopride was injected as a bolus over one minute and emission data were acquired for 60 minutes in 26 time frames of progressively longer duration while participants continued listening to music. After hearing each musical selection participants were asked: (1) how many chills they experienced; (2) rate the

intensity of each chill on a 10-point scale; and (3) rate the overall degree of pleasure they felt in response to the musical excerpt on a 10-point scale.



Figure 9. Measures of ANS activity during PET scanning. Participants were fitted with psychophysiological equipment to record heart rate, respiration rate, electrodermal activity or galvanic skin response (GSR), blood volume pulse (BVP) amplitude, and body temperature. These sensors consisted of 11mm Ag/AgCl dry electrodes placed on the ring and middle fingers for recording electrodermal activity and secured with Velcro straps, a photoplethysmograph sensor placed on the middle finger for recording heart rate and BVP amplitude also secured with Velcro straps, and a digital thermometer inserted inside the BVP attachment strap on the index finger for recording peripheral skin surface temperature. A Hall effect respiration sensor was placed around the diaphragm to record respiratory rate. Physiological data were collected with the Procom Infinity biofeedback system by Thought Technology (Montreal, Canada). A 5minute silent period was implemented to provide a baseline from which to examine changes in physiological responses due to music listening.



Figure 10. fMRI scans acquired over one session. Functional MRI scans were acquired on a 3 Tesla Siemens TIM Trio scanner using a 1- chanel quadrature coil one to three weeks after completing the PET scan sessions. A high-resolution T1-weighted anatomical scan was obtained for each participant (voxel size = 1 mm3) and $T2^*$ -weighted echo-planar images of BOLD signal were acquired (35 slices interleaved, 64×64 matrix, voxel size = 4 mm3) aligned with Sylvian fissure and covering the whole brain (TE = 30 ms, TR = 2.1 s). Cardiac gating was used to synchronize image acquisition to a constant phase of the cardiac cycle. High-fidelity headphones were used (MR confon GmbH, 39118 Magdeburg, Germany), containing electrodynamic transducers for a broad, flat frequency response and construction-grade Peltor earmuffs for passive damping of gradient noise. A paradigm similar to the PET scanning was adopted, where individuals listened to their self-selected pleasurable excerpts and other individuals' excerpts which they considered neutral. Participants were also asked to rate the degree of pleasure they were experiencing to the music in real-time (1) = Neutral, 2 = Low-Pleasure, 3 = High-Pleasure) using three separate buttons on an MR-compatible 4-button input device. They were required to hold down the appropriate button as long as they were experiencing the respective degree of pleasure, and press a fourth button when they were experiencing a chill. Individuals were always holding down one button, to ensure that neural activity

involved in button pressing and anticipation of button presses were equally distributed. Five 3-minute excerpts of PM and five 3-minute excerpts of the NM were played in an alternating sequence during a 40-minute run, with a 1-minute break in between excerpts to reduce carry-over effects. To ensure that peak pleasurable responses were maximized, the three minutes that were played in the fMRI scanner were carefully selected according to the following criteria: (1) each selection included the peak pleasure segment (i.e., chills); (2) peak pleasure was placed towards the end of the clips to ensure sufficient "build-up time"; and (3) participants were asked to select the three minutes themselves to ensure that the most subjectively pleasurable minutes were used for this section.

[¹¹C]raclopride positron emission tomography (PET). Two datasets were discarded due to participant discomfort during the first session. Data from the remaining eight participants were analyzed. PET emission frames were reconstructed and corrected for gamma ray attenuation and scatter. All PET images were corrected for head motion using a coregistration-based method, which performs inter-frame realignment and compensates for emission-transmission mismatches (Costes et al., 2009). The motion-corrected PET data were summed over the time dimension and aligned to the subject's anatomical MR image. Anatomical MRI were transformed into standardized stereotaxic space by means of automated feature matching algorithm to the MNI template (Collins, Peters, & Evans, 1994). All transformed images were visually inspected to ensure that there were no alignment errors.

Parametric images were generated in the native PET space by computing $[^{11}C]$ raclopride binding potential (binding potential = B_{Avail}/K_D , where B_{Avail} is the density of available receptors and K_D is the dissociation constant) at each voxel of interest (Gunn, Lammertsma, Hume, & Cunningham, 1997; Lammertsma & Hume, 1996). Voxelwise $[^{11}C]$ raclopride binding potential was calculated using a Simplified Reference Region method (Gunn et al., 1997; Lammertsma & Hume, 1996), with the cerebellum chosen as reference region because it does not contain specific D₂ receptor-like binding sites, and can be used for the

determination of nonspecific binding and free radioligand in the brain (Litton, Hall, & Pauli, 1994). The gray matter of the cerebellum assigned as reference region was initially segmented in Talairach space from a probabilistic atlas (Collins & Evans, 1997) and a neural net classifier (Zijdenbos, Forghani, & Evans, 1998). The $[^{11}C]$ raclopride binding potential maps were then transformed into MNI space (Collins et al., 1994) using the previously determined transformation parameters. Statistical parametric t-maps of binding potential change were produced by comparing the parametric binding potential maps of the two scan sessions (PM and NM), using a previously described method (Aston et al., 2000). This calculation uses the residuals of the least-squares fit of the compartmental model, which improves the sensitivity to small changes by providing better estimates of the standard deviation at the voxel, and by increasing the degrees of freedom. It is assumed that a reduction in $[^{11}C]$ raclopride binding potential is indicative of an increase in extracellular dopamine concentration (Endres et al., 1997). Clusters of significant change were defined as all contiguous striatal voxels on the t-map exceeding a magnitude threshold of 3.11. This threshold is considered significant (p < 0.05, corrected for multiple comparisons) for a search volume equal to the striatum and an effective spatial resolution of 8 mm full-width at half maximum (FWHM) (Worsley et al., 1996). Mean binding potential values were extracted from each significant cluster for each individual and percent change in binding potential was calculated [(BP_{neutral} – $BP_{pleasurable}$ × 100 / $BP_{neutral}$], and compared with subjectively reported postlistening ratings of the number of chills, intensity of chills, and degree of pleasure experienced.

Functional magnetic resonance imaging (fMRI). One scan was terminated due to claustrophobia. FMRI data were corrected for motion using inhouse software. To increase the signal-to-noise ratio, the images were spatially smoothed (or low-pass filtered) with an 8-mm FWHM isotropic Gaussian kernel. Image analyses were performed with fMRISTAT, which consists of a series of MATLAB scripts that utilize the general linear model for analyses (Worsley et al., 2002). The general linear model ($Y = X\beta + \varepsilon$) expresses the response variable

(BOLD signal) Y in terms of a linear combination of explanatory variables (events) X, the parameter estimates (effects of interest) β , and the error term ϵ . Temporal drift was modeled as cubic splines and removed by inclusion into the general linear model as a variable of non-interest. The linear model was solved for the parameter estimates β with least-squares, yielding estimates of effects, standard errors, and t statistics for each contrast and for each run.

Before group statistical maps for each contrast of interest were generated, in-house software was used to linearly transform anatomical and functional images from each subject into standard MNI stereotaxic coordinate space, using the MNI 305 template (Collins et al., 1994). A mixed-effects linear model was subsequently used to combine data across subjects; the SD images were smoothed with a Gaussian filter so that the ratio of the random-effects variance divided by the fixed-effects variance results in approximately 100 degrees of freedom. Because the main purpose of the fMRI analyses was to measure BOLD activity within predefined striatal regions, we adopted an uncorrected statistical threshold of p < .01.

For the main analysis, three events were defined: (1) the Peak Emotional Response (PER) condition represented all epochs during which the participant was pressing the "chills", (2) the Anticipation condition represented 15-second epochs immediately preceding the onset of the PER condition defined post-hoc, and (3) the Neutral condition represented all epochs during which participants were pressing down the "neutral" button. Note that these neutral epochs are different from the NM condition, which were not used in this case since the NM condition contrasted with the PM condition shows less activity in the striatum. As such, any epoch selected from the PM condition, even those not related to peak pleasure, could have shown increased striatal activity and overestimate the results of the study. The anticipation period was defined as the 15 seconds before the PER based on previous findings that this is the time-frame during which psychophysiological responses begin to increase significantly relative to mean responses throughout the excerpt (Salimpoor et al., 2009). The times at which participants pressed the "low pleasure" and "high pleasure" buttons were also included in the model to ensure that they are not contributing to baseline. A 0.1 second epoch was incorporated into the model each time a button was pressed to account for neural activity involved in button pressing. The BOLD data from times when participants were responding to questions were excluded from the analysis. The planned comparisons for the main analysis were then entered into the analysis: (1) Anticipation of PER = Anticipation condition minus Neutral condition and (2) Experience of PER = PER condition minus Neutral condition.

Timeseries Analysis. To further investigate the temporal dynamics of the reward response we calculated the timeseries of hemodynamic activity in the caudate and NAcc clusters. To avoid the "circularity" problem (Kriegeskorte, Simmons, Bellgowan, & Baker, 2009), we derived our voxels of interest (VOI) from the PET data, which are independent of the fMRI data. We first identified the voxel showing the maximum dopamine release during the [11C]raclopride PET scan, in the caudate and NAcc clusters. We then extracted the mean signal for each VOI during the entire fMRI run obtained from each volume, and calculated the percent BOLD signal change relative to the mean of the run during the epochs when PER were reported. Participants often experienced multiple chills one after another. For the purposes of this analysis, the percent signal change during the first chill of the series was used, which ranged in duration from 1-4 seconds. The BOLD response for each of those seconds is plotted in Figure 13c of the results section. Mean signal change for each second preceding this response for each individual – up to 15 seconds was also plotted to demonstrate hemodynamic timeseries during the anticipation period. Due to cardiac gating a different number of frames were acquired for each person during this 15 second period and acquisition time varied from 2.1 to 3 seconds depending on the individual's heart rate. As such, the VOI values obtained at each frame were interpolated to provide an estimate of signal during each second preceding the peak response. The mean number of frames sampled for calculating timeseries was 5.3 (s.d. = 1.3) during anticipation and 1.6 (s.d. = 1.2) during chills. The mean signal change during "neutral" button-presses was also calculated for each voxel of interest separately and plotted in Figure 13B for reference. Finally, the

percent signal change for five seconds preceding the anticipatory response were also plotted for reference.

Conjunction analysis. Since [¹¹C]raclopride binds with D2 receptors mainly in the striatum (Slifstein et al., 2010), our fMRI data analysis was also limited to this region, masked by areas that showed dopamine release. A spatial conjunction analysis was performed to examine the temporal aspects of hemodynamic activity in areas that had shown changes in [¹¹C]raclopride binding potential on PET. A mask of striatal areas that had revealed significant changes in binding potential using the stated threshold ($t \ge 3.11$) was created to spatially mask both contrasts (outlined in the fMRI data analysis section): (1) Anticipation of PER and (2) Experience of PER. This procedure allowed us to measure BOLD changes only within voxels that had shown binding potential differences in the PET study.

3.5. Results

3.5.1. Positron emission tomography data: dopamine release and emotional arousal. PET scanning took place over two sessions: participants listened to either PM or NM during the entire session while both subjective and objective indicators of emotional arousal were collected. Subjective responses from rating scales included self-reports of (1) number of chills, (2) intensity of chills, and (3) degree of pleasure experienced from each excerpt. The mean number of chills for each PM excerpt was 3.7 (SD = 2.8). A paired-samples t-test confirmed that greater pleasure was experienced during the PM condition over the NM condition; t(49)=25.0, p < .001. More importantly, there was a significant positive correlation between the reported intensity of chills and the reported degree of pleasure (r=.71, p<.001), suggesting that the chills response is a good representation of pleasure experienced amongst this group.

Objective measures of psychophysiological signals indicative of emotional arousal (e.g., increases in heart rate, respiration, electrodermal response, and decreases in temperature and blood volume pulse amplitude) collected during the two PET scanning sessions showed significantly higher ANS activity during the PM condition in all variables measured (Table 2). More importantly, subjective
reports of the intensity of the chills response collected via rating scales during PET scanning were significantly correlated with the degree of ANS arousal on all measures (Fig. 11; Table 2). This finding further verified that the chills response is a good objective representation of peak emotional arousal amongst this group.

Analysis of PET data showed increased endogenous dopamine transmission, as indexed by decreases in [¹¹C]raclopride binding potential, bilaterally in both the dorsal and ventral striatum (p < .001; Fig. 12a) when contrasting the PM to the NM condition. The percentage of dopamine binding potential change was highest in the right caudate and the right NAcc (Fig. 12b; Table 3). These results provide direct evidence that the experience of pleasure while listening to music is associated with dopamine release in striatal reward systems.



Figure 11. Positive correlation between emotional arousal and intensity of chills during PET scanning. The mean intensity of chills reported by each participant during the PET scanning session was significantly correlated with psychophysiological measurements also acquired during the scan indicative of increased sympathetic nervous system activity, suggesting that the intensity of chills is a good marker of peak emotional arousal (Table 2). Y-axis represents standardized z-scores for each biosignal.

Psychophysiological	NM	PM	Welch	Correlation with	
Measurement	Condition	Condition	T-statistic	Intensity of Chills	
⊗ Heart Rate	14.15 (8.09)	17.10 (6.07)	4.04*	n = .34*	
\otimes Respiration	16.59 (4.93)	20.68 (4.88)	18.14**	n = .31*	
⊗ Skin Conductance	33 (.24)	21 (.35)	3.98*	r = .40 * *	
⊗ Temperature	40 (2.06)	-1.40 (.99)	9.63*	$\underline{r} =31*$	
⊗ BVP Amplitude	1.57 (1.62)	12 (1.67)	23.63**	$\underline{r} =38*$	

Table 2. ANS activity measurements during PET scanning. Emotional arousal was assessed by measuring changes in heart rate (beats per minute), respiration rate (breaths per minute), skin conductance (microsiemens) peripheral skin temperature (degrees Celsius), and BVP amplitude (reflectance). Mean values during NM and PM conditions subtracted from baseline recordings obtained during pre-listening resting phase are reported. Welch's t-tests revealed significant differences between PM and NM scan conditions on all measures. More importantly, within the pleasurable condition, the intensity of chills experienced across excerpts was correlated with the degree of autonomic nervous system arousal: increases in heart rate, respiration, and skin conductance and decreases in temperature and BVP amplitude. (*p<.05, **p<.01)



Figure 12. Evidence for dopamine release during pleasurable music listening. (a) Statistical parametric maps (t-statistic on sagittal, coronal and axial slices) reveal significant [¹¹C]raclopride BP decreases bilaterally in the caudate, putamen, and NAcc (white arrows) during pleasurable compared to neutral music listening (Table 3), indicating increased dopamine release during pleasurable music. (b) Changes in binding potential values plotted separately for each individual; note that the change was consistent for the majority of people at each site.

