ANHEDONIA AND DEFICITS IN POSITIVE EMOTIONAL EXPERIENCE IN INDIVIDUALS WITH GENETIC LIABILITY FOR SCHIZOPHRENIA

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The undersigned, appointed by the dean of the Graduate School,

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Presented by Anna Docherty

A candidate for the degree of

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And hereby certify that, in their opinion, it is worthy of acceptance.

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1. INTRODUCTION

Overview

There is growing evidence that anhedonia--the extent to which an individual reports pleasure or interest in social and physical stimuli--is important to the pathophysiology of schizophrenia. Anhedonia has been associated with genetic liability to schizophrenia in several studies (Clementz, 1992; Kendler, 1996; Docherty & Sponheim, 2008) and has predicted the future development of schizophrenia-spectrum disorders (Kwapil, 1998, Gooding, 2006). At the same time, in patients with schizophrenia, anhedonia has been associated with poor long-term outcome (Fenton & McGlashan, 1991).

Despite the importance of anhedonia as an endophenotype of schizophrenia, there are unanswered questions about what anhedonia *is*, and how anhedonia relates to the pathogenesis of the disorder. It has long been thought that the symptom might reflect emotion deficits (Burbridge & Barch, 2007). In multiple studies using standardized stimuli, we found that anhedonia in nonclinical individuals is associated with decreased self-reported positive affect (PA) intensity (Kerns, Docherty & Martin, 2008). However, the association of anhedonia with decreased PA intensity has not yet been examined in people with schizophrenia or their biological relatives.

At the same time, some research has suggested that there are different facets of positive affect experience, such as liking vs. wanting (Berridge & Robinson, 1998). Previous research has not directly examined the relationship between anhedonia and task measures of liking and wanting.

In addition to decreased PA intensity, other research has found evidence that anhedonia is associated with specific risk alleles. In particular, in one prior study we found that relatives with a high-activity polymorphism of the Val158Met COMT gene (rs4680) responsible for dopamine regulation have higher levels of anhedonia (Docherty & Sponheim, 2008). Importantly, previous research has consistently found evidence for an involvement of dopamine in the experience of PA (DePue, 1999). This suggests that decreased PA intensity in anhedonia might be related to COMT alleles. However, previous research has not examined the relationship between anhedonia, PA intensity, and COMT alleles.

In addition to COMT, recent research on a large Finland cohort found an association of DISC1 alleles with social anhedonia (Tomppo et al., 2009). DISC1 has been found to regulate cell migration in the developing hippocampus (Meyer & Morris, 2009) and previous research has implicated the hippocampus in emotion functioning and the experience of low levels of PA (Kumari et al., 2003). However, previous research has not examined the relationship between anhedonia, PA intensity, and DISC1 alleles.

The National Institute of Mental Health has sought enhancements in measurement that will facilitate the reduction of heterogeneity in studies of genetic etiology, and further the search for the genetic basis of psychopathology (NIMH, 2009). The following study attempted to address that aim. Given difficulty locating risk genes for schizophrenia in recent genome-wide association studies, and the historic heterogeneity of results of single nucleotide polymorphism association studies, it is beneficial to refine alternative phenotype

constructs like anhedonia with behavioral measures, and to assess gene associations with more sensitive clinical measures of schizophrenia phenotypes, rather than with categorical diagnoses. It is important, moreover, to compare gene-endophenotype associations in biological relatives and nonpsychiatric controls. Thus broadly, the research for this dissertation examined whether:

1. First-degree relatives of people with schizophrenia will report a decrease in PA intensity, as measured by ratings of standardized affectively-valenced stimuli, similar to that found in college students with increased self-reported anhedonia.
2. A decrease in PA intensity will be specifically associated with level of anhedonia in people with schizophrenia and in their first-degree relatives.
3. Clinical ratings of anhedonia in patients, and self-report ratings of anhedonia in relatives, are associated with decreased self-reported and behavioral liking and wanting of stimuli.
4. Any association of reduced PA intensity with anhedonia symptoms will not be accounted for by current levels of positive mood or depression.

This dissertation project was part of a study (run by this applicant and funded by NIMH) examining genotype-endophenotype associations. In addition to the above specific aims, I am also examining whether COMT Val158Met and DISC1 polymorphisms will moderate the presence of both increased anhedonia and decreased PA intensity in first-degree relatives of people with schizophrenia.

However, DNA collected for the NIMH-funded project is ongoing and remains separate from this dissertation.

Overall, the current translational research used behavioral genetics to identify mechanisms that could affect the anhedonia phenotype. At the same time, it is hoped that by examining emotion processing associated with anhedonia-like symptoms, this research can inform interventions for the treatment-refractory negative symptoms of schizophrenia. The NIMH has encouraged the identification of measures of positive and negative affect for the examination of mood and psychosis (NIMH, 2003), and research has emphasized the importance of studying endophenotype-genotype associations (e.g., Gottesman, 2003; Braff, 2007; Kendler & Neale, 2009). By refining our understanding of endophenotypes, it is hoped that we can better examine distinct neurophysiological and behavioral changes in schizophrenia, predict the onset of the illness, and develop effective preventative treatment (Horan et al., 2008).

Background and Significance

The benefits of genotype-endophenotype association studies in relatives of people with schizophrenia. Schizophrenia is a debilitating illness that affects approximately 1% of the population (Freedman, 2003). Although the underlying causes of schizophrenia are unknown, evidence from family, twin, and adoption studies indicates that genetic factors make a substantial contribution (Kendler & Diehl, 1993). Family members of people with schizophrenia exhibit similar, yet milder, neurobiological abnormalities to those found in affected individuals (Faraone et al., 1995; Lawrie et al., 1999; McDonald et al., 2002;

Byrne et al.,2003; McIntosh et al.,2005). For example, research with first-degree relatives of people with schizophrenia has revealed similar neurological soft signs, structural brain changes, and impairments on measures of emotional, social and cognitive functioning (Berenbaum et al., 2006; Raine, 2006). In addition, research has found evidence that abnormalities exhibited in relatives are positively associated with the genetic proximity to an affected relative (Lawrie et al., 2001; Seidman et al., 2002; McIntosh et al., 2005, 2006). This suggests that research on endophenotypes in relatives of people with schizophrenia may be used to understand the genetic and biological substrates of the disorder.

