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Trait anhedonia is associated with reduced reactivity and connectivity of mesolimbic and paralimbic reward pathways

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ABSTRACT

Anhedonia is the inability to experience pleasure from normally pleasant stimuli. Although anhedonia is a prominent feature of many psychiatric disorders, trait anhedonia is also observed dimensionally in healthy individuals. Currently, the neurobiological basis of anhedonia is poorly understood because it has been mainly investigated in patients with psychiatric disorders. Thus, previous studies have not been able to adequately disentangle the neural correlates of anhedonia from other clinical symptoms. In this study, trait anhedonia was assessed in well-characterized healthy participants with no history of Axis I psychiatric illness. Functional magnetic resonance imaging with musical stimuli was used to examine brain responses and effective connectivity in relation to individual differences in anhedonia. We found that trait anhedonia was negatively correlated with pleasantness ratings of music stimuli and with activation of key brain structures involved in reward processing, including nucleus accumbens (NAc), basal forebrain and hypothalamus which are linked by the medial forebrain bundle to the ventral tegmental area (VTA). Brain regions important for processing salient emotional stimuli, including anterior insula and orbitofrontal cortex were also negatively correlated with trait anhedonia. Furthermore, effective connectivity between NAc, VTA and paralimbic areas, that regulate emotional reactivity to hedonic stimuli, was negatively correlated with trait anhedonia. Our results indicate that trait anhedonia is associated with reduced reactivity and connectivity of mesolimbic and related limbic and paralimbic systems involved in reward processing. Critically, this association can be detected even in individuals without psychiatric illness. Our findings have important implications both for understanding the neurobiological basis of anhedonia and for the treatment of anhedonia in psychiatric disorders.

Anhedonia, or the inability to experience pleasure from normally pleasant stimuli and life events, is a common symptom of many psychiatric disorders, including major depressive disorder and schizophrenia (Chapman et al., 1976). As a clinical symptom, anhedonia has a significant impact on the functioning of psychiatric patients and has been associated with psychosocial and functional disability in both depression and schizophrenia (Buckner et al., 2008; Wolf, 2006). In psychiatric illnesses, anhedonia is not adequately treated by pharmacological and psychosocial interventions (Buckner et al., 2008; Horan et al., 2006; Wolf, 2006), and it persists even after the remission of other symptoms (Barkham et al., 1996; Kopta et al., 1994; Shelton and Tomarken, 2001). Although anhedonia has been studied more widely in clinical populations, individual differences in anhedonia are also present in non-clinical populations (Franken et al., 2007; Harvey et al., 2007). Little is currently known about the neurobiological basis of anhedonia, and addressing its dimensional aspects remains an important open question for both basic and clinical affective neuroscience.

The primary goal of our study was to investigate the neural correlates of trait anhedonia in healthy adults without a history of psychiatric illness. Both the recently conceptualized "liking" and

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"wanting" components of anhedonia (Berridge and Kringelbach, 2008; Horan et al., 2006) involve the mesolimbic reward system (MRS) and its associated pathways (Der-Avakian and Markou, 2012). The structural core of the MRS consists of the nucleus accumbens (NAc) and the ventral tegmental area/substantia nigra (VTA/SN) (Haber and Knutson, 2010; Knutson et al., 2001), which are connected by the medial forebrain bundle (MFB). The NAc, in particular, has been consistently linked to processing pleasurable stimuli, including those that do not involve explicit reward (Padoa-Schioppa and Cai, 2011). The VTA is the site of mesolimbic dopamine neuron cell bodies that project to the NAc, and dopamine release by the VTA is known to be crucial for reward processing (Padoa-Schioppa and Cai, 2011). The MFB not only connects the VTA to the NAc, but also has distal connections to basal forebrain and frontal lobe regions that are important for reward and motivation (Coenen et al., 2012). Together, brain structures associated with the MRS and MFB are critical for reward seeking as well as maintaining equilibrium between positive and negative affective states (Coenen et al., 2011). Indeed, clinical studies using deep-brain stimulation on brain regions linked by the MFB have been shown to be effective in alleviating depression symptoms by increasing reward seeking desires (Coenen et al., 2011; Schoene-Bake et al., 2010). Brain imaging studies in humans have also reported a consistent pattern of MRS co-activation in response to various rewards, including food (Small et al., 2001), money (Knutson et al., 2001), humorous cartoons (Mobbs et al., 2003), music (Koelsch et al., 2006; Menon and Levitin, 2005), and pleasant pictures (Lane et al., 1997). Mesolimbic and mesocortical pathways involving the VTA, NAc, amygdala, OFC and medial prefrontal cortex are thought to be critical for reward processing, anticipation and learning (Buckholtz et al., 2010; Chiavaras et al., 2001; Schlaepfer et al., 2008), but little is known about the relation between anhedonia and functional interactions within mesolimbic and mesocortical pathways that link these regions.