Region	Peak MNI Coordinates		t-value	Cluster size	BP change % (SD)	
	x	у	z		(mm ³)	
Ant. R Caudate	10	19	-2	6.13	868	10.1 (12.4)
R Caudate	12	6	15	4.45	733	7.9 (5.2)
L Caudate	-13	11	7	5.32	896	6.4 (3.5)
R Putamen	26	-2	0	6.99	4426	7.4 (4.2)
L Putamen	-29	-12	-8	6.34	2952	6.6 (8.4)
R NAcc	14	10	-10	4.89	1267	9.2 (8.3)
L NAcc/Ventral	-21	9	-10	4.94	414	6.5 (14.4)
Putamen						

Table 3: [11C]raclopride binding potential changes between pleasurable and neutral music listening. Significant (p<.001) [11C]raclopride BP decreases between PM and NM listening conditions in the caudate, putamen, and NAcc. The highest degree of change was found in the anterior right caudate and right NAcc.

3.5.2. Functional magnetic resonance imaging data: temporal

specificity of reward responses. To gain information about the dynamics of dopamine release over time, fMRI scan were acquired during presentation of pleasurable and neutral music excerpts. Listeners indicated by button press when they experienced chills (mean = 3.1 chills per excerpt; SD = 0.9); these responses were then used post-hoc to identify "anticipation" and "peak experience" time periods (Fig. 13a). Anticipation epochs were defined as 15 seconds before the peak experiences. BOLD responses for each of these epochs were compared with periods at which participants reported feeling "neutral" during the same musical excerpts. The result of this contrast for each of the events was then spatially conjoined with a mask of regions that had shown dopamine release from the

[¹¹C]raclopride PET scan. Results revealed that hemodynamic activity in the regions showing dopamine release was not constant throughout the excerpt, but restricted to moments before and during chills, and critically, anatomically distinct. During peak pleasure experience epochs, as compared with neutral epochs, there was increased BOLD response in the right NAcc (x,y,z,= 8,10,-8; t=2.8; Fig. 13b). In contrast, increased BOLD response was also found during the anticipation epochs, but largely confined to the right caudate (x,y,z,= 14,-6,20; t=3.2; Fig. 13b).

The temporal dynamics of the reward response and its relationship to the caudate and NAcc clusters can be more specifically analyzed by examining the percent BOLD signal change occurring over time in relation to peak pleasure. To avoid the "circularity" problem (Kriegeskorte et al., 2009), we derived our VOI from the PET data, which are independent of the fMRI data. This procedure also allows us to better integrate the hemodynamic and neurochemical results. The results show increasing activity in both the caudate and NAcc during anticipation as compared with the mean signal during the "neutral" epochs for the same pieces of music, with larger increases in the caudate (Fig. 13c). During the peak emotional response, however, the caudate activity decreases while the NAcc continues to increase. These findings support the fMRI contrast results, and provide temporal information of how hemodynamic activity in the regions showing dopamine release may be contributing to reward processing in real time.



Figure 13. Combined fMRI and PET results reveal temporal distinctions in regions showing dopamine release. (a) $\int^{11} C$ raclopride PET scan results were spatially conjoined with the fMRI results by creating a mask of significant dopamine release overlayed on BOLD response t-maps during each condition. (b) Hemodynamic responses and dopamine activity are maximal in the caudate during anticipatory phases, but shift more ventrally to NAcc during peak emotional responses. (c) Percent signal change in BOLD response relative to the mean was calculated from the peak voxel of the caudate and NAcc clusters based on the $\int [I^{1}C]$ raclopride PET data. Voxels showing maximum dopamine release in the caudate and NAcc (Table 3) were identified and percent BOLD signal change was calculated during the fMRI epochs during peak emotional responses; values were interpolated for each second preceding this response for each individual – up to 15 seconds, which was defined as the "anticipatory" period based on previous findings (Salimpoor et al., 2009) (see Methods for additional details). *Results show increased activity during anticipation (A1-A15) and decrease during* peak emotional response (C1-C4) for the caudate, but continuous increase in *NAcc* with a maximum during peak emotional responses. The mean signal for "neutral" epochs for the NAcc and caudate clusters are also plotted for reference, as are five seconds preceding the anticipation epochs.

3.5.3. Brain-behaviour relationships. Once the caudate and NAcc had been identified as contributing to the anticipation and experience, respectively, of peak pleasure moments during music listening via the fMRI data, we returned to the PET scan data to further explore the brain and behaviour relationships in these clusters. Mean [¹¹C]raclopride binding potential values from the NAcc and caudate clusters was plotted against behavioural data obtained during PET scanning, which required participants to give an indication of the total number of chills, mean intensity of chills, and mean subjective pleasure experienced during each piece of music. Results revealed that the number of chills was significantly correlated with binding potential differences in the right caudate, but not the NAcc, whereas the intensity of chills and overall degree of pleasure experienced were most significantly correlated with binding potential change in the right NAcc, but not the caudate (Fig. 14; Table 4). This finding further supports a functional dissociation in the contribution of these anatomical regions to pleasure associated with music listening.



Figure 14. Brain and behavior relationships involving temporal components of pleasure during music listening. Left: Sagittal slices showing binding potential (BP) differences in dorsal (top) and ventral (bottom) striatum that also show hemodynamic activity during anticipation vs. experience of chills, respectively. Right: Behavioral ratings of the number and intensity of chills, and pleasure reported during the PET scans plotted against [¹¹C]raclopride binding potential changes in the two clusters. The number of chills reported was positively correlated with percent binding potential change in the caudate $(p < .05^*)$, which was linked to BOLD response immediately preceding chills (i.e., anticipatory periods), consistent with the idea that a greater number of chills would result in greater anticipation and result in more activity in the areas associated with anticipation. The mean intensity of chills and reported pleasure were positively correlated with the NAcc ($p < .05^*$ and $p < .01^{**}$, respectively), which was linked to BOLD response during chills, confirming that this region is involved in the experience of the highly pleasurable component of music listening.

Subjective Reports	BP changes in Right Caudate	BP changes in Right NAcc
Number of Chills	<i>r</i> =.71*	<i>r</i> =.21
Intensity of Chills	<i>r</i> =.26	r=.80*
Degree of Pleasure	<i>r</i> =.19	<i>r</i> =.84**

 Table 4: Relationships between [11C]raclopride binding potential
changes in striatal regions and subjective reports during music listening. We examined the relationships between subjective reports of pleasure and individual change in [11C]raclopride BP in each of the three clusters that showed significant changes in both BP and BOLD response during anticipation and experience of PER. First the maximum percent change in BP from each significant cluster was extracted for each participant. This value was then plotted against subjective ratings collected during the PET scanning session, namely: (1) the total number of PER reported, (2) the mean intensity of PER, and (3) the mean degree of pleasure. Pearson correlation values were calculated to determine the relationship between BP change and behavioral measures in each of the three significant clusters. The number of chills experienced during the PM session was significantly correlated with BP differences in the right caudate, but not the NAcc. The intensity of chills and overall degree of pleasure experienced were most significantly correlated with the right NAcc, but not the caudate. (*p<.05, **p<.01)

An additional question is whether increases in pleasure alone, in the absence of chills, result in increased hemodynamic responses in the same areas as during the experience of chills – although perhaps not to the same extent. We examined this question by determining whether there was a linear relationship between increases in pleasure and hemodynamic activity in the right NAcc irrespective of chills, and how this compared to other striatal regions showing dopamine release. This analysis was done by excluding all the epochs during which individuals experienced chills, and examining BOLD signal changes that relate to increasing pleasure in the right NAcc. Using the voxel that showed the maximum dopamine release in the NAcc during the [11C]raclopride scan, we calculated the percent BOLD signal change as subjective pleasure ratings increased from "neutral" to "low-pleasure" to "high-pleasure" (excluding chills) for each individual. Note that this analysis, unlike the one presented above, does not take into account the temporal component, because all epochs rated as having the same pleasure were averaged, regardless of when they occurred with respect to chills. A regression analysis revealed a significant linear trend, where the percent signal change in the right NAcc accounted for 67% of the variability in subjective pleasure ratings; t(19) = 6.18 (p < .001). This finding demonstrates that increases in subjective pleasure correspond to increases in neural activity in the NAcc, in the same regions as those involved in the chills responses and those that showed dopamine release in the PET study, even though this analysis excluded all chills epochs.

Next, to ensure that increases in pleasure, irrespective of chills, are not better predicted by activity regions of the striatum other than the right NAcc, we performed a similar analysis in all anatomical clusters that had shown dopamine release in the PET study. We first selected peak voxels from each cluster showing dopamine release from the PET data, and then extracted the percent BOLD signal change as listeners reported increases in pleasure from the fMRI data; as before, all chills epochs were excluded. A stepwise multiple regression analysis was performed to examine which cluster's hemodynamic responses were best able to

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predict pleasure states. This analysis confirmed that hemodynamic increases in the NAcc cluster was the most significant predictor (p < .01) of increasing subjective pleasure (Table 5). However, at a lower statistical threshold of p < .05, bilateral caudate clusters and the left NAcc/ventral putamen cluster can also predict pleasure states, but to a lower degree (31% and 43% for left and right caudate, respectively, and 37% for the NAcc/ventral putamen). Recruitment of the caudate is not surprising considering that anticipatory periods result in a culmination of pleasurable emotional experiences, and we showed above that the caudate is recruited during these pleasant anticipatory moments. Indeed, the mean subjective pleasure rating provided by listeners during the "anticipatory" epochs was 2.51 (s.d.=.55), which is significantly higher than that of the entire excerpt (mean=2.11 (s.d.=.019); t(246)=8.5, p < .001).

Region	Р	eak MN	NI	r
	Coordinates			(Excluding Chills)
	x	у	z	
Ant. R Caudate	10	19	-2	.44
R Caudate	12	6	15	.66
L Caudate	-13	11	7	.55*
R Putamen	26	-2	0	.33
L Putamen	-29	-12	-8	.18
R NAcc	14	10	-10	.82**
L NAcc/Ventral	-21	9	-10	.58
Putamen				

Table 5: Relationships between real-time pleasure ratings during musiclistening and percent signal change in hemodynamic responses in voxelsshowing dopamine release.To determine whether dopamine is involved inpleasure responses independent of the experience of chills, we excluded all chills

epochs and compared hemodynamic activity in the NAcc voxel that showed maximum dopamine release during PET scanning with real-time pleasure ratings (i.e., "neutral", "low-pleasure", and "high-pleasure" button- presses) during fMRI scanning. The mean BOLD percent signal change was extracted for each of the three conditions, and a regression analysis was performed to assess whether a change in hemodynamic response can predict pleasure state. To examine whether *NAcc* was uniquely related to pleasure responses, percent BOLD signal change was extracted for the peak voxels from all other clusters that showed significant dopamine release during PET scanning. A step-wise multiple regression was performed to determine the ability of the signal change in each cluster to predict pleasure state (p value was set at .01). Regression analyses were performed to examine how well changes in percent BOLD signal change relative to the mean for each voxel showing significant dopamine release could predict real-time pleasure states reported during music listening. The "chills" epochs were not included in this analysis. The results showed that signal changes in bilateral *NAcc and caudate clusters could each account for some of the variability in* subjective ratings when considered individually (represented by r in the table). However, when all clusters were considered in a stepwise multiple regression, signal change in the right NAcc was the single best predictor of increases in subjective ratings, further accounting for much of the variability in the other clusters, particularly that of the right caudate and left NAcc. Signal change in the left caudate could still account for some of the variability in the pleasure ratings not accounted for by right NAcc, since this region was also significant in the multiple regression when thresholds were lowered to p < .05. (** p < .001, *p < .05)

Finally, when the percent BOLD signal change during the chills epochs was included in the multiple regression analysis (**Fig. 15**), it was apparent that the experience of chills represents the highest point of hemodynamic activity in the NAcc. These findings hence converge to suggest that the dorsal and ventral subdivisions of the striatum are most involved during anticipation and experience of the peak emotional responses during music listening, respectively.



Real-time subjective pleasure rating

Figure 15. Brain and behavior relationships involving parametric increases in pleasure during music listening. Relationship between real-time ratings of pleasure during music listening and percent BOLD signal change relative to the mean in regions showing dopamine release as identified via PET. The "chills" epochs (shaded) were excluded from the analysis (values shown here only for reference) to examine activity related to increases in pleasure irrespective of chills. A regression analysis showed that the NAcc, and to a lesser extent the left and right caudate, significantly predicted increases in pleasure ratings during each of the conditions (Table 5). This analysis shows that activity in these regions increases with pleasure even when no chills are experienced.

3.6. Discussion

These experiments make two major contributions. First, we provide the first direct evidence that the intense pleasure experienced to music is associated with dopamine activity in the mesolimbic reward system, including both dorsal and ventral striatum. This phylogenetically ancient circuitry has evolved to reinforce basic biological behaviours with high adaptive value. However, the rewarding qualities of music listening are not obviously directly adaptive. That is, musical stimuli, similar to other aesthetic stimuli, are perceived as rewarding by the listener, rather than exerting a direct biological or chemical influence. Furthermore, the perception that results in a rewarding response is relatively specific to the listener as there is large variability in musical preferences amongst individuals. Therefore, through complex cognitive mechanisms, humans are able to obtain pleasure from music (Dube & Lebel, 2003), a highly abstract reward consisting only of a sequence of tones unfolding over time, which is comparable to the pleasure experienced from more basic biological stimuli.

One explanation for this phenomenon is that it is related to enhancement of emotions (L. B. Meyer, 1956; Salimpoor et al., 2009; Sloboda & Juslin, 2001). The emotions induced by music are evoked, among other things, by temporal phenomena, such as expectations, delay, tension, resolution, prediction, surprise, and anticipation (Huron, 2006; Huron & Hellmuth Margulis, 2009). Indeed, the second important finding of this study was the temporal dissociation between distinct regions of the striatum while listening to pleasurable music. The combined psychophysiological, neurochemical, and hemodynamic procedure in this experiment demonstrated that peaks of ANS activity that reflect the experience of the most intense emotional moments were associated with dopamine release in the NAcc. This region has been implicated in the euphoric component of psychostimulants such as cocaine (Volkow et al., 1997), and is highly interconnected with limbic regions that mediate emotional responses, such as the amygdala, hippocampus, cingulate, and ventromedial prefrontal cortex (Haber & Knutson, 2010). In contrast, immediately prior to the climax of emotional responses there was evidence for relatively greater dopamine activity in the caudate. This subregion of the striatum is interconnected with sensory, motor, and associative regions of the brain (Haber et al., 2006; Haber & Knutson, 2010), and has been typically implicated in learning of stimulus-response associations (Haber & Knutson, 2010; Valentin & O'Doherty, 2009), and in mediating the reinforcing qualities of rewarding stimuli such as food (Small, Jones-Gotman, et al., 2003). Our findings demonstrate that a sense of emotional expectation, prediction, and anticipation in response to abstract pleasure can also result in dopamine release, but primarily in the dorsal striatum. Previous studies have demonstrated that amphetamine-induced dopamine release in the NAcc spreads to more dorsal regions after repeated exposure to the drug (Boileau et al., 2006), which suggests that this area may be involved in improved predictability and anticipation of a reward. Similarly, previous studies involving rewards such as food and smoking that contain a number of contextual predicting cues (e.g., odour and taste) also show dorsal striatum dopamine release (S. P. Barrett et al., 2004; Small, Jones-Gotman, et al., 2003). Conversely, in studies where there have been no contextual cues or experience with the drugs involved, dopamine release was largely observed in the ventral striatum (Boileau et al., 2003; Leyton et al., 2002). Finally, evidence from animal research also suggests that as rewards become better predicted the responses that initiated in the ventral regions move more dorsally in the striatum (Everitt & Robbins, 2005). These results are consistent with a model in which repeated exposure to rewards associated with a specific context gradually shift the response from ventral to dorsal, and further suggest that contextual cues that allow prediction of a reward, in our case the sequences of tones leading up to the peak pleasure moments, may also act as reward predictors mediated via the dorsal striatum.