Tyrone Cannon, in a presentation at the 2009 annual meeting of the International Congress of Schizophrenia Research," A Translational Genetics Approach to Schizophrenia: The Example of DISC1 and Memory-Related Endophenotypes," presented a model using the structure of tributaries to a watershed to conceptualize the contributions of both genes and environment to endophenotypes and the disease itself. Implicit in this model is the notion that certain critical endophenotypes or symptom domains—branch points "upstream"—should be a focus for translational genetics. The approach that Cannon proposed encourages researchers to link genes with validated schizophrenia endophenotypes rather than the occurrence of the disorder itself.

Anhedonia as an endophenotype for schizophrenia. One phenotype associated with genetic risk for schizophrenia is anhedonia, or a self-reported lack of pleasure (Meehl, 1975). Anhedonia affects most people with schizophrenia (Andreason, 1982; Fenton & McGlashan, 1991), remains treatment refractory,

and indicates poor prognosis for the illness (Fenton & McGlashan, 1991). In addition, elevated anhedonia has been associated with increased risk of disorder. For example, anhedonia, as measured by the Revised Social Anhedonia and Physical Anhedonia Scales (Chapman, Chapman, Eckblad & Kwapil, 1978), has been the only self-reported schizotypal trait to consistently differentiate first-degree relatives of people with schizophrenia from controls (i.e. Kendler, 1996, Docherty & Sponheim, 2008). Moreover, anhedonia scores have been found to be higher in family members of schizophrenia patients with severe anhedonic symptoms (Berenbaum & McGrew, 1993; Fanous et al., 2001). In contrast, in bipolar disorder anhedonia has been unassociated with increased familial risk for the disorder (Etain et al., 2007). At the same time, two longitudinal studies have found that elevated social anhedonia specifically predicts the future development of schizophrenia-spectrum disorders (Gooding et al., 2005; Kwapil, 1998). For example, in one longitudinal study, 24% of people with elevated social anhedonia developed schizophrenia-spectrum disorders within 10 years. Thus anhedonia is a phenotype associated with genetic risk for schizophrenia that predicts the development of schizophrenia-spectrum disorders.

Anhedonia and positive emotion deficits. It has long been thought that anhedonia might reflect deficits in emotion, especially deficits in positive emotional experience (Henry et al., 2007; Henry et al., 2008; Kring and Werner, 2004). Previous research has identified three ways that positive emotion deficits could be related to individual difference characteristics. One positive emotion deficit is a general decrease in positive emotions. For example, the personality

trait extraversion has been associated with a decrease in the experience of positive emotions (Lucas & Baird, 2004). A second positive emotion deficit is a decrease specifically in the liking of positive events (Gard et al., 2006). A third positive emotion deficit is a decrease specifically in the wanting of positive events, or in anticipatory pleasure (Gard et al., 2006). Hence, anhedonia in schizophrenia could reflect one or more of at least three different emotion deficits: (1) general decrease in PA; (2) decreased liking; or (3) decreased wanting.

There is some previous research that anhedonia might be associated with decreased wanting and not with decreased liking. In particular, in a study assessing wanting and liking using a questionnaire measure, anhedonia in 51 people with schizophrenia was associated with decreased anticipatory pleasure (i.e., wanting). In contrast, anhedonia was only weakly or inconsistently associated with decreased liking. However, to our knowledge possible positive emotion deficits have not been examined in relatives.

Anhedonia and decreased PA intensity in real-world settings. Previous research suggests that anhedonia may be related to a decrease in PA intensity. In past studies I have examined whether anhedonia is related to deficits in positive emotion. In one study (Kerns, Docherty, & Martin, 2008), we examined whether anhedonia was associated with decreased PA in people's daily lives. Importantly, previous research has found discrepancies between self-reported trait measures of affect and people's reports of affect in their daily lives (Robinson & Clore, 2002). Hence, it is possible that although some individuals might report increased

anhedonia on a questionnaire measure these same individuals may not actually report decreased positive affect for their very recent emotional experiences.

To examine this in anhedonia in people identified as at-risk for schizophrenia, we used the Day Reconstruction Method (DRM; Kahneman et al., 2004). On the DRM, participants recall everything that happened to them on the previous day. Then participants rate how they felt during every part of the previous day. By obtaining emotion ratings for their experiences on the previous day, it is thought that the DRM minimizes retrospective memory biases for previous emotional experiences. We found that on the DRM people with extremely elevated social anhedonia (>1.96 standard deviations from the mean) reported decreased PA intensity for events in their daily lives compared to control participants and to people with extremely elevated positive schizotypy. This decrease in PA intensity was found in both social and in non-social situations, suggesting that it may not be merely due to a dislike of social interactions.

Interestingly, there were no group differences in PA frequency. Hence, it did not appear that people with social anhedonia reported less frequent positive emotions or positive emotional experiences. However, instead social anhedonia was associated with decreased intensity of PA when PA was experienced. In addition, we also used another emotion rating task where people rated how they felt the last time they felt recent types of experiences (e.g., last time went to a sporting event). On this task, again people with social anhedonia reported decreased PA intensity but not decreased PA frequency. Therefore, this research

suggests that anhedonia might be specifically associated with decreased PA intensity.