The strong overlap between anhedonia and other clinical symptoms in disorders such as depression, has made it difficult to isolate the neural correlates of anhedonia. In other words, because anhedonia is often assessed within the context of psychiatric or neurological disorders, it is difficult to separate the effects of anhedonia from the effects of the disorder. In depressed patients, Dunn and colleagues (2002) reported negative correlations between anhedonia severity and response in subcortical regions, including the ventral striatum. Keedwell and colleagues (2005) also examined depressed patients and found significant positive and negative correlations between anhedonia severity and response to happy stimuli primarily within the ventromedial prefrontal cortex and striatum, respectively. They suggested that anhedonic depressed patients attend more closely to the rewarding stimulus in an attempt to enter a happy mood. However, depression severity scores were also correlated with neural activity of the ventral striatal structures. Thus, previous brain imaging studies have not been able to adequately disentangle anhedonia from other clinical symptoms.

Only one study to date has examined the association between trait anhedonia and brain activity in healthy controls. Harvey et al. (2007) used structural and functional brain imaging to examine hedonic capacity in non-clinical participants. They found that when participants viewed positively valenced pictures during an emotional memory task, trait anhedonia was positively correlated with activity in several structures, including the ventromedial prefrontal cortex, superior temporal gyrus, insula, superior parietal lobule and occipital cortex. Surprisingly, MRS and ventral striatal responses were not significantly correlated with trait anhedonia. More recently, Wacker and colleagues (2009) examined individual differences in hedonic capacity in a mixed sample of healthy adults and adults with psychiatric illness and found that anhedonia, but not depression or anxiety, correlated with reduced NAc activity in response to reward. The contradictory findings reported in these two studies may partly be attributable to methodological and sample differences. Harvey et al. (2007) used the Chapman physical anhedonia scale (Chapman et al., 1976) to determine hedonic capacity. On the other hand, Wacker and colleagues (2009) used the Mood and Anxiety Symptom Questionnaire anhedonic depression scale (MASQ-AD) (Watson et al., 1995a, 1995b) to measure anhedonia, which is a more recently developed and encompassing assessment of anhedonia, but anhedonia was not assessed in close temporal proximity to the brain imaging session. Furthermore, 25% of their sample had a history of psychiatric illness, which highlights the potentially confounding effects of psychiatric disorders on anhedonia. Finally, neither study examined how functional interactions between the MRS and the rest of the brain are altered by trait anhedonia.

To overcome limitations of previous studies, we examined a well-characterized group of healthy adults without any history of psychiatric illness. Importantly, we used the positive affect factor of the MASQ-AD to assess trait anhedonia. Using factor analysis, the MASQ-AD has been shown to consist of an 8-item depression factor and a 14-item reverse scored positive affect factor (Nitschke et al., 2001; Watson et al., 1995a, 1995b). The items of the MASQ-AD positive affect factor inquire about wide-ranging situations (e.g., "Looked forward to things with enjoyment" and "Felt like I had a lot of interesting things to do") and thus encompass components beyond physical and social anhedonia. Thus, by using the positive affect factor of the MASQ-AD, we were able to more directly examine the neural basis of trait anhedonia. We also used music to effectively probe the MRS because it is a naturalistic "real-world" auditory stimulus that is relevant to everyday experiences that are impaired in individuals with trait anhedonia. Music represents a dynamic form of emotion and the conveying of emotion is considered to be the essence of music and the reason that most people report spending large amounts of time listening to music (Juslin and Sloboda, 2001). Music is capable of evoking exceptionally strong emotions (Koelsch et al., 2006), including feelings of pleasure (Krumhansl, 1997; Sloboda and Juslin, 2001) and frisson (Berridge and Kringelbach, 2008; Mesulam, 1998). Even passive music listening is known to evoke the same strong physiological changes, such as frisson, shivers, and heart rate changes that often accompany strong emotional stimuli (Panksepp, 1995).

Critically, because music elicits a robust response in the ventral striatum (Blood and Zatorre, 2001; Blood et al., 1999; Menon and Levitin, 2005), we hypothesized that music would help capture trait anhedonia effects that might be missed by other less emotionally evocative and pleasurable stimuli. Both PET and fMRI have shown that activity in brain regions thought to be involved in reward/motivation and emotion, including striatum, midbrain, amygdala, orbitofrontal cortex (OFC) and ventromedial prefrontal cortex, is related to the subjective experience of music listening (Blood and Zatorre, 2001; Blood et al., 1999; Mitterschiffthaler et al., 2007). Research using fMRI connectivity analysis have further shown that compared to spectrally matched scrambled music, listening to music strongly modulated activity in a network of MRS structures including the NAc and the VTA/SN as well as associated structures in the hypothalamus, insula and OFC, which are thought to be involved in regulating autonomic and physiological responses to rewarding and emotional stimuli (Menon and Levitin, 2005). More recently, Salimpoor et al. (2011) combined PET with fMRI to demonstrate dopamine release in multiple MRS structures in conjunction with fMRI activation during music listening. These results suggest that listening to pleasant music evokes robust and reliable response in the MRS as well as in related structures such as the ventromedial prefrontal cortex and insula.