Another noteworthy finding is the correspondence between behavioural and imaging results, which strengthens the evidence for the distinct roles of dorsal and ventral striatum. A positive correlation was found between subject-reported intensity of chills and dopamine release in the NAcc during [¹¹C]raclopride PET scanning (Fig. 14), which confirms the fMRI results that peak pleasure responses

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are associated with this region. Furthermore, the number of chills reported by listeners during the PET scan was correlated with dopamine release in the caudate (Fig. 14), which is consistent with the fMRI results showing increased activity in this region during anticipation of peak emotional responses; since greater number of chills suggests increased incidence of anticipation, greater dopamine release would be expected in this area.

It is important to note that chills are not necessarily pleasurable per se, as in other contexts they can be unpleasurable (e.g., as a result of intense fear). Rather, chills are physiological markers of intense ANS arousal (Blood & Zatorre, 2001; Grewe et al., 2009; Rickard, 2004; Salimpoor et al., 2009), which in turn is believed to underlie peak pleasure during music listening (Blood & Zatorre, 2001; Salimpoor et al., 2009); we used chills here only to allow objective quantification of a highly subjective response, which would otherwise be difficult to measure, and because it affords precision as to the time at which the peak pleasure occurred. As such, chills are byproducts, and not a cause of the emotional responses. Thus, it is important to clarify that while chills index peak emotional responses in this group of people, the specific experience of chills is not necessary to result in neural activity in the striatum, a finding which is consistent with lessspecific analyses performed in previous studies (Koelsch et al., 2006; Menon & Levitin, 2005; Mitterschiffthaler et al., 2007). This conclusion is confirmed by our findings that even when the chills epochs were excluded from the analysis, there was still a significant linear relationship between increases in self-reported pleasure and increases in hemodynamic activity in the regions that showed dopamine release (Fig. 15). Furthermore, when chills were reported, maximal signal was seen in the NAcc voxels that showed a linear increase as participants progressed from "neutral" to "low-pleasure" to "high-pleasure", further confirming that chills represented the peak of pleasure in this group. This finding is also consistent with the finding that the degree of binding potential decrease in the NAcc for each participant was positively correlated with the degree of pleasure reported from listening to the musical excerpts, irrespective of the number of chills that were experienced (Fig. 14).

It should be noted that at lower statistical thresholds there is some activity in the ventral striatum during the anticipation phase, consistent with other studies using different stimuli (Haber & Knutson, 2010). What is novel about the present study is that during the anticipatory phase there is also increased BOLD response in the caudate (more so than the NAcc), which then shifts more ventromedially as participants report experiencing peak reward (Fig. 13). This is an important finding because the stimulus that we are using is a dynamic reward with a temporal component, allowing examination of the reward in real time as it progresses from anticipation to peak pleasure states, which is generally not possible due to limitations with movement inside the PET scanner. Some studies administer the pleasurable stimulus (e.g., food) immediately before the scan, and measure subsequent dopamine release (Small, Jones-Gotman, et al., 2003), in which case anticipation and consumption cannot be distinguished. Other studies measure the anticipation phase online, with the promise of the delivery of the tangible reward after the scan, in which case the consumption phase is missed (Koepp et al., 1998; Zald et al., 2004). Music is a unique reward that allows assessment of all reward phases online, from the point that a single note is heard to the point where maximum pleasure is reached.

The anatomical dissociation between the anticipatory and consummatory phases during intensely pleasurable music listening, suggest that distinct mechanisms are involved. This distinction may map onto the "wanting" and "liking" phases of a reward in an error prediction model (Zald & Zatorre, 2011). The anticipatory phase, set off by temporal cues signaling that a potentially pleasurable auditory sequence is coming, can trigger expectations of euphoric emotional states and create a sense of "wanting" and reward prediction. This reward is entirely abstract, and hence may involve such factors as suspended expectations and a sense of resolution. Indeed, composers and performers frequently take advantage of such phenomena, and manipulate emotional arousal by violating expectations in certain ways, or delaying the predicted outcome (e.g. by inserting unexpected notes or slowing tempo) before the resolution to heighten the motivation for completion. The peak emotional response evoked by hearing

the desired sequence would represent the consummatory or "liking" phase, representing fulfilled expectations and accurate reward prediction. We propose that each of these phases may involve dopamine release, but in different subcircuits of the striatum, which have different connectivity and functional roles. The notion that dopamine can be released in anticipation of an abstract reward (a series of tones) has important implications for understanding how music has become pleasurable. However, the precise source of the anticipation requires further investigation. A sense of anticipation may arise through one's familiarity with the rules that underlie musical structure, such that listeners are anticipating the next note that may violate or confirm their expectations, in turn leading to emotional arousal; or alternatively it may arise through familiarity with a specific piece, and knowing that a particularly pleasant section is coming up (Huron & Hellmuth Margulis, 2009). These components are not mutually exclusive, since the second likely evolves from the first, and the overall anticipation is likely to be a combination of both. Nonetheless, the subtle differences that exist between them will need to be disentangled through future experiments that are specifically designed to parse out this distinction. Abstract rewards are largely cognitive in nature, and this study paves the way for future work to examine non-tangible rewards that humans consider rewarding for complex reasons.

Dopamine plays a pivotal role in establishing and maintaining behaviour. If music-induced emotional states can lead to dopamine release, as our present findings show, it may begin to explain why musical experiences are so valued. They further speak to why music can be effectively used in rituals, marketing, or film to manipulate hedonic states. These findings provide neurochemical evidence that intense emotional responses to music involve ancient reward circuitry, and serve as a starting point for more detailed investigations of the biological substrates that underlie abstract forms of pleasure.

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Chapter 4: Neural Interactions that give Rise to Pleasurable Responses to Music

4.1. Preface

This final study of the dissertation was designed to investigate questions raised in the previous experiments, and formulate a coherent model of how we derive pleasure from abstract and "aesthetic" rewards, such as music. In the second study, we found dopamine release in the NAcc during peak responses to music. Here, we examined which other neural regions in the brain interact with the NAcc to give rise to rewarding responses to music using multivariate connectivity analysis methods with fMRI scanning data. The second important finding of our second study was that dopamine was released during anticipation of peak pleasure moments, suggesting an important role for expectations and predictions during music listening. We investigated the source of this anticipation during music listening by ruling out expectations related to explicit knowledge about a piece of music by using new music that participants had not heard before. We hypothesized that if anticipation was due to an implicit understanding of music structure, we would observe activity in the same striatal regions of the brain when participants listen to music they find rewarding.

This manuscript has been submitted for publication. (Salimpoor, V. N., van den Bosch, I., Kovacevic, N. McIntosh, A. R., Dagher, A., Zatorre, R. J., Interactions between nucleus accumbens and cortical sensory processing predict music reward value).

4.2. Abstract

We used fMRI to examine the neural processes that underlie how a piece of music gains reward value the first time it is heard. To assess reward value objectively, listeners were given the chance to purchase the music via an auction paradigm. The degree of activity in mesolimbic striatal regions, especially the NAcc, during initial processing of music was the best predictor of the amount listeners were subsequently willing to spend. Importantly, we found a dissociation in reward-related processes as the auditory cortices, amygdala, and ventromedial prefrontal regions were active to a similar extent during all listening conditions requiring valuation, but did not predict reward value of items, which was instead predicted by increasing functional connectivity of these regions with the NAcc as reward value increased. This finding provides direct evidence that aesthetic rewards arise from the interaction between mesolimbic reward circuitry and cortical networks involved in perceptual analysis and valuation.

4.3. Introduction

Music is arguably one of the most potent rewards, existing in all cultures from prehistory, and reported to be amongst the most pleasurable stimuli (Dube & Lebel, 2003). Yet, the mechanisms by which mere sequences of sounds become highly rewarding remain largely unknown. Prior studies have demonstrated hemodynamic activity in the mesolimbic dopaminergic reward circuits during pleasurable music listening (Blood & Zatorre, 2001; Koelsch, 2010), and that dopamine is released in the striatum during peak responses to music (Salimpoor, Benovoy, Larcher, Dagher, & Zatorre, 2011). Reward circuits exist in phylogenetically simpler organisms to reinforce biologically adaptive behaviours, including eating and sex (Berridge, Ho, Richard, & DiFeliceantonio, 2010; Melis & Argiolas, 1995). However, appreciation of music seems to be unique to humans, and is highly dependent on sociocultural factors as well as experience and memory, suggesting an integrative role for cortical processes in interaction with these reinforcement circuits. Here, we examine how cortical and mesolimbic systems interact for complex, aesthetic rewards such as music. We minimized any effect of previously experienced associations by using music that had not

been heard before. We show that the reward value of a musical sequence is predicted by activity in mesolimbic areas, and the interaction of these regions with sensory and evaluative cortical systems when the music is heard for the first time.

Mesolimbic dopamine activity is involved in incentive salience and reward prediction, leading to expectation, anticipation, and the desirability of an item (Leyton, 2010). In typical experimental paradigms, dopamine is released when a desired item is craved during an appetitive or anticipatory phase (Volkow et al., 2006; Wong et al., 2006), or when the expectation for the receipt of a desirable item is met or surpassed during a consummatory phase (Phillips, Stuber, Helen, Wightman, & Carelli, 2003; Schultz, 2007). But unlike most other rewards, the consummatory phase of music does not involve ingestion of a substance, or a concrete stimulus, but rather an abstract experience. While each isolated sound in a piece of music has little meaning in itself, music gains significance and emotional meaning through the combination of elements unfolding in time. Consistently, the principal affective impact of music is thought to be elicited by the creation of expectancies through temporally-rooted phenomena, such as delay, anticipation, and surprise (Huron, 2006). Zald and Zatorre (Zald & Zatorre, 2011) suggested that a prediction-error model (Schultz et al., 1997) may apply to music, such that temporal expectancies impact emotional arousal, leading to predictions being fulfilled or surpassed, mediated via a dopaminergic response. A previous study showed that dopamine is released in the ventral striatum during peak pleasure moments in music (marked by "chills"), but importantly, the period of build-up leading to the peak pleasure results in dopamine release in the dorsal striatum (Salimpoor et al., 2011), a structure implicated in cue-elicited cravings and habitual knowledge that a previously experienced reward is coming (Belin & Everitt, 2008; Boileau et al., 2006; Wong et al., 2006). The source of this anticipation is not clear, as it could arise from explicit knowledge of the musical passage or from cognitive predictions based on implicit schematic knowledge of musical expectancies (Huron, 2006). In line with the established role of dopamine in habitual expectations of a desirable event, explicit knowledge of how sounds will unfold is highly plausible as an explanation of why we enjoy familiar

music, but cannot account for how unfamiliar music can be appreciated. Schematic expectancies (J. Bharucha, 1994) represent the rules of how sounds are organized together, based on all of the musical knowledge that an individual has implicitly gained through exposure to various musical sounds throughout their lives. The possibility that a prediction-error model shapes the biological response to music independently of explicit knowledge has not been tested, and was another of our principal aims because it has important implications for deciphering the processes that are initially involved in appreciating music, which may be different for each individual depending on their previous auditory experiences.

To examine whether brain areas implicated in positive prediction error would be involved when a novel piece of music becomes highly valued, we selected music that was novel, but similar to previously heard material in terms of structure and style to ensure the presence of a schematic form of prediction. As musical preferences are highly individualized, music recommendation software was used to find a stimulus set that could be potentially rewarding to a carefully selected group of participants with homogeneous preferences ("Materials and methods are available as supporting material on Science Online,"). Our hypothesis was that a desirable new piece of music would evoke activity in the same dopaminergic prediction-error regions as that of familiar music, due to schematic expectations accumulated through previous auditory experience, independent of explicit expectations.

Listener ratings of how much a musical selection is liked may be overly subjective and prone to bias. To obtain an objective and ecologically valid measure of how much individuals wanted or desired the music, they were given a budget and a chance to purchase the items. We applied an auction paradigm that has been well-established in behavioural economics (Becker, DeGroot, & Marshak, 1964), and to further increase ecological validity, we used similar time frames and prices as that of the popular music purchasing software iTunes. While undergoing fMRI scans, 11 participants (5 female) listened to seventy different 30-second music clips that they had not heard before, but were likely to find rewarding based on their stated musical preferences. Each participant was given a budget of \$10. After hearing each excerpt they were asked to rate how much they liked the item, and how much they were willing to spend on it (\$0, \$.99, \$1.29, \$2). Participants were told that they could keep the remaining amount from the budget, along with any music won through the auction. This procedure created an environment where individuals were spending their own money on the music they heard, and thereby provided an objective measure of the music's reward value to the individual.

4.4. Methods

4.4.1. Participants. Over 250 individuals were recruited through advertisements around university campus. We aimed to select amongst these a group of individuals with the most homogeneous preferences in music so that music recommendation websites could be used to select the same set of stimuli for all eventual participants. Respondents completed a musical preferences questionnaire over email, listing their favorite artists and songs, as well as the music they had purchased over the last month. The most commonly emerging genre of music that participants listed as their preferred music was 'Indie', 'Rock' or 'Electronic'. As such, we selected a final sample of participants who had listed these genres and showed overlap in their preferred artists and songs with other selected participants. A total of 33 subjects (mean age = 25; range of 18 to 50) and a wide variety of musical experience participated in the experiment. All subjects were believed to be healthy and free from any psychological or neurological disorder and gave written informed consent before participating in the study. The protocol was approved by the Montreal Neurological Institute Research Ethics Board.

4.4.2. Stimuli. Musical stimuli were selected by using music recommendation programs such as Pandora (<u>http://www.pandora.com</u>) and Last.fm (<u>http://www.last.fm/</u>). The participants' preferred artists and songs were entered into the program and the final list of musical stimuli was selected amongst the recommendations produced by the program. Once the recommendations were produced, we implemented additional selection criteria by: (1) selecting songs

that were most recent to increase the chances of the participants' not having heard them before; (2) consulting with local music stores to inquire about which albums individuals who had music preferences similar to ours were likely to purchase. Once the titles had been selected, to increase ecological validity and to obey copyright issues, the same 30 seconds that are used as samples of the complete songs in the iTunes Store (<u>http://www.apple.com/itunes/what-is/store.html</u>) were recorded using Audacity software (<u>http://audacity.sourceforge.net/</u>).