Although anhedonia has been associated with decreased PA intensity in daily life, this could be interpreted in at least two ways. First, it could indicate that anhedonia is associated with a decreased capacity to experience pleasure. Second, it could indicate that anhedonia is not associated with a decreased ability to experience intense PA but instead is associated with experiencing less intense positive events. This latter interpretation predicts that if standardized lab stimuli were used, thereby controlling for the intensity of people's experienced events, then anhedonia would no longer be associated with decreased PA intensity. To examine these possibilities, in a number of studies, I have examined reports of positive emotion in anhedonia in response to standardized lab stimuli.

In one study (Docherty & Kerns, 2009), I specifically looked at the identification of positive emotion in standardized stimuli in anhedonia. In this study, participants viewed standardized pictures and rated each picture for how positive or how negative they thought they picture was. Overall, in a non-clinical sample, anhedonia was associated with finding the pictures less positive. Interestingly, this is consistent with a recent study reporting that anhedonia was associated with poorer emotion identification on an emotional intelligence task (Lee et al, 2008). Hence, it appears that people with increased anhedonia find standardized stimuli less positive than other people.

Anhedonia and decreased PA intensity for standardized stimuli. In three studies (Kerns, Docherty & Martin, 2008; Docherty & Kerns, 2009) I have

also examined whether anhedonia was associated with decreased PA intensity for standardized lab stimuli. One of these studies involved an extreme scoring social anhedonia group at increased risk for schizophrenia and the other two studies involved large non-clinical samples and measured both physical and social anhedonia continuously (rather than categorically).

In all three studies, both social and physical anhedonia were associated specifically with decreased PA intensity in rating their emotional reactions to standardized picture stimuli. In addition, anhedonia was still associated with decreased PA intensity even after removing shared variance with current mood and current depression symptoms. As found for reports from people's daily lives, anhedonia was not associated with differences in PA frequency. In addition, in these studies, anhedonia was not associated with reports of negative affect for negative pictures. Furthermore, in contrast to anhedonia, in these studies PA intensity was not associated with positive schizotypy.

Therefore, this research suggests that anhedonia might be associated with decreased PA intensity for standardized lab stimuli. Hence it does not appear that decreased PA in anhedonia can be totally explained as a result of experiencing less intense positive events in people with anhedonia. However, previous research has not examined whether anhedonia in people with genetic liability for schizophrenia is also associated with decreased PA intensity. In addition, previous research has also not examined whether decreased PA intensity is associated with risk alleles associated with anhedonia.

Anhedonia and liking versus wanting. As previously discussed, some research suggests that two facets of positive emotional experience might be liking versus wanting. In another study, we examined whether anhedonia, in people at-risk for schizophrenia, was associated with a decrease in either liking or in wanting. In this study, participants completed the TEPS (Temporal Experience of Pleasure Scale; Gard et al., 2006), which was developed to assess differences in liking versus wanting and has been used in previous schizophrenia research (Gard et al., 2007). In research with schizophrenia patients (n = 51) Gard et al. (2007) found that clinical ratings of anhedonia as measured by the SANS were associated with TEPS Wanting subscale scores, but not TEPS Liking subscale scores.

In our research with at-risk individuals, we found that people with extremely elevated social anhedonia (n = 54) differed from control participants in reports both of liking and of wanting. However, there was no differential association between anhedonia and either liking or wanting (e.g., the group X TEPS subscale interaction was not significant, p = .78). Hence in this study we did not find that anhedonia was only associated with a deficit in wanting, finding that anhedonia was associated with decreased liking and wanting.

This result seems somewhat inconsistent with the results of Gard et al. (2007) who reported that wanting was more consistently associated anhedonia. However, even in that study, liking was associated somewhat with anhedonia (e.g., r = -.62 between physical anhedonia and liking). Hence, it remains unclear whether anhedonia might be associated with both decreased liking and decreased wanting. Until now, liking versus wanting has not been examined in first-degree

relatives of people with schizophrenia. In addition, previous relative and patient research has not examined whether anhedonia is associated with tasks that specifically assess liking versus wanting.

To our knowledge previous research has not examined liking vs. wanting in patients and relatives using tasks with standardized emotional stimuli. For example, one task designed to reflect wanting of positive events is the Effort Expenditure for Rewards Task (EEfRT; Treadway et al., 2009). Interestingly, in a relatively small (n = 60) non-clinical sample, anhedonia was associated with decreased effort expenditure on the EEfRT, suggesting an association between anhedonia and decreased wanting (Treadway et al., 2009). However, in this same study, the association of liking of positive events with anhedonia was not examined.

One neurotransmitter that has been consistently associated with positive emotions is dopamine (Ashby et al., 1999; DePue, 1999). For example, DA depletions result in a reduced willingness to expend effort in order to obtain rewards (Corea, 2002; Salamone, 2007, Worden, 2009). In addition, studies of rodent strains have found consistent relations between greater ventral tegmental DA neuron number and/or heightened DA transmission in the ventral tegmental-nucleus accumbens DA pathway and an increased self-administration of stimulants. In humans, neuroimaging studies have found that activity in those same brain regions (i.e., the ventral striatum) is sensitive to degree of reward magnitude and probability (Dreher et al., 2006; Rolls et al., 2008). Hence, given

the role of dopamine in positive emotions, it might be expected that anhedonia might also be associated with dopamine functioning.

Anhedonia and COMT. The COMT gene contains a functional polymorphism at codon 108/158 that results in a change from a valine (Val) to a methionine (Met) amino acid in the COMT enzyme. This change is associated with a three-fold decrease in enzyme activity (Lotta et al., 1995). Catechol-O-methyltransferase has a pivotal role in the extracellular degradation of dopamine (for a review, see Bilder et al., 2004). In addition, COMT has been found to be expressed not only within the prefrontal cortex, but also in the human amygdala and striatum (Hong et al., 1998), regions of the brain involved in emotional experience (Blood et al., 2001). It has also been thought that COMT alleles might be associated with dopamine abnormalities in schizophrenia (e.g., Tan et al., 2009; Prata et al., 2009).