4.4.3. Task. Participants listened to 30-second music excerpts presented on headphones (70 clips during the first behavioural session and 60 during the fMRI session; Fig 16) and after hearing each expert provided the following ratings presented individually on a visual analogue scale on a computer screen using response buttons on a keyboard:

1. Subjective pleasure experienced (from -5: "hated it" to +5: "loved it")

2. Subjective arousal experienced (from 0: "calm" to 10: "extremely excited")

3. Familiarity with the musical selection (from 0: "never heard before" to 10: "know very well").

4. How much money they are willing to spend on it (see below) Purchasing behaviour was used to assess reward value. While participants can claim that they like a piece of music, willingness to spend their own money on it is a more valid indication of how much they want it. For this reason, we gave participants a chance to purchase the music. Each participant was given a budget of \$10, and could keep the amount that was not spent. To further increase ecological validity, the prices were modeled after that of iTunes (\$0, \$.99, \$1.29, \$2). We intended to mimic purchasing situations as much as possible, where an individual listens to a 30-second music clip, as they would on iTunes, and then decide if they would like to purchase it. To ensure that participants did not have to keep track of how much money was spent, we used the Becker-Degroot-Marschak (BDM) auction paradigm (Becker et al., 1964), which has been wellestablished in economics and allows each item to be treated individually. The paradigm works by asking participants to place "bids" on each excerpt after hearing it (according to the prices listed above). This bid should be the maximum

that the participant would be willing to spend on this item. They were told that we have also allotted a randomly selected price for each item. At the very end of the experiment, they were informed that we would randomly select five pieces of music. If the bid that they placed on the item was higher than the random price that we had allotted to it, they would receive that item, but they would have to pay for it out of their budget. If their bid was lower than the allotted price, they would not get the music, but could keep the money. The rules of the BDM auction create a situation in which the optimal strategy for the individual is to bid exactly what they are willing to pay for a given item. Furthermore, individuals do not have to worry about spreading their budget over the different items. Instead, they can treat each trial as if it were the only decision that counted. At the end of the experiment, each song successfully purchased by the participant was purchased and downloaded from the iTunes Store and burned on a CD for the participant. The amount remaining from their budget was given to them in cash. Participants were also reimbursed for their time with gift certificates from the iTunes Store (in the amount of 10- and 50-dollars for the first and second sessions, respectively). We selected this form of compensation for two reasons: (1) to increase the perceived worth of the \$10 budget participants were given to place bids with since they were not receiving any additional cash, and (2) to ensure that we were recruiting participants who typically purchase music from the iTunes Store otherwise they might not have been interested in this compensation method. The titles of musical selections were not revealed to the participants at any time to ensure that they knew they could not download the songs for free outside of the experiment. This step was implemented to ensure that they would accurately bid on the music that they would like to own during the experiment.

4.4.4. Procedures. Testing took place over two sessions. For the first session participants listened to new music in the laboratory. The purpose of the behavioural session was to implement a screening measure by selecting the individuals whose music preferences were successfully matched by our music recommendation tools. As such, only a subset of the participants from the first session were asked to continue with the second session. A different set of musical

selections were used in the second session that were more specifically geared towards the preferences of the group continuing with the study. During the second session the subset of participants who were asked to continue with the study performed the same tasks as the first session, but inside the fMRI scanner.

Session 1: Behavioural testing. After arrival and giving informed consent, subjects were given instructions and acquainted with the task on three practice trials. Music was played through Sennheiser headphones and volume was adjusted to a comfortable listening level. The task consisted of listening to seventy 30-second music excerpts over two sessions (35 trials per session, separated by a 10-minute break). During the break, subjects were asked to complete questionnaires assessing their musical training, listening habits, musical preferences, and additional demographics information.

Session 2. Functional magnetic resonance imaging scanning. Twentyfive participants were selected from the behavioural session to continue with the brain scanning session, if interested. Individuals were selected based on how well we were able to predict the music that they would like and purchase. In other words, we selected the subjects who liked and purchased the largest percentage of the music that we selected for the experiment. Nineteen participants (10 female, 9 male) agreed and were available to continue with the study. Scans were acquired with a 3 Tesla Siemens TIM Trio scanner using an 8-chanel quadrature coil. A high-resolution T1-weighted anatomical scan was obtained for each participant (voxel size=1mm³) and T2^{*}-weighted echo-planar images of BOLD signal were acquired (35 slices interleaved, 64×64 matrix, voxel size=4mm³) aligned with Sylvian fissure and covering the whole brain (TE=30ms, TR=2.1s). High-fidelity headphones were used (MR confon GmbH, 39118 Magdeburg, Germany), containing electrodynamic transducers for a broad, flat frequency response and construction-grade Peltor earmuffs for passive damping of gradient noise. The task consisted of listening to sixty 30-second music excerpts over two sessions (30 trials per session, separated by a 10-minute break during which the high-resolution anatomical scan was acquired). An additional difference between the behavioural and fMRI scan session was the inclusion of four 30-second silent

rest periods within each run (after every sixth trial). This was intended to record baseline neural activity during periods at which scanner noise was present but music was not.

4.4.5. Data analysis. FMRI data were corrected for motion. To increase the signal-to-noise ratio of the imaging data, the images were spatially smoothed (or low-pass filtered) with an 8-mm FWHM isotropic Gaussian kernel. Image analyses were performed with fMRISTAT, which consists of a series of MATLAB scripts that apply the general linear model (GLM) for analyses (Worsley et al., 2002). The design matrix of the linear model was convolved with a hemodynamic response function modeled as a difference of two gamma functions that coincided with the acquisition of each slice. Temporal drift was modeled as cubic splines and removed by inclusion into the GLM as a variable of non-interest. One covariate was added per each two minutes of scan time. Spatial drift was removed by adding a covariate in the whole volume image. The contrasts are described below. Next, the runs were combined using a mixed effects linear model for the effects (as data) with fixed effects standard deviations. A random effects analysis was performed by first estimating the ratio of the random effects variance to the fixed effects variance, then regularizing this ratio by spatial smoothing with a Gaussian filter. The variance of the effect was then estimated by the smoothed ratio multiplied by the fixed effects variance. The amount of smoothing was chosen to achieve 100 effective degrees of freedom. Before combining subjects' standard deviation and effect files, all images were resampled to standard space using the MNI 152 template. The anatomical images were also standardized and averaged.

Neural correlates associated with items that were purchased. To examine the neural activity associated with hearing the 30 seconds of music clips that were subsequently purchased compared with those that were not, each excerpt was categorized into a "purchased" (any bid higher than \$0) or "not purchased" event (bids of \$0), which were then set up in a contrast in the GLM. Items that were rated as familiar were not included in the analysis (6% of the total excerpts). The mean purchased items (events) for each individual was 28.3 excerpts (SD = 9.2) and non-purchased was 27 excerpts (SD = 8.5). Once the tstatistic maps were generated, the spatial extent of activated regions (clusters) was used to determine significance (Worsley et al., 2002; Worsley et al., 1996). First, a threshold of p<.0001 uncorrected was used to determine which clusters were significant. The resulting threshold for the spatial extent of clusters is the extent threshold of 638mm³. Thus, any cluster of neighbouring voxels above a threshold of 3.17 with a volume larger than 638 voxels is significant at p<.05.

Neural correlates associated with increasing reward value. To examine how each region identified in the above contrast mediates reward value, the change in signal in each region was compared with the amount of money bid on each item heard. First, three additional contrasts were modeled to examine the following comparisons: (1) \$2 compared to \$0; (2) \$1.29 compared to \$0; (3) \$.99 compared to \$0. Next the voxel that showed the largest response within each cluster from the purchased versus non-purchased comparison was selected for each region. The peak VOI used in this analysis are listed in Table 6. Each contrast produces a map of effect sizes in addition to a t-map. The effect size was extracted for each contrast at the coordinates of the VOI for each subject. A linear stepwise regression was then performed to see which of these regions could best predict the amount of spending.

Connectivity changes associated with increasing reward value. We were interested in examining how the signal fluctuations in the VOI correspond to activity in other regions of the brain and how this activity changes as items are considered more rewarding to the individual. For this analysis we applied a multivariate approach: partial least squares (PLS), to identify functional networks of spatially distributed regions whose activity is correlated across subjects (McIntosh, Bookstein, Haxby, & Grady, 1996). This procedure can examine the relationship between BOLD signal in a target region (seed voxel) and brain activity across the whole brain as a function of the different experimental conditions – in this case, willingness to pay for the musical excerpts. First, the timeseries for the two VOIs calculated in the previous analysis were concatenated for each condition and each individual. Next, the correlation coefficients between

the BOLD timecourse of each VOI and every other voxel in the brain were calculated. Task-based PLS was implemented to determine the significant changes in the correlation coefficients between the two conditions. Significance was assessed using 500 permutation tests of the singular value associated with each latent variable. Bootstrap resampling, with 100 iteration, can reveal how robust the effects are across subjects. The bootstrap ratio was set to 3, which corresponds roughly to a 95% confidence interval.



Figure 16. Experimental Paradigm. (A) BOLD activity was collected while participants listened to 30-second new music clips specifically selected to match their musical preferences through music recommendation programs, with an opportunity to make bids to purchase the items through an auction paradigm. Each excerpt was categorized into a desirability condition (\$0, \$.99, \$1.29, \$2) for each subject depending on his or her bid. (B) The first analysis compared BOLD response associated with all items on which bids greater than \$0 were made with those that were not purchased (bid = \$0). Once ROIs associated with purchasing were identified (Fig 17a), a multiple linear regression was performed to determine which ROI BOLD response change best corresponds to increasing value of the music (Fig 17b). (C) Activity changes in the right NAcc during listening was identified as the best predictor of subsequent value of the music to the individual, and therefore used as a seed in a partial least squares multivariate analysis to identify connectivity changes between this region and the rest of the brain as reward value increases to individuals during music listening (Fig 18).

4.5. Results

Over half of the musical selections presented during the fMRI session were purchased (mean=54%; SD=16), indicating that we were able to find novel music that participants found desirable. Whole-brain analysis of hemodynamic activity during the 30-second listening period of all items that were subsequently purchased (\$.99, \$1.29. \$2 bids) compared to those that were not purchased (\$0 bids) showed increased activity in the dorsal and ventral striatum, dorsal anterior cingulate cortex (dACC), insula, premotor area (BA6/8), and temporal pole (Fig. 17A). Multivariate regression was applied to determine which regions from this contrast are directly related to increases in reward value, marked by the bid amount on each item, and not just related to economic purchasing decisions. Reward value was most directly related to the degree of activity in the right NAcc in the ventral striatum, a key region associated with positive prediction error (Kuss et al., 2011; Niv, Edlund, Dayan, & O'Doherty, 2012), during initial processing of music: 35% of variability in bids was accounted for by NAcc activity. The right caudate nucleus, a part of the dorsal striatum, also accounted for a smaller proportion of variability (10%) in bid value, while the other clusters from the contrast in 17A did not show a significant contribution.



Figure 17. Neural activity associated with reward value of novel music. (A) A whole-brain contrast revealed areas active during initial processing of items on which a subsequent bid was made (\$.99, \$1.29, and \$2 bids) compared to processing of items not desired by participants (\$0 bids; p < .05 cluster-level threshold; Table 6). (B) The peak voxel from each cluster in Figure 16A was selected and the effect size from the general linear model (a measure of percent BOLD signal change; see Methods) was plotted against the amount that participants were willing to spend on the items. A stepwise regression revealed that the signal change in right NAcc accounted for 32% of the variability in the amount spent and the change in caudate accounted for an additional 10%, while other regions did not contribute significantly. (C) BOLD signal at each acquisition frame for the right NAcc (x=12, y=8, z=0) and right caudate (x=18, y=-4, z=10) are displayed. NAcc = nucleus accumbens, dACC = dorsal anterior cingulate cortex.

Area	Peak Voxel	Cluster	X	У	Z
L Cerebellum	5.64	2064	-32	-64	-50
R Insula/temporal pole	e 5.34	9760	48	14	-8
R Premotor/SMA	5.11	2288	52	4	50
R NAcc	4.73	3216	12	8	0
L NAcc	4.63	1200	-8	6	0
R Dorsal Striatum	4.59	3216	18	-4	10
R Cerebellum	4.56	1640	24	-66	-50
L Insula	4.40	4768	-38	24	2
Dorsal ACC	3.93	680	-2	26	36

Table 6. Contrast: Music Purchased vs Music Not Purchased. Wholebrain contrast revealed areas active during initial processing of items on which a subsequent bid was made (\$.99, \$1.29, and \$2 bids) compared to processing of items not desired by participants (\$0 bids; p < .05 cluster-level threshold). To examine the neural activity associated with hearing the 30 seconds of music clips that were subsequently purchased compared with those that were not, each excerpt was categorized into a "purchased" (any bid higher than \$0) or "not purchased" event (bids of \$0), which were then set up in a contrast in the GLM. Clusters with a volume of larger than 638 voxels are reported here (see Methods).

To determine how neural activity in these subcortical areas interacts with other brain regions to induce the reward value that we associate with complex aesthetic stimuli, we used the partial least squares method (McIntosh, Chau, & Protzner, 2004), a multivariate procedure that allows us to examine the temporal correlations in activity between multiple regions, and how this functional connectivity changes across conditions (see Methods). We examined the correlated activity in the right NAcc with all other voxels in the brain, and evaluated the changes in co-activity as items increase in reward value for the listener. The NAcc showed highly robust increases in connectivity with large portions of the superior temporal gyrus (STG), encompassing the primary auditory cortices and surrounding auditory processing regions bilaterally when individuals listened to items they subsequently spent the maximum amount of money on, compared with those they did not purchase (Fig 18A). This effect was highly robust and demonstrated by all participants. Importantly, these auditory regions overlap with those that showed increased activity during music listening compared with silence (Fig 18B), and likely are related to perceptual processing of music (Zatorre & Zarate, 2012). The activity in these regions remained high during processing of all music excerpts and did not distinguish between items that were subsequently valued with high monetary bids versus low bids (Fig 18C). Rather, what distinguished auditory cortex activity during processing of music with high bids was its enhanced connectivity with the NAcc.

Other areas that showed an increase in correlated activity with the NAcc as music value increased included the VMPFC, OFC, amygdala, hippocampus, right inferior frontal gyrus (IFG), ACC, and clusters in the somatosensory and motor areas (Table 7). Similar to the auditory cortices, the VMPFC, OFC, and right amygdala also showed activity during music listening (Fig 17B) that was independent of reward value (Fig 18C), yet showed increased connectivity with the NAcc when items were more highly valued (Fig 18A). This is of particular interest as this network of regions is well-established in assigning and maintaining value to items during reward processing (O'Doherty, 2004; Rushworth et al., 2011).