At the same time, previous evidence has suggested that the COMT val allele is associated with negative symptoms in people at-risk for schizophrenia. For example, Avramopoulos et al. (2002) reported that the val allele was associated with high schizotypy scores in a male normative sample. Stefanis et al., (2004) replicated these results and found that the val allele was specifically related to the negative and disorganization dimensions of schizotypy. Schurhoff et al. (2007) studied relatives of schizophrenia and bipolar patients and found the presence of the val allele to be associated with negative schizotypy. Although none of these studies examined anhedonia specifically, in an analogue study using tolcapone, an inhibitor that blocks COMT, mice were found to exhibit anhedonia-

like symptoms (Moreau et al., 1994). Hence, previous research on the COMT val allele is at least generally consistent with an association between COMT and anhedonia.

In addition to research on decreased PA and anhedonia, I have also examined whether anhedonia might be associated with COMT alleles in first-degree relatives of people with schizophrenia (Docherty & Sponheim, 2008). In this research, consistent with previous research, I found that anhedonia was increased in first-degree relatives of schizophrenia patients. In addition to this, I also found that anhedonia in relatives was associated with having the val COMT allele. Although anhedonia was associated with the COMT val allele in relatives of people with schizophrenia, in contrast, in relatives of people with bipolar disorder anhedonia was not associated with the COMT val allele. This suggests that the association between anhedonia and COMT might be diagnostically specific.

Lastly, it was found that relatives with a high-activity polymorphism of the Val158Met COMT gene accounted for all of the Cluster A symptomatology in the first-degree relative sample (Docherty & Sponheim, 2008). Hence, this research suggests that the COMT val allele is associated with anhedonia in people at genetic risk for schizophrenia. However, previous research has not examined whether the association between anhedonia and decreased PA intensity might be moderated by the COMT gene.

Anhedonia and DISC1. In addition to COMT alleles, a recent study has also found that anhedonia in a large cohort was associated with DISC1 (Tomppo

et al., 2009). At the same time, DISC1-altered mice have previously been shown to exhibit anhedonia-like deficits (Hikida et al., 2007). In addition, it has been reported that in a discordant twin sample, a DISC1 haplotype was associated with deficits in sociability (Cannon et al., 2007), decreased sociability being associated with some aspects of anhedonia (i.e., social anhedonia). Research suggests that the DISC1 gene influences hippocampal structure and development (for a detailed analysis, see Hikida et al., 2007). In analogue research, neonatal ventral hippocampal lesions in mice have appeared to induce a reduction in reward-seeking behaviors in adulthood, mimicking anhedonia observed in people with schizophrenia (LePen et al., 2002). In a functional neuroimaging study of patients with schizophrenia, negative symptoms including anhedonia were negatively associated with the volume of the right hippocampus (Szendi et al., 2006). Hence, previous research is generally consistent with anhedonia being associated with the DISC1 gene. However, previous research has not examined whether anhedonia in relatives of people with schizophrenia is associated with the DISC1 gene or whether any association of anhedonia with positive emotions is moderated by DISC1.

Research Aims

Our previous research has replicated an association of anhedonia with decreased PA intensity in non-clinical samples. However, no previous research has yet examined whether anhedonia is associated with decreased PA intensity in people with schizophrenia or in their first-degree relatives. In addition, it is unclear whether anhedonia in people with schizophrenia or in their first-degree

relatives is associated with task measures of either liking or wanting. Previous research has also found evidence that anhedonia is associated with both the COMT val allele and with the DISC1 gene. However, previous research has not examined whether the DISC1 allele is associated with anhedonia in first-degree relatives of people with schizophrenia. Furthermore, previous research has not examined whether any association between anhedonia and PA intensity can be statistically mediated by COMT or DISC1 genes.

To examine research questions relating to emotional experience in people with genetic liability for schizophrenia, the dissertation involved people with schizophrenia and examined whether interviewer-rated anhedonia in schizophrenia was associated with decreased PA intensity for standardized lab stimuli. In addition, this study examined whether anhedonia in people with schizophrenia was associated with decreased liking or wanting, using self-report and tasks to assess both liking and wanting of positive stimuli. The dissertation also examined first-degree relatives of people with schizophrenia and nonpsychiatric controls to assess whether self-reported anhedonia in relatives was differentially associated with decreased PA intensity for standardized lab stimuli. This study also examined whether anhedonia in relatives was associated with decreased liking or wanting using tasks to assess liking and wanting.

In the study design, I also addressed several questions and concerns not addressed in the previous emotion literature:

1. I addressed a general lack of psychometrically-matched liking and wanting measures in studies of emotion in schizophrenia, by using multiple measures of both constructs.
2. I addressed the question of whether any emotion differences are generalized or limited to sensory modality, by using tasks with both visual (pictures) and olfactory (nasochemical) stimuli.
3. I addressed the problem of method and measure biases by using several different methods (questionnaire, interview-rating, behavioral task) and several measures presumably tapping the same construct.
4. I used tasks thought to measure both "state" and "trait" emotion to examine the influence of current affect on trait emotion measures.
5. I used a sample of first-degree relatives to examine genetic liability of emotion traits.
6. I separated positive affect from negative affect. This allowed us to examine behavioral measures of ambivalence.
7. I also separated the components of emotion frequency and intensity.
8. I used measures of both standardized lab stimuli and behavior in daily life.
9. I examined both social and non-social settings with the use of an interview to gauge social engagement and quantify social activities.

10. Last, I was able to separate high and low arousal emotions to examine arousal in the three groups.

In addition, though not included in this dissertation, I will also be evaluating whether anhedonia in relatives is associated with the Val158Met COMT val allele and with DISC1 polymorphism, and whether any association between decreased PA intensity and anhedonia is moderated by the COMT val allele or the DISC1 gene (details on the genotyping part of this research are located in Appendix I).