Figure 18. Changes in NAcc connectivity during music listening when maximum vs minimum amount of money is spent. Partial least squares analysis reveals that the NAcc shows robustly increased connectivity with a number of cortical and subcortical regions the first time individuals hear music that they consider highly desirable (\$2 bids) compared with music they do not desire to hear again (\$0 bids) (Table 7). A subset of these regions (A) are encompassed within areas that show higher activity during music listening compared to rest (B), suggesting that they are recruited to process incoming musical information. Importantly, peak voxels showing overlap between increased connectivity with the NAcc as items become more rewarding and music listening compared to rest (i.e., "music valuation" condition) did not show significant changes in BOLD magnitude as items became more rewarding (C). Rather, these regions show equally high activity during all "music valuation" conditions compared with rest, but their connectivity with the NAcc increases as items become more desirable. *Correlation coefficients between NAcc and the peak voxel in each ROI during* each condition are displayed in boxes in section A.
Area B	Bootstrap Ratio	Cluster	x	У	Z						
Positive Correlations (stronger connectivity with NAcc when bid is \$2)											
R Planum Temporale/STO	G 14.47	3200	54	-16	2						
L Planum Temporale/STC	G 10.03	1686	-50	-26	4						
ACC	9.48	687	-4	-10	42						
R Ant Tem Lobe/Amyg/H	Iipp 8.96	389	28	10	-28						
R IFG/Pars Triangularis	6.24	288	42	26	12						
R Lat Occipital Cortex/ P	ole 6.14	335	26	-72	18						
L Postcentral/Superior Pa	rietal 6.03	432	-52	-26	44						
R Postcentral/Supramargi	nal 5.79	39	42	-32	44						
VMPFC	5.72	147	6	54	-10						
R Lateral Occipital Cortex	x 5.49	212	18	-56	72						
L Precentral Gyrus	5.41	136	-32	-10	70						
L Fusiform/Lingual Gyru	s 5.19	57	-34	-54	-6						
R Superior Frontal	5.13	27	16	28	48						
L Fusiform/Parahippocam	npal 5.06	26	-38	-12	-36						
L Orbitofrontal Cortex	4.79	33	-10	44	-20						
R Intracalcarine Cortex	4.67	41	18	-68	10						
L Superior Frontal Gyrus	4.49	44	-24	0	52						
L Cuneus/Precuneus	4.38	65	-18	-74	32						
R Superior Parietal Lobul	e 4.15	40	34	-40	60						
R Frontal Operculum	4.11	26	42	16	8						
R Orbitofrontal Cortex	4.07	21	26	40	-8						
Negative Correlations (s	tronger connect	tivity with NA	.cc when bid	is \$0)							
R Lateral Occipital Cortex	x -10.63	4232	22	-78	-26						
R Frontal Pole	-7.81	662	32	52	4						
L Frontal Pole	-7.07	820	-30	56	-2						
L Frontal Operculum	-6.54	133	-46	22	-8						
R Subcallosal cortex	-6.13	44	6	18	-24						

-5.90

-5.67

R Middle Temporal

L IFG/Pars Triangularis

49

57

68

-56

-34

28

-18

L Middle Temporal	-5.62	38	-52	2	-24
L Inferior Temporal Gyrus	-5.59	25	-54	-60	-10
L Cerebellum	-5.55	23	-8	-58	-50
R Superior Parietal Lobe	-4.77	33	36	-50	40
R Inferior Temporal Gyrus	-4.77	23	54	-38	-28
R Precuneus	-4.43	34	10	-56	50
L Subcallosal cortex	-4.41	22	-12	22	-12
L Inferior Temporal Gyrus	-5.59	25	-54	-60	-10
R Cerebellum	-4.50	65	36	-44	-42
L Frontal Orbital	-4.40	29	-28	24	-22
L Superior Frontal	-4.14	29	-4	24	66

Table 7: Changes in Connectivity Patterns of Right NAcc while Participants Listen to Highly Rewarding Music (\$2 bid) as Compared with Music that was not Purchased (\$0 bid). Partial least squares analysis reveals connectivity of a seed placed at the peak cluster that best predicted reward value: NAcc (x=12, y=8, z=0) during processing of music that individuals consider highly desirable (\$2 bids) compared with music they do not desire to hear again (\$0 bids). Positive correlations reveal regions that show higher connectivity with the NAcc during processing of music excerpts on which participants later bid the maximum amount. Negative correlations showed decreased connectivity in the \$2 versus \$0 comparison, revealing the regions that showed stronger connectivity with the NAcc during processing of music excerpts on which participants did not purchase. It should be noted that NAcc activity during the minimum bid (\$0) condition was significantly lower than the maximum bid (\$2) condition. Clusters with a volume of larger than 20 voxels and bootstrap ratio of 4.0 are reported here.



Figure 19: Changes in Connectivity Patterns of Right NAcc while Participants Listen to Highly Rewarding Music (\$2 bid) as Compared with Music that was not Purchased (\$0 bid). Axial slices reveal results of a partial least squares analysis to connectivity of a seed placed at the peak cluster that best predicted reward value: NAcc (x=12,y=8,z=0) during processing of music that individuals consider highly desirable (\$2 bids) compared with music they do not desire to hear again (\$0 bids). The largest differences can be observed in the superior temporal gyri, bilaterally, suggesting that the connectivity of these regions with NAcc best predicts whether an excerpt of music is considered highly desirable during listening. For list of other connectivity changes see Table 7.

4.6. Discussion

Our results reveal important dissociations in reward-related processes, summarized as follows: (i.) A network of regions thought to be involved in incentive salience, namely the insula, dorsal ACC, mesolimbic striatum, and temporal pole (Seeley et al., 2007) was recruited during the processing of desired items, but only the mesolimbic regions (particularly the NAcc) demonstrated activity proportional to the reward value of the stimulus. (ii.) Primary and secondary auditory regions were active in response to music listening compared with silence, and showed enhanced connectivity with the NAcc when participants heard music that they considered highly desirable. (iii.) While a number of key regions involved in reward processing and valuation, namely the OFC, VMPFC, and amygdala (O'Doherty, 2004) were equally active during processing of all stimuli regardless of reward value, they also showed enhanced patterns of connectivity with the NAcc as reward value for the individual increased. This suggests that interaction between the NAcc and both sensory and limbic regions gives rise to the rewarding responses to music.

We show that online consumption of a desirable item (as measured by a monetary bid) involves increased activity in the dorsal and ventral striatum, dACC, insula, premotor area (BA6/8), and the temporal pole. These findings are consistent with studies using other types of stimuli and tasks involving reward, salience, and purchasing (Haber & Knutson, 2010; O'Doherty, 2004). However, as an important novel contribution, our findings show that amongst this network only the right NAcc and dorsal striatum are directly related to reward value of the items during real-time processing of musical stimuli, and not just related to economic purchasing decisions. These areas were the same regions that showed dopamine release in a ligand-based neuroimaging study (Salimpoor et al., 2011), in which dopamine was released during the anticipation and experience of peak pleasure moments with highly familiar music. The current results demonstrate that dopamine activity in the previous study was unlikely to be accounted for solely by anticipation of specific episodic events, and likely depends on a form of implicit anticipation that is not necessarily related to explicit knowledge of how the music will unfold, since that information was not available to participants in the current study. In sum, taken together, these results support the model whereby dopaminergic reward prediction signals in response to musical sequences give rise to the rewarding sensation of music.

The second important finding is that the desirability of the music is not specifically related to increased activity in auditory cortical areas, but rather to the enhanced interactions between these and striatal areas involved in assessing positive prediction errors (McClure, Berns, & Montague, 2003; O'Doherty, 2004;

Pessiglione, Seymour, Flandin, Dolan, & Frith, 2006). Moreover, while activity in areas involved in valuation of stimuli (e.g., VMPFC and amygdala) does not predict reward value, the interaction of these regions with the striatal areas does. Therefore, the findings here suggests that auditory cortices, VMPFC, and amygdala are involved in sensory processing of stimuli irrespective of reward value, and that the interaction between NAcc and these areas determines reward value to the individual.

Collectively, these results suggest that our appreciation of new music is likely to be related to (i) highly individualized accumulation of cortical stores of auditory information based on previous listening experiences, (ii) the corresponding temporal expectations that stem from an implicit understanding of the rules of music structure and probabilities of the occurrence of temporal and tonal events, and (iii) the positive prediction errors that result from these expectations. This conclusion is consistent with theories of influential musicologists that emphasize temporal expectations as one of the main dimensions resulting in the affective impact of music (Huron, 2006; Lerdahl & Jackenodoff, 1977; L. B. Meyer, 1956). Here, both dorsal and ventral striatal regions were involved in these interactions whereas in our previous study (4) the two structures were temporally dissociated according to anticipation versus experience of peak pleasure. The present finding is consistent with the idea that during music listening there are ongoing, possibly overlapping, processes of expectancy and evaluation as musical events unfold, thus giving rise to activity in both striatal regions.

Appreciation of music is abstract to the extent that it does not involve a concrete and tangible reward, but rather a combined sensory and cognitive experience that can manipulate affective responses. The present data provide important new evidence that show robust interactions between sensory and affective systems: the subcortical regions work in concert with the auditory sensory cortices to establish a potentially rewarding stimulus that is being experienced for the first time as desirable. The auditory cortices are involved in auditory sensory memory and imagery, extraction of sound relationships, and

discrimination and organization of sound patterns (Zatorre & Zarate, 2012). These cortical stores may contain templates of previously heard sounds, making them an ideal location for feedback regarding predictions in temporal unfolding of music, which in combination with the NAcc, can contribute to the rewarding nature of musical sounds. Moreover, this result is not merely an attention effect since the STG is equally active during music listening regardless of how much individuals were willing to pay; instead, cortical activity becomes correlated with NAcc activity when items are considered more rewarding, compared to those that are not purchased. Further support linking musical reward with temporal expectancies and positive prediction errors comes from the finding that highly desirable items are marked by enhanced NAcc connectivity with the premotor areas (BA 6/8), operculum, and pars opercularis and triangularis regions of the IFG that represent the right hemisphere homologue of Broca's area and are thought to be involved in harmonic expectancy and processing structure in music (Koelsch, 2011). As these frontal areas are more generally involved in attentional processes, sequencing, and working memory, and are also connected to the STG (Petrides & Pandya, 2002b), they are in prime position to integrate auditory information over time and form syntactic predictions. Music processing also involves sensory-motor interactions coupling auditory with premotor and frontal regions, a link which has also been proposed as related to musically elicited emotion (Zatorre et al., 2007).

Dopamine is involved in incentive-based learning. Our data suggest a mechanism through which dopaminergic regions in the mesolimbic areas interact with sensory coding, possibly serving as a learning process when new sound patterns are considered rewarding to an individual. Through the temporal dimension, previously neutral cues – tones and other sounds that have no independent reward value – interact with higher-order cognitive brain regions to gain incentive significance, which then influences sensation, perception, and affective regions in the brain and impact behavioural decisions or desirability of the items.

Chapter 5: Discussion

5.1 Overview

The collection of studies presented in this thesis were designed to test a number of hypotheses (as outlined in Sections 1.7) and to investigate and elaborate on the idea that rewarding responses related to music listening represent an abstract form of pleasure that involves integration of the reward circuits of the brain with sensory, affective, and cognitive processes, some of which involves neural circuitry unique to humans.

The hypotheses that we tested can be categorized into four main themes: (1) The relationship between pleasure and emotional arousal, (2) the relationship between emotional arousal and dopamine release in the brain, (3) temporal distinctions in dopamine release and implications for music processing, and (4) neural interactions that give rise to rewarding responses during music listening. For the purposes of discussion, we have categorized the findings according to their contributions to the literature.

5.2. Emotional arousal underlies pleasurable responses to music.

5.2.1. A direct link between emotion and pleasure. The main question we aimed to examine was: Why is music pleasurable? We begin by testing our first hypothesis that the pleasure individuals experience to music is related to emotions induced by the music. This hypothesis is based on prominent ideas of music and psychology, almost all of which suggest a role for emotional enhancement during music listening (see Section 1.5.1). In the first experiment (Chapter 2), we asked participants to rate their experience of pleasure continuously while they were listening to self-selected music and assessed any changes in emotional arousal, measured objectively through ANS activity. The results revealed a robust positive correlation between online increases in self-

reported pleasure and simultaneously measured increases in ANS activity, including increases in heart rate, respiration rate, electrodermal skin response, and decreases in peripheral temperature and blood volume pulse amplitude (Figure 4). These physiological reactions, related to the sympathetic branch of the nervous system and implicated in "fight or flight" responses (Cacioppo et al., 2007) and thought to be automated and difficult to control, and therefore believed to be reliable measures of emotional arousal.

5.2.2. Top-down interactions lead to emotional arousal. Our results further demonstrate that two people can show very different psychophysiological responses to the same piece of music depending on how much they liked that piece. For example, while many participants rated Samuel Barber's Adagio for Strings as a calming, "neutral", or "boring" piece of music, a number of people showed strong ANS arousal to the excerpt and rated it high on pleasure. Importantly, there were no significant psychophysiological changes for participants who did not find the pieces pleasurable during the same time frames where sympathetic nervous system activity increases were observed with participants who found the music pleasurable. This finding provides strong support for the claim that musical pleasure is tightly correlated with emotional arousal. It also further demonstrates that psychophysiological changes were over and above bottom-up effects related to psychoacoustical parameters of the music, which would have been consistent across all individuals, suggesting a role for topdown influences that interact with incoming auditory information to shape our emotional responses to music.

5.2.3. Implications. The results of this study provided direct evidence for the long-standing proposition that the pleasure experienced in response to music is related to the emotional arousal felt in response to music, an important initial step in understanding why music is pleasurable. This is further consistent with brain imaging results that have found activity increases in regions of the brain implicated in both emotion and reward processing (see Section 1.6.1).

This study has additional implications for music psychology, as it helps explain why some individuals may enjoy listening to negatively valenced (e.g., sad) music. In our study, participants reported many of their musical pieces as "sad", and "intending to create sadness", but still reported feeling pleasure to them. Consistent with our hypothesis presented in Section 1.5.3, individuals may be more interested in experiencing the emotional arousal induced by the music, which may be pleasurable, rather than actually feeling depressed as a result. This finding contributes to an ongoing debate in the literature about whether music is able to induce "real" emotions (similar to those experienced in everyday life towards specific objects) (Kallinen & Ravaja, 2006; Konecni, 2005, 2008; Zentner et al., 2008) or not. While a detailed review of this literature is beyond the scope of this thesis, our contribution to this literature is that "sad" music may induce a pleasurable sadness, which may be different from feeling sad in real life (e.g., if your dog has died) (also see Huron, 2011). As discussed in Section 1.5, one reason for this may be that individuals are feeling the emotional arousal associated with an emotion, without the impact of any consequences, typically associated with emotions experienced in "real life".

While there is little question that music can induce powerful emotions (Section 1.5), we now have evidence that these are directly linked to pleasure. Next we turn to the mechanisms through which emotional arousal can become rewarding.

5.3. Intense emotional responses to music lead to dopamine release in the mesolimbic regions of the brain, namely NAcc.

Once the link between pleasure and emotional arousal was established, we proceeded to the next hypothesis, to investigate whether emotional responses to music could result in dopaminergic activity in the reinforcement circuits of the brain, suggesting a mechanism through which these responses could be considered rewarding. The idea that the rewarding responses to music may be tapping into the dopaminergic reinforcement circuitry in the brain is not a new one; there is an abundance of references in popular culture comparing the "highs" from music to that of sex and drugs (e.g., "sex, drugs, and rock and roll!"). The dopaminergic systems initially evolved presumably to give an organism a sense of

pleasure or reward and thereby reinforce adaptive behaviours. Yet, through a man-made twist in evolution, humans learned to stimulate this system through other means more potently and efficiently. Many natural and synthetic drugs of abuse (e.g., cocaine and amphetamines) specifically target this system, increasing dopamine to create feelings of intense euphoria (see Section 1.1.3). The possibility that an aesthetic stimulus such as music may be naturally targeting this system has important implications for understanding why music gives such pleasure.