2. METHODS

Participants

Participants included 38 outpatients with schizophrenia (n = 32) or schizoaffective disorder (n = 6), 35 first-degree relatives of patients with schizophrenia or schizoaffective disorder, and 30 healthy controls. Information about some participants excluded from analyses due to final diagnoses of bipolar disorder or other conditions can be found at the end of the "Symptom interviews" section on page 21. Table 1 presents data on the demographic characteristics of participants. Proband participants were 18-65 year old males and females without current drug abuse or dependence, or alcohol abuse or dependence within the last month, as assessed by the SCID at the date of the first study visit. First-degree relative participants were males and females with a first-degree relative with schizophrenia or schizoaffective disorder who had participated in the study. Proband participation in each family was a prerequisite for relative participation,

in order to confirm a proband diagnosis. Thus, generally relatives were recruited by phone with the permission of a proband who had already participated in the study. Relatives and probands were assured that their information would remain confidential and would not be shared with other family members participating in the study. Data collected from patients were gathered within the context of a larger family study in which patients with schizophrenia and schizoaffective disorder were recruited from the Minneapolis VA Medical Center, community outpatient programs, and a county mental health clinic by paid research assistants to Dr. Scott Sponheim, the co-sponsor.

The entire protocol consisted of three visits of 4-7 hours each (no more than 15 hours total) for which participants were compensated monetarily ($210.00 total for all visits) and were provided with transportation to and from appointments, and with lunch each day. The first visit consisted of clinical interviews and questionnaires, the second of cognitive tasks and emotion measures, and the third consisted of an EEG and additional basic intelligence testing.

The laboratory worked in collaboration with the Head of Psychiatry at the University of Minnesota to enroll university medical center patients in VA studies of schizophrenia. The study also successfully enrolled subjects from county mental health centers (e.g., Hennepin County Mental Health Clinic), community nonprofits in the Twin Cities (e.g., People Incorporated, Tasks Unlimited), and advocacy groups (Minnesota chapter of the National Alliance for the Mentally Ill). All participants completed an informed consent process and were assured that

their information would not be shared with family members enrolled in the same study (those participants are discussed below). The Minneapolis VA Health Care System and University of Minnesota Institutional Review Boards approved the study protocol.

Measures

Symptom interviews. After completing an informed consent process, proband participants first completed the *Structured Clinical Interview for DSM-IV Axis I Disorders* (SCID-I; First et al., 1996) along with a supplemental Medical History and Psychosis Modules of the *Diagnostic Interview for Genetics Studies* (DIGS; Nurnberger et al., 1994), and the *Social Functioning Scale* (SFS; Birchwood, 1990), administered by the applicant and by a trained research coordinator working for Dr. Sponheim. The SFS is a structured interview designed to quantify and characterize social and recreational engagement in psychiatric populations, and aides in assessing social and work role functioning in probands. Lifetime Axis I diagnoses for subjects were determined for a majority of the probands by doctoral-level psychologists, the research assistant, and the interviewer through a consensus process consistent with published guidelines (Leckman et al., 1982) which involved review of SCID-I, symptom ratings, and patient medical history. Medical records were reviewed when available with signed consent from the proband. Interviewer ratings of symptomatology in proband participants were made using the *Scale for the Assessment of Negative Symptoms* (SANS; Andreasen 1981) and the *Scale for the Assessment of Positive Symptoms* (SAPS; Andreasen 1983), which are embedded in the DIGS.

Global scores for negative symptomatology domains (i.e., alogia, affective flattening, avolition-apathy, anhedonia-asociality, and attention), delusions, hallucinations, and positive formal thought disorder were calculated according to the guidelines of Andreasen (1981, 1983). The SANS and SAPS are used extensively in schizophrenia research to assess symptoms and show good reliability and consistency, and were used in conjunction with the self-report measures of schizotypal traits administered to the sample. Cronbach's α for this measure was .92. Interviewers also made ratings using the *Brief Psychiatric Rating Scale* 24-item version (BPRS; Ventura et al., 2000) to quantify mood and other behavioral characteristics of clinical state. Cronbach's α for this measure was .84.

Relatives and control participants also completed the *Structured Clinical Interview for DSM-IV Axis I Disorders* (SCID-I; First et al., 1996), as well as the *Structured Interview for Schizotypy* (SIS; Kendler et al., 1989), in order to fully characterize Cluster A personality traits in the relatives and controls. In addition, the supplemental Medical History and Psychosis Modules of the *Diagnostic Interview for Genetics Studies* (DIGS; Nurnberger et al., 1994) were administered by the applicant and by trainees working for Dr. Sponheim. Interviewers also made ratings using the *Brief Psychiatric Rating Scale* 24-item version (BPRS; Ventura et al.,2000) to quantify mood and other behavioral characteristics of clinical state.

During the consensus process, three probands and one relative were removed from the final data analyses due to a diagnosis of bipolar disorder in the

proband, rather than of schizoaffective disorder. One control participant was diagnosed with schizoid personality disorder as assessed by the SIS and was excluded from the final data analyses. None of the relatives met full criteria for any Cluster A personality disorder as assessed by the SIS.

Measurement of anhedonia. The primary measure of anhedonia in the probands was the anhedonia subscale of the SANS. In a review of anhedonia assessment, it has been argued that the SANS assesses anhedonia "most directly and comprehensively" (Horan, Kring et al., 2006; p. 260). This subscale consists of items regarding recreational interests and activities, sexual activity, ability to feel intimacy and closeness, and relationships with friends and peers. The Anhedonia subscale correlates strongly with other measures of negative symptoms and it correlates with measures of trait positive affect (Blanchard et al., 2006). It also has been found to exhibit adequate test-retest reliability (Horan, Kring et al., 2006). In addition, although it has varied considerably in some studies, the internal consistency for this subscale is considered moderate to good (Horan, Kring et al., 2006).