5.3.1. Striatal dopamine release in response to music. A number of previous studies have found changes in blood oxygenation or blood flow in mesolimbic regions of the brain in response to music (see Section 1.6). However, as there are a number of neurotransmitters that are released in these areas, it was not possible to determine whether dopamine was involved. Using [11C] raclopride PET we provided the first empirical evidence that listening to highly emotional music can lead to dopamine release in the mesolimbic striatal areas (Figure 12). These findings demonstrate that an aesthetic stimulus, such as music, can naturally target the dopaminergic systems of the brain that are typically involved in highly reinforcing and addictive behaviours. This finding has important implications for neuroscientific and evolutionary theories of music, contributing to our understanding how music can be reinforcing and why it has persisted through cultures and generations.

5.3.2. Neuroanatomical distinction in the stiratum. A noteworthy finding was that while dopamine binding was found in both the dorsal and ventral striatum, dopamine release in the NAcc (ventral striatum) was positively correlated with emotional arousal (i.e., participant reports of the intensity of the chills response), and dopamine release in the caudate (dorsal striatum) was positively correlated with the number of chills experienced. This finding hinted at the possibility that these two regions might be contributing to different aspects of the emotional and pleasurable responses experienced to music.

5.3.3. Peak emotional experience (Chills) is associated with dopamine release in ventral stiratum. The analysis of the combined ligand-based PET and fMRI data revealed that precisely during the experience of chills, the area that shows hemodynamic activity and dopamine release is the NAcc (Figure 13). This is a significant finding as this area is most connected to limbic and paralimbic regions in the brain (Figure 2), implicated in emotional processing, thereby providing strong support for the link between emotion and reward during music listening. This finding is strengthened by two additional results of the study: (1) the self-reported intensity of the chills (peak measures of emotional arousal) was correlated with degree of dopamine binding in this area (Table 4) and (2) self-reported increases in pleasure throughout music listening were parametrically related to degree of dopamine binding in this region (Figure 15).

5.3.4. Implications. These findings have important implications for the fields of neuroscience and aesthetics, as they suggest that an aesthetic stimulus without any clear survival value is able to target ancient reward circuitry that has evolved to reinforce adaptive behaviours. Moreover, this stimulus is entirely abstract in that it does not produce a tangible reward, but rather a cognitive or intellectual reward that may be uniquely experienced by humans, perhaps fundamental to human nature (also see McDermott & Hauser, 2005; Stevens, 2012).

The results of our study further reveal the neuroanatomical circuitry that underlies the pleasurable nature of intense emotions with higher specificity than ever before. It is noteworthy that previous studies have found dopamine binding in the same regions (NAcc) while participants consume highly addictive dugs, such as intranasal cocaine (Cox et al., 2009). Perhaps music provides a natural way of involving this system, with implications for music therapy and addiction research.

5.4. "Anticipation" and music

As outlined in Sections 5.2 and 5.3, listening to music can impact emotional arousal, and intense emotional arousal can lead to dopamine release in the mesolimbic regions of the brain. The next question revolves around the mechanisms that make this possible. How are emotions formed in response to music and how does this target the dopaminergic system?

To answer this we turn to music theorists, where the most prominent theories of how music induces emotional responses relate to the idea that music creates a sense of anticipation (see Section 1.5.2). This is highly relevant to the finding that dopamine is involved in pleasurable responses to music, as dopamine is primarily implicated in identifying reward-related cues and anticipating reward outcomes (see Section 1.1.4).

5.4.1. Dopamine release during anticipation of peak pleasure. We therefore examined whether anticipation may play a role in dopaminergic activity during music listening. During the fMRI data analysis, an "anticipation" period was defined as the time period immediately preceding chills. This was based on psychophysiological measurements from the first study (Chapter 2), which revealed that approximately 15 seconds preceding the chills moment ANS activity shows significant differences in most participants (Figure 6).

These results revealed another important finding: dopamine was also released during the anticipation phase, in a separate anatomical region, the caudate nucleus. As such, it is not just during the peak emotional moments that dopamine is released, but also their anticipation. Dopaminergic neurons fire to reward-predicting stimuli (see Section 1.1.4). Unlike many other rewards, the consummatory phase of music does not involve a concrete object, but an abstract experience. Our findings suggest that anticipating an abstract aesthetic stimulus can also target the dopaminergic system.

Caudate and anticipation. Importantly, the caudate is considered to be a part of the "associative loop" of the striatum (Alexander, Crutcher, & De Long, 1990; Parent & Hazrati, 1995) and has intricate anatomical connections with a number of cortical regions including the frontal cortex (Figure 2). Further

support for the dopaminergic link between the caudate and frontal lobe comes from functional connectivity studies, where decreased dopamine availability impairs fronto-striatal connectivity during tasks that recruit frontal lobe function (Nagano-Saito, Leyton, Monchi, He, & Dagher, 2008). A meta-analysis of 126 fMRI and PET studies showed that the caudate shows functional connectivity to the dorsolateral prefrontal cortex (DLPFC), ACC, inferior frontal gyrus (IFG), and medial prefrontal cortex during performance of many frontal lobe function tasks (Postuma & Dagher, 2006), further confirmed by transcranial magnetic stimulation studies (Monchi, Petrides, Strafella, Worsley, & Doyon, 2006).

As discussed in Section 1.2, the frontal lobes, particularly the prefrontal cortices, are involved in executive function tasks, such as temporal maintenance of information in working memory and relating information back to earlier events, temporal sequencing, planning ahead, creating expectations, anticipating outcomes, and planning movement towards the reward. These cognitive processes are highly significant during musical processing, and it would be consistent that striatal circuits would provide a mechanism for the temporal nuances that give rise to feelings of anticipation and craving, reinforced by dopamine release in the caudate.

Additional support implicating the caudate in anticipation comes from other studies which implicate the dorsal striatum in anticipating desirable stimuli, when the behaviour is habitual and expected (Belin & Everitt, 2008; Boileau et al., 2006; Wong et al., 2006). In this way, the signals that predict the onset of a desirable event can become reinforcing per se. In the case of music, this may include a sound sequence that signals the onset of the highly desirable part of the music. Previously neutral stimuli may become conditioned to serve as a cue signalling the onset of the rewarding sequence. The dorsal striatum has also been implicated in processing syntactically unexpected events during music (Koelsch, Fritz, et al., 2008; Tillmann, Janata, & Bharucha, 2003) suggesting that it might be involved in keeping track of temporal unfolding of sounds events. It is important to note however that the NAcc has also been demonstrated to play a role in anticipation with other types of stimuli, such as monetary rewards (Knutson, Adams, et al., 2001; Knutson & Cooper, 2005). The functional roles of these structures are therefore not simply attributable to any one dimension, but are dynamically altered as a function of a variety of factors, not all of which have yet been identified.

5.4.2. Expectations and anticipation during music listening.

Consistently, the principal affective impact of music is thought by many music theorists to be elicited via the creation of expectancies through temporally-rooted phenomena, such as delay, anticipation, and surprise (Cooper & Meyer, 1960; Huron, 2006; Lerdahl & Jackenodoff, 1977; Lerdahl & Jackenodoff, 1999; Lerdahl & Krumhansl, 2007; L. B. Meyer, 1956; Monelle, 1992). More specifically, as individuals listen along with music, temporally mediated patterns of sound are recognized and expectations are generated, which then lead to predictions and a sense of anticipation. Acoustical patterns are organized according to rules and conventions that are specific to particular genres, styles, and cultures. Explicit or implicit knowledge of these rules, allows for pattern completion and predictions of how sounds are organized through the tonal and temporal dimensions.

Empirical evidence for this model comes from a large body of music cognition research showing that listeners form temporally-based expectations when they are listening to music (Jones, 1990; Jones, Johnston, & Puente, 2006; Krumhansl, 1990; Schmuckler, 1989; Tillman, 2005). The first line of evidence shows that when listeners are asked to indicate whether pitches of a melody go up or down, they are faster to respond when the melodic contours conform to their expectations (Aarden, 2002; Margulis & Levine, 2006). A second line of evidence shows similar results with studies that examine expectations implicitly and through priming paradigms (J. Bharucha & Stoeckig, 1986; Bigand & Pineau, 1997; Tillmann, Bigand, & Pineau, 1998). Third, expectations may be culturally-dependent. For example, Western listeners were better at identifying changes in Western scales compared with Javanese scales (Lynch, Eilers, Oller, & Urbano, 1990), presumably because previous exposure to the familiar scales made them more predictable. Consistently, even when listening to Western music the

participants performed best on typical pitch sets (e.g., major scales) as compared with those that were less common (e.g., augmented scale) (Lynch & Eilers, 1992). Finally, changes in psychophysiological responses such as electrodermal activity and heart rate have (Koelsch, Kilches, Steinbeis, & Schelinski, 2008; Steinbeis et al., 2006), hemodynamic responses (Koelsch, 2006), and event-related potentials (Garza Villarreal, Brattico, Leino, Ostergaard, & Vuust, 2011; Koelsch, Fritz, et al., 2008; Leino, Brattico, Tervaniemi, & Vuust, 2007; Loui, Grent-'t-Jong, Torpey, & Woldorff, 2005; Patel, Gibson, Ratner, Besson, & Holcomb, 1998; Rohrmeier & Koelsch, 2012) are associated with incongruous chords violating the rules of harmony. These results provide strong evidence that people form continuous expectations of how the next sound will unfold before it is heard. But how do expectations and anticipation translate to emotional arousal?

5.4.3. Expectations and anticipation, and emotional arousal: A role for dopamine. While many organisms are likely to make predictions about reward-related phenomena, humans, in particular, would be expected to make more complex predictions due to more advanced cognitive abilities (Suddendorf, 2006). These would be largely expected to depend critically upon the highly evolved prefrontal cortices, with tight connections to the lower-order mesolimbic regions responsible for anticipation or perhaps craving of a reward. It is likely that once these anticipations are met (e.g., the listener feels a sense of fulfillment after hearing the sound events they expected or craved), dopamine is released in the NAcc via dopaminergic pathways from the VTA (Figure 1), which is specifically thought to be involved in prediction errors (Schultz et al., 1997; Hollerman and Schultz, 1998; Bayer and Glimcher, 2005; Bayer et al., 2007). When an organism makes a correct prediction about its environment, the confirmation of that expectation results in zero prediction error. If the organism gets something better than expected, there will be a positive prediction error, and if it gets something less desirable than expected, there will be a negative prediction-error (Schultz et al., 1997; Sutton & Barto, 1998). It has been wellestablished that positive prediction errors can be measured in the NAcc (McClure et al., 2003; O'Doherty, 2004; Pessiglione et al., 2006), where positive predictionerrors lead to an increase in dopamine release and negative prediction-errors inhibit dopamine release. This is ultimately thought to serve as a learning signal. Another important point is that the degree of uncertainty of a prediction also leads to dopamine release (Section 1.1.4). A less predictable outcome can results in more dopamine release than an outcome is certain and perfectly predictable. Moreover, the delay of an otherwise expected outcome can also lead to uncertainty, thereby creating increased anticipation and craving.

5.4.4. Expectations and anticipation, and emotional arousal in music. Prediction signals in the striatum can further apply to the temporal expectations created during music listening, which can be subdivided into several different classes.

Pattern recognition and emotional arousal: what to listen for, and when to listen for it. Listening to music involves tracking a series of sound events over time. As humans are experts in pattern recognition, constant predictions would be formed, creating a sense of anticipation. Moreover, unexpected events in the music can lead to tension, which can then lead to emotional arousal (e.g., Steinbeis et al., 2006). This tension in turn can be followed with a resolution or prediction confirmation and a sense of completion. To explain how assessments of musical patterns can trigger basic neurobiological responses and lead to emotional arousal, Huron has proposed the ITPRA model, which involves the cognitive processes of Imagination, Tension, Prediction, Reaction, and Appraisal. These ideas represent an expansion of a theory first proposed by Leonard Meyer six decades ago, in his book *Emotion and Meaning in Music* (L. B. Meyer, 1956).

In Huron's model, Prediction is based on implicit knowledge of how music is formed based on previous experiences (see Statistical Learning, below) and Imagination and Tension are related to anticipation of an expected event. Imagining an event that will happen in the future has an emotional aspect relating to motivation, and intellectual aspects relating to uncertainty and an assessment of the likely outcomes and their valences. The feelings of uncertainty can trigger Tension, which can then prime survival responses in the autonomic nervous system, such as fight or flight, to prepare for anticipated events. Reaction and Appraisal related back to the Prediction, and the outcome of the events.

Composers can strategically manipulate musical structure as an attempt to achieve a response in the listener (Huron, 2006; Krumhansl, 1990; Lerdahl & Jackendoff, 1983; L. B. Meyer, 1956; Narmour, 1990; Schoenberg, 1978). For example, structural variations in frequency, timing, intensity and timbre can manipulate the expressivity of a piece of music by shaping expectations through compositional devices such as suspension, delay and retardation, deceptive or evaded cadences, or applied dominants (Clarke, 1988, 1989; Palmer, 1997; Repp, 1990, 1996; Rohrmeier & Koelsch, 2012; Sloboda, 1983).

Expectations generally relate to what will happen, and when it will happen. The part of *what* event to expect involves predictions that relate to which notes the listener expects to hear next and the boundary of a phrase. For example, Western listeners may develop expectations based on step inertia – a tendency for notes in a melody to move in the same direction, pitch proximity – the tendency for notes to be close to each other, melodic regression – the tendency for notes far from the mean note of a melody to be followed be followed by notes that are closer to the mean note of the melody, and melodic arches – the tendency for a melodic phrase to rise in the beginning and fall towards the end of a phrase (Huron, 2006; Margulis, 2005; L. B. Meyer, 1956; Narmour, 1991; Schellenberg, 1996). Additional expectations of chords or harmonic structure follow based on a lexicon of tonal chords.

The part of *when* to expect an event, involves matching the structure of the music heard with metrical or rhythmic templates that can be extrapolated in the future. Timing may be explicit or implicit: explicit timing refers to deliberate estimations of discrete duration for comparison with a previously memorized standard, and implicit timing is engaged when sensorimotor information is temporally structured to predict duration of future events (Coull, Cheng, & Meck, 2011; Coull & Nobre, 2008). A number of theories have been proposed to account for how timing of musical events can impact our expectations (Large & Jones, 1999; Large & Palmer, 2002; Rohrmeier & Koelsch, 2012), which may

also impact emotional arousal (e.g., tempo may be slowed to delay the expected resolution.) It is important to note here that the dorsal striatum has been implicated in rhythm and timing in numerous brain imaging paradigms (Coull, Vidal, Nazarian, & Macar, 2004; Dhamala et al., 2003; Ferrandez et al., 2003; Grahn & Rowe, 2012; Lewis et al., 2007; Nenadic et al., 2003; Penhune, Zatorre, & Evans, 1998; Ramnani & Passingham, 2001; Schubotz & von Cramon, 2001). There is evidence that nigrostriatal dopamine (Figure 1) may be mediating this process, as individuals with Parkinson's Disease show impairments with tasks involving timing of isochronous intervals (Harrington, Haaland, & Hermanowitz, 1998; O'Boyle, Freeman, & Cody, 1996), and tasks involving beat-based rhythm discrimination (Grahn & Brett, 2009). Furthermore, dopaminergic treatment improves motor timing (O'Boyle, 1997; O'Boyle et al., 1996; Pastor, Artieda, Jahanshahi, & Obeso, 1992) and time perception (Malapani et al., 1998). Expectations associated with rhythm and beat constitute an important component of temporal predictions in music; for further reading on this and related topics, see (Coull et al., 2011; Grahn, Parkinson, & Owen, 2008; Large & Jones, 1999; Large & Palmer, 2002; Rohrmeier & Koelsch, 2012; Zatorre et al., 2007)

Importantly, expectations may be created on a micro-level, based on local events such as note-to-note and phrase-to-phrase expectations, and also on a macro-level, relating to the larger structure of the music (J. Bharucha & Stoeckig, 1986; L. B. Meyer, 1956; Palmer & Krumhansl, 1990; Zald & Zatorre, 2011). What is common to the expectations is that they are goal-directed, and aimed towards achieving a resolution to complete a certain pattern. This is further relevant for the role of dopamine, as it is released in response towards achieving goal-directed rewards, particularly when there is an element of high desire, high anticipation (delay of gratification), and when the outcome is better than expected (e.g., element of pleasant surprise, or positive prediction error) (Section 1.1.4).