In this study, I also used subscales from the *Social Functioning Scale* that are designed to reflect social and recreational activity in daily life. These interview ratings provided an additional way of measuring anhedonia, by quantifying actual social and non-social behaviors as reported by the proband.

I also assessed related social and emotional deficits with subscales from the self-report *Schizotypal Personality Questionnaire* (SPQ; Raine, 1991). The SPQ contains nine subscales that assess DSM-III-R Schizotypal Personality Disorder symptoms. The interpersonal factor of the SPQ is thought to be most relevant to

anhedonia, particularly because previous research has found that two subscales, "No Close Friends" (9 items) and "Constricted Affect" (8 items), are strongly associated with social anhedonia in non-clinical samples (with social anhedonia measures also asking about absence of close friends; Cicero & Kerns, 2010; Kerns, 2006). The first subscale contains items such as "I find it hard to be emotionally close to other people", "I have little interest in getting to know other people", and "I attach little importance to having close friends". The second subscale contains items such as "I am poor at returning social courtesies and gestures", and "I do not have an expressive and lively way of speaking". Hence, I also used these two SPQ subscales to measure self-reported anhedonia-like social and emotional deficits in probands (α's for this study = .71 and .63, respectively). These subscales were used to form a composite no close friends/constricted affect score (α = .80). At the same time, to examine specificity of associations with self-reported anhedonia, I also examined two other SPQ subscales that assess non-anhedonia social deficits, "Social Anxiety" (8 items; α = .82) and "Suspiciousness" (8 items; α = .76), which can lead to social isolation but are separable from anhedonia.

In addition to the questionnaire and task measures administered to the proband sample, relative and control participants completed a “Survey of Attitudes and Experiences” which included a pseudo-random mixture of true-false questions from the *Revised Social Anhedonia Scale* (RSAS), the *Physical Anhedonia Scale* (PAS), the *Magical Ideation Scale* (MIS) the *Perceptual Aberration Scale* (PerAb) the *Chapman Infrequency Scale*. The RSAS is a 40-item true-false questionnaire designed to measure lack of relationships and lack of

pleasure from relationships. The PAS is a 61-item true-false questionnaire designed to measure the amount of pleasure gained from taste, smell, sight, and sex. These scales have been used in numerous studies with non-psychiatric controls and with relatives of people with schizophrenia, relatives typically scoring higher than control participants, and have exhibited high test-retest reliability and internal consistency (Horan et al., 2006). Cronbach's α for the RSAS in this study was .74, and for the PAS, .80. While originally intended for use, the SAE was removed from the proband protocol due to constraints on the protocol length and the large number of other self-report questionnaires and tasks administered to each outpatient. Other SAE scales, the *Magical Ideation Scale* and the *Perceptual Aberration Scale*, measure aspects of positive schizotypy (i.e., unusual and psychotic-like beliefs and experiences) that are distinct from anhedonia. Altogether, the SAE scales yield a Cronbach's α of greater than .7 consistently (e.g., Kerns, 2006, Horan et al., 2008). The *Infrequency Scale* was added to detect careless responding. The L and K scales were added to examine differences in defensive responding between participant groups. The entire survey took approximately 30 minutes for relatives and controls to complete.

On-line assessment of positive affect intensity and frequency. A computer task assessing PA intensity, the *Picture Rating Task* (PRT; Kerns et al., 2008, was administered. The PRT by Kerns et al. uses the same pictures reported in Barrett et al. (2004) and records affective ratings of positive stimuli. Positive affect intensity is thought to be the positive affect elicited online by a stimulus.

Rather than a measure of liking, enjoying, or wanting more of the stimulus, this construct reflects one's self-reported affect following the viewing of a picture.

On this task, participants are presented with a series of pictures, with each picture appearing for 10 seconds. After seeing each picture, participants first rated whether they experienced a particular emotion presented on the screen. This provided a measure of emotion frequency. If the emotion was experienced, participants then rated its intensity on a scale from one to six. Following previous research (Kerns et al., 2008; Schimmack & Diener, 1997), the dependent variable for PA intensity was the average intensity of all positive emotions that all participants indicated that they experienced while viewing positive pictures. The task contained 16 pictures including positive, neutral, and negative pictures, and took approximately 8 minutes to complete. Following Barrett and Russell (1999), 16 different emotions were rated for each picture, including positive high arousal emotions (happy, excited, alert, and elated), positive low arousal emotions (relaxed, contented, serene, and calm), negative high arousal emotions (stressed, nervous, upset, and tense), and negative low arousal emotions (lethargic, fatigued, sad, and depressed). Hence, this allowed for the assessment of both emotional valence (positive vs. negative) and emotional arousal (high vs. low). In previous research, our studies found that anhedonia in non-clinical samples was associated with decreased PA intensity for both high and low arousal positive emotions in college students (Kerns et al., 2008).

People with schizophrenia are thought to accurately and reliably report on their feelings, despite cognitive and language disturbances that can accompany

schizophrenia (for a review, see Kring & Moran, 2008). Emotion words can easily assess a broad range of emotions that sample from the entire range of the affective circumplex (Posner et al., 2005; Kring et al., 2003). At the same time, the current picture rating task was preferable to other assessment techniques that do not allow for an assessment of emotion frequency (i.e., if people need to rate their emotion reaction from 1 to 9). Another advantage of the picture rating task was that all emotion reports involved reactions to the same stimuli across all participants. At the same time, it is an on-line assessment of emotional experience and presumably eliminated any memory distortion that could occur in reporting previous emotional experience.

In addition to PA intensity and frequency, the PRT can also provide measures of emotional ambivalence. Ambivalence, or strongly mixed emotions (Raulin & Brenner, 1993), is thought to be a potentially critical emotional construct in schizophrenia (Bleuler, 1911/1950) and it has been rated as the amount of negative affect for positive stimuli and the amount of positive affect for negative stimuli. Hence, in supplemental analyses, I also examined between-group differences in amount of ambivalence on the PRT.