As expected, different styles of music will utilize different features towards manipulating expectations to maintain the listener's attention and interest. For example, popular music often employs abrupt breaks or changes in orchestration, timbre or soundscape (Grewe, Nage, Kopiez, & Altenmuller, 2007;

Sloboda, O'Neil, & Ivaldi, 2001). These manipulations can delay macro-level resolutions (goals) in the music and create new sets of micro-level expectations. These structural manipulations may add new layers of cognitive predictions that may lead to enhanced dopamine activity.

Pattern predictability. While excessive predictability may not be desirable (see below), a number of studies have suggested that music is most appreciated when some level of predictability is present; this factor may explain why unfamiliar music is appreciated more after the first time it is heard (Green, Baerentsen, Stodkilde-Jorgensen, Roepstorff, & Vuust, 2012; Wilson, 1979). This effect is likely to be a result of enhanced ability to predict how the music will unfold, while still maintaining some level of novelty. Familiarity with a song that has been heard more than once relates to explicit knowledge of how the music will unfold, and will be discussed below. However, familiarity with a musical style may relate to more implicit expectations, even if the music has not been heard before. The concepts of predictability can be further extend to why individuals tend to seek out music from the genres they prefer as those are the styles that they are more familiar with. When selecting stimuli for the third experiment, we used music recommendation programs such as *Pandora* and Last.fm to select music that sounds acoustically and structurally similar to participants' preferences (see section 4.4: Methods), to ensure that some level of predictability may be present. This may be one reason why many individuals tend to understand and appreciate music from styles that they are most familiar with.

Excessive predictability. Excessive predictability may fail to maintain one's interest. Research with non-musical stimuli show that when the outcome of an event becomes too predictable, there is no longer an increase in dopamine release (Schultz, 1998), which may also explain why music that is heard frequently or is too simple and excessively predictable to begin with, may not be as pleasurable. The key is to create a constant interplay between adherence and deviation from typical convention, to allow for some level of predictability combined with uncertainty, or extensions in achieving resolution. More complex music is often best able to achieve this. Complexity may be one reason why large

works of classical music remain popular today whereas many popular songs that are not as complex have a tendency to drop out of fashion. Consistently, individuals with greater musical experience prefer more complex and less predictable pieces of music (J. D. Smith & Melara, 1990), possibly because they are better able to extract more complex patterns that lead to appreciation of the expectancies and their resolution.

5.4.5. The source of expectations and anticipation. If anticipation gives rise to emotional arousal while listening to music, what is the source of this anticipation? Is it the case that when people are explicitly familiar with a piece of music, that they know exactly when the peak pleasure moments are approaching (and perhaps even anticipating the pleasurable chills response)? Or is the anticipation also rooted in a more implicit understanding of the schematic rules of how musical sounds within a given culture are organized, based on many years of auditory experience?

Veridical and schematic expectations. Jamshed Bharucha applied the terms veridical and schematic to describe these forms of anticipation, respectively (J. Bharucha, 1994). According to Bhuracha, veridical expectations rely on knowledge of how a particular, known musical work unfolds. Schematic expectations are also related to musical syntax or style knowledge, and rely on an understanding of how music of one's culture unfolds in general. This concept relates largely to music theory and principles surrounding melody, harmony, and rhythm, generally acquired through listening to music over years. In other words, the implicitly acquired knowledge about rules and principles that surrounding the combination of discrete elements, in this case musical tones, into sequences (Patel, 2003). Importantly, veridical and schematic forms of expectations are not mutually exclusive, but omnipresent during listening to familiar pieces.

How can we determine which of these is underlying the pleasurable responses to music? While it would be extremely difficult to rule out schematic expectations, we can rule out veridical expectations by using new music that people have not heard before. As such, listeners would have no episodic

associations with the music and any temporal expectations that are created would be based on their schematic expectations.

5.5. Neural Interactions that Give Rise to Rewarding Responses:

The next study examined the neural correlates of processing pleasurable "new" music that had not been heard before, to rule out any possibility of veridical expectations. We predicted that the anticipatory responses that listeners experience when listening to music are not exclusively related to familiarity with music, but largely related to schematic expectations and predictions based on knowledge of musical structure. We proposed that if participants show similar activity in the striatal regions as that of the second experiment, which used highly familiar music, we can rule out the possibility that anticipatory responses resulted from veridical expectations due to explicit knowledge of how the music would unfold.

More importantly, another main goal of this experiment was to examine the neural processes that make a piece of music rewarding, based on the first time that it is heard. We were particularly interested in examining the interactions between reward-related areas with various regions in the brain thought to be involved in processing different aspects of music, and better understanding how these interactions are related to pleasurable responses.

Our results demonstrated that neural activity during initial listening that best predicted whether a piece of music was considered desirable (i.e., a bid higher than \$0) showed increased activity in the insula, dACC, striatum, and the right temporal pole (Figure 17A). However, a parametric analysis revealed that amongst these regions, on the activity in the NAcc and caudate were related to reward value of the stimuli (i.e., how much individuals were willing to bid) (Figure 17B). It should be noted that the regions that showed increased activity while participants listened to any music that they found desirable compared to those that they did not bid on is highly consistent with a number of other studies that have found similar activity with reward-related stimuli (Seeley et al., 2007), and have been implicated as a part of a saliency network. As such, our results provide the important contribution that activity in these areas may not be directly related to the value of a reward, but more generally related to salience associated with a reward, or economic purchasing decision in this experiment. Consistently, Knutson and colleagues have found increased insular activity when individual consider prices associated paying for a potentially rewarding stimuli, suggesting that this activity is implicated in economic decision making, but not directly related to the reward value of the item (Knutson, Rick, Wimmer, Prelec, & Loewenstein, 2007).

A finding of high significance was that the best predictors of music that individuals found highly rewarding was the amount of activity in the NAcc and caudate (Chapter 4: Figure 17), similar to the results of our previous study (Chapter 3: Figure 13) which demonstrated dopamine release in these regions. Importantly, both the caudate and NAcc (areas previously implicated in "anticipation" and "prediction error" respectively) were active, providing strong support that listening to new music does involve expectations and predictions about how the sound events will unfold. More importantly, parametric analyses revealed that NAcc activity was a much better predictor of whether a piece of music would be highly desirable, suggesting that as individuals are listening to music positive prediction errors (corresponding to increased activity in the NAcc) seem to be the best predictor of whether that music will be considered rewarding. For a better understanding of what these auditory predictions are based on, we examined NAcc connectivity with other regions in the brain (as discussed in the next section).

Our findings also have important implications for better understanding the dynamic roles of dorsal and ventral striatum (see Section 5.4.1). The results of the second and third study collectively suggest that the NAcc (ventral striatum) may be more related to the experience of new rewards and positive prediction errors, such as with novel music used in the third study, and as rewards become more habitual or expected their anticipation may lead to increased dopamine release in the dorsal striatum, such as with highly familiar (but still pleasurable) music used in the second study. This possibility is highly consistent with the

results of a study by Boileau et al., (2007), where individuals administered amphetamines showed activity in the NAcc, and when re-examined in two additional sessions (14 days and again one year later) dopamine release progressively extended to the dorsal caudate and putamen. These results provide support for the idea that initial experience with rewarding situations (in this case, positive prediction errors during music listening) lead to dopamine release in the NAcc and as experience with a reward increases and a rewarding situation becomes more habitual or predictable (as music becomes more familiar), dopamine release may also be observed in the dorsal regions during anticipatory moments, as certain sound sequences trigger the onset of upcoming peak events in the music. It is likely that dopamine release in the dorsal striatum may be related to preparation of motor responses towards obtaining an anticipated reward, as these areas are critical for goal-oriented movements (Badgaiyan, Fischman, & Alpert, 2007; Balleine & O'Doherty, 2010).

5.5.1. Integration of cortical and mesolimbic networks:

To examine our hypothesis that this subcortical regions work in concert with higher-order cortical regions to give rise to aesthetic pleasure, we implemented a multivariate procedure (partial least squares), to capture correlations in activity of multiple regions simultaneously. Our results showed robust changes in connectivity with a number of cortical areas when individuals listened to highly desirable music, namely the auditory cortices, VMPFC, OFC, amygdala, hippocampus, inferior frontal gyrus, amongst others. These results are highly significant as these regions are those that are involved in auditory perception, high-level temporal sequencing, emotional processing and valuation, and formation and retrieval of memories.

Areas involved in auditory perception. Perhaps the most interesting finding was the connectivity enhancements with the STG of the auditory cortices. These regions house the tonotopically organized primary auditory areas (Brodmann areas 41 and 42), encompassing Heschl's gyrus (Da Costa et al., 2011) and secondary or association auditory cortices (auditory belt), including

planum temporale (Wericke's area; Brodmann Area 22) (Galaburda & Sanides, 1980; Kaas & Hackett, 2000).

In our study, when participants listened to music both the primary and secondary auditory cortices showed increased activity, regardless of how rewarding they found the excerpts (Figure 18). However, when individuals listened to music that they found highly rewarding, the NAcc showed increased connectivity with large clusters encompassing the entire STG and surrounding regions in both the left and right hemispheres (Figures 18 and 19). This connectivity suggests an interaction between areas involved in forming rewardrelated predictions and the superior temporal cortex.

Proportions of the superior temporal cortex are involved in a wide range of auditory processing relevant to music, including processing pitch (Patterson, Uppenkamp, Johnsrude, & Griffiths, 2002; Zatorre, 1988), extraction of pitch relationships (Hyde, Peretz, & Zatorre, 2008; Johnsrude, Penhune, & Zatorre, 2000; Liegeois-Chauvel, Peretz, Babai, Laguitton, & Chauvel, 1998), encoding tonal patterns (McKenna, Weinberger, & Diamond, 1989; Samson & Zatorre, 1988) and melodies (Liegeois-Chauvel et al., 1998; Zatorre, Evans, & Meyer, 1994), categorical perception of musical intervals (Klein & Zatorre, 2011), auditory scene analysis and stream segregation (T. Griffiths & Warren, 2004), combining multiple auditory streams (Janata, Tillmann, & Bharucha, 2002), and short term memory for auditory information (Colombo, D'Amato, Rodman, & Gross, 1990). Importantly, the STG is responsible for storing templates of sound events that we have accumulated over the years, also known as the musical lexicon (Peretz & Coltheart, 2003; Peretz et al., 2009). Evidence for this idea comes from a number of structural and functional brain imaging study findings, as well as lesion studies, as discussed below.

Over five decades ago Penfield and Perot found that electrical stimulation of these regions in patients could elicit musical memories in the form of a musical hallucination (Penfield & Perot, 1963), suggesting that auditory information is stored in these areas. More recently, functional brain imaging studies show increased activity in the superior temporal cortex when individuals listen to familiar versus unfamiliar music (Groussard et al., 2010; Peretz et al., 2009). For example, Groussard and colleagues found greater STG activity when participants were asked to assess the familiarity of a piece of music (i.e., compare a new melody with those that they have stored in their semantic memory). They also found that this effect was more pronounced in musicians (Groussard et al., 2010) possibly because they are likely to have more elaborate templates of musical sound organization. Indeed, in this particular study musician did recognize more melodies. Other studies have also found that musicians show increased STG activity during music listening than non-musicians (Morrison, Demorest, Aylward, Cramer, & Maravilla, 2003).

If the STG does store information about auditory events and how they are organized, it would be expected that individuals with additional musical experience, exposure, or training would presumably have more elaborate templates of auditory information and thicker cortical matter in these areas. Consistently, structural brain imaging techniques show that individuals with greater music experience (i.e., musicians) show enlarged regions in the superior temporal cortex, including portions of Heschl's gyri (Bermudez, Lerch, Evans, & Zatorre, 2009; Gaser & Schlaug, 2003; Schneider et al., 2002), and planum temporale (Luders, Graser, Jancke, & Schlaug, 2004). Studies examining brainbehaviour relationships have found that the size of regions surrounding Heschl's gyri correlated with auditory skills (Foster & Zatorre, 2010; Hyde et al., 2009). Further, lesion studies of patients with temporal lobe damage show impaired music recognition abilities despite relatively intact low-level perceptual processing of musical input (Ayotte, Peretz, Rousseau, Bard, & Bojanowski, 2000; Eustache, Lechevalier, Viader, & Lambert, 1990; Peretz, 1996), including difficulty with retention of recently heard tonal information (Zatorre & Samson, 1991) and recognition of learned melodies (Samson & Zatorre, 1991, 1992).

Most recently, using advanced fMRI analysis techniques, a number of studies have found that specific patterns of activity in the STG can distinguish types of sound that an individual is listening to. For example, using multivoxel pattern analysis (MVPA), one study was able to distinguish whether an individual was listening to sounds of cats, female singers, or acoustic guitars based on patterns of STG activity (Staeren, Renvall, De Martine, Goebel, & Formisano, 2009). Another study used MVPA to demonstrate that the perceptual interpretations of phonemes that were physically identical, but subjectively ambiguous are represented in the STG (Kilian-Hutten, Valente, Vroomen, & Formisano, 2011). MVPA has also been used to demonstrate that changes in melodic contour (Lee, Janata, Frost, Hanke, & Granger, 2011) and timbral categorization (Casey, Thompson, Kang, Raizada, & Wheatley, 2011), and changes in emotional prosody (Ethofer, Van de Ville, Scherer, & Vulleumier, 2009) are detected in the superior temporal cortex. These studies provide strong evidence that the superior temporal cortex stores representational templates of previously acquired auditory information.

Finally, amongst the most convincing evidence that musical templates are stored in the STG are findings by Halpern and Zatorre, demonstrating that merely imagining a sequence of tones recruits this region in the brain (A. R. Halpern & Zatorre, 1999). Similar results have been demonstrated by others (Kraemer, Macrae, Green, & Kelley, 2005; see Zatorre & Halpern, 2005 for a review). In a recent study, the subjective vividness of auditory imagery as individuals imagined melodies was associated with activity in the superior temporal cortex (Herholz, Halpern, & Zatorre, 2012), reminiscent of Penfield and Perots study five decades ago, which demonstrated that increased stimulation of these regions can lead to auditory percepts.

Collectively these studies provide converging evidence that experience with musical sounds is processed in the STG, creating templates and rules of how sounds are organized, based on our own individual experiences. The connectivity enhancements of the NAcc with these regions suggests that implicit (schematic) expectations of the unfolding of temporal patterns when listening to music are based on stored templates of how musical sounds should be organized, based on previous experiences. These findings also suggest a mechanism whereby different people would have different preferences in music, as each individual has had individualized experiences with sound events in the past. It would be expected that individuals from the same age cohort who listened to similar music in their youth would have somewhat similar preferences to each other later in life.