Liking Measures

The Self-Reported Liking Task. Participants completed a *Self-Reported Liking Task* (SRLT) to rate the pleasantness of visual affective stimuli. This procedure was adapted from the Liking Task by Heerey & Gold (2007) and was modified by the applicant for use in this study. The measure of liking was reflected by how much an individual appraises the pleasantness and

unpleasantness of an on-line visual stimulus. This procedure served as a measure of online hedonic processing and required very little effortful behavior.

First, participants viewed and rated 40 slides, each containing an image from the International Affective Picture System (IAPS; Lang, Bradley, & Cuthbert, 2005) on a computer. Sixteen positive, sixteen negative, and eight neutral slides made up the set. While originally the task by Heerey and Gold contained three pictures on each slide, each with similar content, the number of pictures was reduced because many of the negative pictures were deemed to be highly upsetting. To protect human subjects, pictures of negative and positive valence were selected to reduce both the severity of the negative affect induction and to reduce the visual demands of the task.

The photos on each slide were items of varying content, valence, and arousal. Participants rated the degree to which each slide is experienced as "pleasurable" and "arousing" using 9-point Likert scales, beginning with 1, *extremely [unpleasant/calm]* and moving to 9, *extremely[pleasant/exciting]*. The arousal component of these ratings conveniently provided an additional measure of PA arousal while pleasantness ratings provided the measure of liking. Each rating scale was presented beneath each stimulus, and participants had unlimited time to make their ratings. Slides were removed from the screen after ratings were made. At the end of the task, participants were given the option of viewing additional positive pictures if they felt upset by the task. After the picture tasks participants were offered water and encouraged to take a ten-minute break before continuing with additional protocol measures.

Temporal Experience of Pleasure Scale. Last, *The Temporal Experience of Pleasure Scale* (TEPS; Gard et al., 2006) measures momentary pleasure. One subscale of the TEPS is designed to measure trait "consummatory" pleasure (8 items), so purportedly measures everyday liking. The subscale contains items such as "I enjoy taking a deep breath of fresh air when I walk outside" and "I appreciate the beauty of a fresh snowfall". The TEPS has good reliability and shows satisfactory internal and external validity. The mean theoretical range of the scale goes from 1 to 6, and higher scores indicate more pleasure.

Olfactory hedonic ratings. Another measure of liking was adapted from a nasochemical sensory test developed for medical testing of olfactory sensitivity and identification. The *Sniffin' Sticks* (Hummel et al., 1997) olfactory test consists of 16 scented odor-dispensing pens of varying pleasant and unpleasant odors (rose, garlic, cherry, dead fish, for example). As an odor identification test, this measure has been validated against the University of Pennsylvania Smell Identification Test (UPSIT) and has been used widely in medical practice to identify nomosmic and anosmic individuals. While the *Sniffin' Sticks* threshold and identification tests were intended to be administered to every subject, the international shipping of the test to my laboratory at the Minneapolis VA occurred after some subjects had already completed the study protocol. Thus, only a subset of participants piloted this task. After completing a smell threshold test, each participant was instructed to close his/her eyes and was administered each scented pen-like device in a pseudorandom order by the applicant. Upon each administration, the participant was prompted to make a hedonic rating of how

pleasant or unpleasant they found the odor on a rating form (see Appendix II for the administration instructions and rating form), on a 1 to 9 pleasantness scale identical to that of the SRLT. Cronbach's α for this measure of hedonic ratings was .79.

Wanting Measures

Tapping for Reward Task. A behavioral task measuring effort expenditure for reward, the *Tapping for Reward Task* (TRT), was administered to participants. The TRT is titrated to the ability level of the individual, and is a multi-trial task in which participants are given an opportunity on each trial to choose between two different task difficulty levels in order to obtain monetary rewards. Subjects begin by using their non-dominant index finger to tap on a spacebar as fast as they can for two trials of ten seconds each. The program calculates the tapping speed of each individual participant in order to calibrate the parameters for the 30 following trials.

Subjects are then presented with information regarding the reward magnitude of hard and easy tasks before each trial (uniformly 14 and 7 cents per trial, respectively, across all 30 trials) and are instructed to choose the condition (hard/maximum reward vs. easy/minimum reward). This is followed by time trials of twenty seconds when subjects make rapid spacebar presses to complete the chosen task (difficult or easy condition).

Subjects receive feedback after each trial as to whether they earned the money for that trial, and at the end of the 30 trials subjects are presented with the total amount they have earned up to $4.20. The task took approximately 20

minutes to administer. As discussed in the Introduction, a similar task of effort expenditure for reward has been found to be associated with anhedonia in a nonpsychiatric sample (see Treadway et al., 2009). While the Treadway et al. task was administered successfully in a nonclinical sample, parameters of that task involving risk (a gambling component) were deemed overly complex for individuals with possible cognitive deficits, thus we created the similar but more straightforward task of effort for reward described above without a risk variable.

Temporal Experience of Pleasure Scale. *The Temporal Experience of Pleasure Scale* (TEPS; Gard et al., 2006) was used to measure self-reported trait anticipatory pleasure with a 10-item subscale, and purportedly measures wanting. The subscale contains items such as "I don't look forward to things like eating out in restaurants" and "I look forward to a lot of things in my life". As noted above, the TEPS has good reliability and shows satisfactory internal and external validity. The mean theoretical range of the scale goes from 1 to 6, and higher scores indicate more pleasure.

Self-reported current mood. Tasks and questionnaires were administered on day two of the study, in a room with the interviewer. Twenty items from the *Positive and Negative Affect Schedule*-Extended Form (PANAS-X; Watson & Clark, 1994) reflecting different negative and positive emotions was administered during the initial stage of the protocol. A list of the emotions used can be found in Appendix III. Participants made ratings on a 1 *(very slightly/not at all)* to 5 *(extremely)* Likert scale.