Areas involved in high-level temporal sequencing. Music is merely a series of acoustical events organized over time. To appreciate music is to recognize these patterns. This process involves sequencing structural information, recognizing the underlying structure, and predicting sequential information (Janata & Grafton, 2003). These cognitive operations are high-level, and not limited to musical processing. For example, similar functions are required for processing language, or math, or other tasks that require hierarchical organization (Janata, Tillmann, et al., 2002; Koelsch, 2011). Consistent with this, there is some evidence that learning music capability may be related to improved syntax processing skills in children (Jentschke & Koelsch, 2009), and children who show language impairments also show abnormal music syntactic processing (Jentschke, Koelsch, Sallat, & Friederici, 2008).

Not surprisingly, these abstract operations involve the highly-evolved frontal cortices of the brain. Consistent with this, the results from our study also revealed increased connectivity of the NAcc with the right inferior frontal cortex, specifically within the pars triangularis (BA 45) and pars opercularis (BA 44). These regions correspond to the right hemisphere homologues of Broca's area (BA 44 and 45 of left hemisphere), and surrounding regions also implicated in processing language (Freidrich & Friederici, 2009; Makuuchi, Bahlmann, Anwander, & Friederici, 2009). The left IFG has been well demonstrated to be involved in processing structural aspects of language, for example tracking, sequencing, and organizing linguistic information over time (Friederici, 2002; Friederici, Rueschemeyer, Hahne, & Fiebach, 2003). There is also some evidence that the right hemisphere equivalent of these regions is involved in similar processes with music (Abrams et al., 2011; Levitin & Menon, 2003, 2005). The pars opercularis, in particular, has been implicated in processing melodies (Janata, Birk, et al., 2002; Zatorre et al., 1994), chord sequences (Garza Villarreal et al., 2011; Koelsch, Fritz, Schulze, Alsop, & Schlaug, 2005; Koelsch et al., 2002;

Maess, Koelsch, Gunter, & Friederici, 2001; Tillmann et al., 2003), and subtle instrumental and sung musical violations (Tillmann et al., 2006).

It is interesting to note that the IFG and STG are often co-activated (Abrams et al., 2011; Garza Villarreal et al., 2011; T. D. Griffiths, Johnsrude, Dean, & Green, 1999; Janata, Tillmann, et al., 2002; Koelsch et al., 2005; Peretz et al., 2009; Platel et al., 1997; Tillmann et al., 2006), possibly working in concert to process various aspects of music (also see Koelsch, 2006). A lesion study of a patient with damage to both the opercular regions and the temporal lobe showed intact abilities with simple music processing tasks, such as judging the direction of pitch changes and differences in melodic contour in short melodies, however, was unable to tell the difference between tonal and atonal musical pieces (Peretz et al., 1994). Additional evidence comes from studies of congenital amusics, in whom disruption of STG-IFG pathways has been observed (Hyde et al., 2007; Hyde, Zatorre, Griffiths, Lerch, & Peretz, 2006; Hyde, Zatorre, & Peretz, 2011; Loui & Schlaug, 2009). These findings further confirm that high-level mechanisms are required beyond those of basic auditory analysis for processing the structure in music. More recently it has been suggested that the auditory cortices may be important for detecting sequential scale patterns while the IFG may be responsible for hierarchical patterns (Garza Villarreal et al., 2011).

It is important to note that many of these processes are unique to humans and other primates cannot perform these cognitive operations, such as the ability to process phrase-structure grammar (W. Fitch & Hauser, 2004). Moreover, the patterns of neural activity observed during music listening suggest that a number of advanced cognitive operations are involved, including multiple forms of working memory, abstract sequencing, and semantic processing (Janata, Tillmann, et al., 2002). This provides additional support for the idea that only humans can appreciate music due to the high-level cognitive architecture that is required for processing this abstract stimulus.

Areas involved in emotional processing and valuation. First it is important to note that along with the auditory cortices, VMPFC, OFC, and amygdala designate the primary regions to which auditory information is relayed via the thalamus during initial stages of higher-order processing (Kaas, Hackett, & Tramo, 1999; LeDoux, 2000; Ongur & Price, 2000). It is important to note that consistent with this information, these four regions were also those that showed increased activity any time that participants were listening to music, regardless of reward value (Figure 18). However, while it is not surprising that the auditory cortex is a target of auditory information, the VMPFC, medial OFC, and amygdala are regions involved in emotional processing, particularly assigning reward-based value detection (Section 1.3.1).

Primate and human studies have found that the OFC is anatomically (Petrides & Pandya, 1988; Romanski, Tian, et al., 1999) and functionally (Frey, Kostopoulos, & Petrides, 2004) connected to the STG. This is of particular relevance since the OFC has been implicated in detecting novelty in relation to previous memories (Butter, 1964; Petrides, 2007), which may play a role in determining the value of new sound combinations heard for the first time. Most importantly, as outlined in section 1.3.1, the VMPFC and OFC regions are not only major components of the extended limbic systems involved in high-level emotional processing by integrating internal states and cognition, but also provide the main cortical inputs to the NAcc. Similarly, the amygdala, a major component of the limbic system, provides the main subcortical glutaminergic input to the NAcc. As such, these regions are ideally suited to integrate, evaluate, and make decisions about reward-related stimuli (Figure 2).

Not surprisingly, these three areas in have been implicated in working together to assign reward value to stimuli to aid in valuation decisions (Chib et al., 2009; O'Doherty, 2004; Plassmann et al., 2007). The critical connections between these regions during reward-related tasks has been demonstrated in a number of animal studies (Baxter, Parker, Lindner, Izquierdo, & Murray, 2000; Roberts, Reekie, & Braesicke, 2007; Schoenbaum & Roesch, 2005; Seymour & Dolan, 2008) and human neuroimaging studies (Hampton, Adolphs, Tyszka, & O'Doherty, 2007; O'Doherty, 2004). A recent meta-analysis found that the striatum, amygdala, and OFC, along with the insula were the areas most commonly showing activity in response to both food and drug cues during human brain imaging studies (Tang, Fellows, Small, & Dagher, 2012); although the insula may play a more general role in arousal during assessment of desirable stimuli. Numerous previous studies have found insular activity during reward related tasks (e.g., Malik, McGlone, Bedrossian, & Dagher, 2008; Malik, McGlone, & Dagher, 2011; Small et al., 2001), including ours (Figure 17A). However, as mentioned in section 5.5, insula activity was not directly related to the increasing reward value of the music (Section 4.5). The insula may be more generally related to a saliency network (Seeley et al., 2007) that is active when individual process reward-related stimuli.

Our study provides the important contribution that while the VMPFC, OFC, and amygdala were active during music listening as compared with rest, their activity was not specifically related to how rewarding a musical excerpt was to an individual. This confirmed that the encoding of stimuli were similar. However, the connectivity of each of these regions to the NAcc determined reward value of the items. In other words, these areas remained equally active during rewarding and non-rewarding conditions, most likely to make online assessments of valuation; however, they showed enhanced connectivity with the NAcc as conditions became more rewarding. This finding has important implications for better understanding how we make valuation decisions and how incoming information may interact with several key regions in a valuation network to assign reward value to environmental stimuli. Other studies have also reported increased medial PFC activity when individuals are exposed to stimuli, before making choices (Glascher, Hampton, & O'Doherty, 2009; Knutson et al., 2007), suggesting that this region may be maintaining the value of items to be carried forward to inform upcoming decisions. The findings of our study strongly support this claim as the VMPFC was consistently activated while individuals were maintaining the value of the heard items "online" before they had to make a decision about the reward value of the item. Furthermore, this activity was most connected to the NAcc when items were considered highly rewarding.

Areas involved in memory formation and retrieval. In addition to cortical areas, the NAcc also shows increased connectivity with the hippocampus as music

becomes more valued. This finding demonstrates that even music that individuals have not heard before can involve recruitment of areas involved in memory retrieval (Henke, 2010; Szapiro et al., 2002), and most importantly, this pattern of activity underlies reward-related responses to music. It is not clear whether this pattern of activity represents enhanced retrieval of familiar auditory patterns that sound similar to familiar music or encoding of novel auditory patterns into memory.

5.5.2. Role of familiarity, statistical learning, and source of individual differences. The connectivity results from the third study suggest that predictions are linked to information that is stored in auditory templates. Next, we turn our attention to how this information may have been stored in cortical templates.

Statistical learning. Huron (2006) and others (Pearce, 2005; Tillmann & McAdams, 2004) suggests that expectancies are based on statistical learning or patterns that we have become accustomed to due to their frequent contingent occurrence. In a series of studies, Saffran and colleagues demonstrated that infants form expectations of linguistic parings based on the likelihood of their cooccurrence, that is, their transitional probabilities (Aslin, Saffran, & Newport, 1998; Saffran, Aslin, & Newport, 1996; Saffran, Newport, & Aslin, 1996; Saffran, Newport, Aslin, Tunick, & Barruecco, 1997). As such, statistical regularities allow infants to discover word boundaries. A number of other similar studies have also confirmed that older children and adults possess statistical learning abilities that proceed automatically as a byproduct of mere exposure (Saffran, Johnson, Aslin, & Newport, 1999). Saffran and colleagues have further demonstrated similar results with non-linguistic musical sounds, where exposure to tonal patterns influenced subsequent expectations (Saffran, 2003; Saffran et al., 1999). Infants heard a string of tones consisting of six three-note 'figures', which were played consecutively such that infants heard a steady stream of pitches with no grouping cues to indicate that the sequences had been constructed out of threenote figures. Using a head-turning paradigm, the researchers then demonstrated that the infants had abstracted the three-note figures, based on their co-occurrence. The outcome of statistical learning through exposure is well demonstrated by the

surprisingly sophisticated abilities of even fairly young infants to discriminate tonal patterns and respond to music that is familiar (Tranor, 2012).

Statistical learning and music. The concept of statistical learning has been carried forward to postulate that exposure to a certain repertoire of sound sequences throughout an individual's life can shape their expectations based on how statistically likely it is that one sound will follow another (Huron, 2006). Huron refers to this as "neural Darwinism", and suggests that neural representations of various musical events compete with each other regarding the prediction of ensuing events. In other words, based on acquired knowledge of frequencies and co-occurrence of certain sounds (tones, chords, and keys), expectations of which sounds are most likely to occur next, and when they should occur (Krumhansl, 1990; Tillman, Bharucha, & Bigand, 2000). For example, within a scale of tones, some tones tend to occur more than others, and Huron argues that we develop expectations about tones that are most likely to occur as a function of their location within a tune. That is, we expect the last note tone to be the tonic because this has been statistically true in Western tonal music.

Through experiences with particular musical styles, incidental learning takes place as listeners internalize regularities in rhythm, melody, harmony, and other aspects of sound organization (Krumhansl, 1990; Large & Palmer, 2002; Large, Palmer, & Pollack, 1995). For example, chord changes have very different likelihoods in Baroque versus reggae music, which would necessitate a different schema or set of expectations to appreciate each style (Huron, 2006). These internalized templates of various genres and styles are subsequently used to integrate and organize musical sequences when one is exposed to music, and make relevant predictions about patterns in music (as reviewed in Section 5.4.4).

The strongest support for implicit learning of music structure through statistical learning comes from the fact that while formal musical training may make individuals explicitly aware of the rules that are involved in musical grouping, most individuals who have not had such a training are nonetheless able to enjoy music in general and form expectations in particular (as reviewed in Section 5.4.2). Furthermore, consistent with the principles of statistical learning,

a number of studies have demonstrated that after exposing individuals to new styles of music, they are able to learn the new rules and become sensitive to violations based on expectations (e.g., Loui et al., 2005; Tillmann & McAdams, 2004). For example Loui and colleagues exposed participants to a novel and unfamiliar musical system by manipulating probabilities with which they heard novel chord progressions. Subsequent electrophysiological responses revealed that the newly acquired patterns elicited similar brain responses as those observed with well-learned Western music (Loui et al., 2005). These results are consistent with research on acquisition of artificial verbal languages (Friederici, Steinhauer, & Pfeifer, 2002).

Individual differences. It would follow from the above considerations that expectations will largely depend on the music people have heard throughout their lives, and perhaps other sounds, such as languages they speak or have been exposed to (Patel, 2003, 2008). This can explain why many individuals are more likely to appreciate music from their own culture, and may have difficulty predicting the direction of music from other cultures (Grewe, Nagel, et al., 2007a). However, once we gain some exposure to a piece of music, the predictive factor becomes more enhanced, which has the potential to make that piece more rewarding. These ideas begin to decipher the underlying reasons why different people appreciate different types of music. Each individual has their own unique set of musical schematic templates, depending on the musical sounds they have previously been exposed to throughout their lives. This experience will vary within different cultures, age cohorts, social groups, and other demographic factors. These templates or schemas could then impact their temporal expectations when listening to music and ultimately influence their appreciation of the music. This proposition would also explain why there are generational similarities in music preferences amongst those who were exposed to the same types of music in their youth.

5.5.3. Implications. In summary, our findings suggest that the mechanisms that make music rewarding involve an intricate interplay between the dopaminergic reward systems, involved in making and assessing predictions and a

number of other regions in the brain, including (but not limited to) the auditory cortices, where templates containing information about the relationships between various sounds are organized; the IFG, involved in tracking structure; the hippocampus, involved in memory formation and retrieval; the hypothalamus, insula, and ACC, involved in regulating emotional arousal and ANS function; the amygdala, involved in integrating emotions with reward value; and the VMPFC and OFC, involved in detecting internal states, assigning reward value to stimuli, and making value-based decisions about reward related stimuli.

Most importantly, none of these regions work in isolation, but rather integrate to perform a number of complex tasks that give rise to musical reward, including recognizing structure or patterns in sounds by comparing them to one's own reservoir of cortically-stored information about the relationships between sounds, forming temporal expectations about how sounds should unfold, some degree of predictability that allows for expectations to be formed, and some degree of uncertainty that creates tension or anticipation thereby creating a craving for a resolution. These processes can lead to emotional arousal and a sense of gratification or pleasure as the patterns are completed and resolution is achieved. These resolutions may happen on a micro- or macro-level, thereby maintaining consistent and ongoing expectations. In this way, music is largely about pattern recognition and therefore a cognitive reward, based on high-level sequencing and analyses of sensory and perceptual information. These advanced processes may explain why its appreciation is unique to humans.

After six decades of research, we have come a long way from Olds and Milner's studies, and know much more about the dopaminergic system. Sixty years ago we realized that merely by stimulating a bundle of nerve fibres to release dopamine in a particular part of the brain, rats were willing to work until they died. We now see how intricate this system can be in more complex organisms, extending connectivity to cortical regions involved in advanced perception, cognition, and emotion to derive pleasure and reinforcement through highly complex stimuli, and achieve many new forms of pleasure unknown to other organisms. Music is an excellent example of how advanced connectivity leads to emergent properties of the nervous system, such that an arrangement of sound patterns through time can influence high-level cognitive processes to produce a wide range of emotions and bring intense pleasure to humans worldwide.
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