Extraversion. The extraversion subscale of *the International Personality Item Pool* was also collected as a measure of sociability and positive affect in each participant sample. This scale is a ten-item self-report questionnaire. Cronbach's α for this study was .80.

Data Analysis

First, distributions of all study variables were examined within the participant samples to avoid any assumption of normality in the data. Age and gender were also examined in relation to study variables. Then I examined convergent and divergent correlations among anhedonia and related measures (Tables 2-3) and I also examined correlations between positive affect measures (Tables 4-6).

For anhedonia, in probands I used both interview and self-report measures of anhedonia. The main interview measure of anhedonia was from the SANS. As an additional interview measure, I also examined associations with the SFS interview subscale scores (quantifying social and recreational behaviors) assessing anhedonia-like social and motivational deficits. In addition to interview-assessed anhedonia, I also examined associations with self-reported anhedonia-like symptoms using a composite measure of the two SPQ subscales no close friends and constricted affect.

In this research, I also wanted to examine the specificity of any associations with anhedonia to examine whether anhedonia was specifically associated with positive emotion variables or whether other schizophrenia symptoms would also be associated with positive emotion. Hence, I also examined associations with the interview-assessed symptom of flat affect (i.e., blunted emotional expression), which is another schizophrenia emotion deficit thought to be potentially distinct from

anhedonia. To examine specificity of associations with self-reported anhedonia, I also examined associations with self-reported social anxiety and suspiciousness on the SPQ. In addition, to examine whether any associations with self-reported anhedonia might be related to common personality traits, I also examined associations between PA intensity and self-reported extraversion.

To test the relationship between anhedonia and PA intensity in the probands, four specific hypotheses were tested. The main hypothesis (hypothesis 1) was that anhedonia would be significantly associated with decreased positive affect intensity ratings for picture stimuli on the picture rating task. To test this hypothesis, I examined correlations between anhedonia measures and the measure of PA intensity from the picture rating task. Hypothesis 2 was that any association of anhedonia with positive affect intensity would not be accounted for by current depression or affect, as measured by the BPRS and current affect ratings. To test this hypothesis, separate regressions were conducted to investigate mood and depression as potential mediators. Hypothesis 3 was that anhedonia would be associated with liking as measured by hedonic ratings on the SRLT, the *Sniffin' Sticks,* and the TEPS Liking subscale. To test this, correlations between anhedonia and liking ratings were examined. Hypothesis 4 was that anhedonia would be associated with wanting as measured by the TRT and the TEPS Wanting subscale. To test this, correlations between anhedonia and anticipatory pleasure measures were conducted.

In addition to analyses in probands, to test the relationship between anhedonia and PA intensity in the relatives and controls, 5 specific hypotheses were tested. The main hypothesis (hypothesis 5) was that self-reported anhedonia would be

significantly associated with positive affect intensity ratings for picture stimuli on the picture rating task in first-degree relatives and in controls. This required examining Spearman *rho* correlations between anhedonia (from the RSAS and PAS) and the measure of PA intensity from the PRT. Hypothesis 6 was that any association between self-reported anhedonia and PA intensity would not be accounted for by current depression or affect, as measured by the BPRS and the mood questionnaire. To test this hypothesis, separate regressions were conducted to investigate mood and depression as potential mediators of the relationship between anhedonia and PA intensity. Hypothesis 7 was that anhedonia would be associated with liking in the first-degree relatives, as measured by the SRLT, the olfactory hedonic ratings, and the TEPS Liking subscale. To test this, correlations between anhedonia and liking ratings were examined. Hypothesis 8 was that anhedonia would also be associated with wanting as measured by the TRT and the TEPS Wanting subscale. To test this, regressions predicting wanting from self-reported anhedonia scores were conducted.

Finally, if anhedonia were related to positive affect measures in at least two of the three subject groups, hypothesis 9 would be that the magnitude of any associations between anhedonia and PA intensity would be greatest for patients, then relatives, then controls, respectively. If associations were detected, we would then examine whether the correlations between anhedonia, interpersonal factor variables, and PA intensity were significantly different between subject groups, using procedures outlined by Meng et al. (1992).

While group comparisons across all tasks are of interest, these analyses come with limitations (as outlined in the Introduction) and are ancillary to the main

hypotheses of the research examining relationships between anhedonia and positive emotional experience and appraisal of stimuli. Thus, these between-group analyses were included as supplemental analyses and are reported after reviewing correlations with anhedonia.

3. RESULTS

Distributions of All Study Variables and Associations with Gender and Age

To examine the psychometric properties of the study variables, distributions of all of the study variables were examined within each group. This was important in considering the feasibility of later correlational analyses; for example, if range was too restricted, power would be reduced. In addition, some previous studies have reported samples of relatives and probands with extremely heterogeneous variance. Also, because I piloted new tasks, there could be unforeseen reasons for influential outliers in each sample.

In instances where variables showed skew and/or kurtosis greater than 1.0, distributions were considered to be non-normal and non-parametric, and Kruskal-Wallis or Wilcoxon rank sum tests for between-group comparisons between probands and relatives were carried out in addition to parametric contrasts between groups. If results varied between parametric and non-parametric analyses, both results were reported. In probands, a study variable showing skew or kurtosis in excess of 1.0 with an absence of outliers was the TEPS Liking score. In both relatives and controls, study variable distributions with skew and/or kurtosis > 1.0 with an absence of outliers were those of the Magical Ideation Scale, the Perceptual Aberration Scale, and the Physical Anhedonia Scale.

In the proband group, an outlier scoring > 2 standard deviations below the group mean was detected on the TRT, as was elevated skew and kurtosis > 1.0. Distributions of scores on the TRT suggested potential ceiling effects across groups, thus a transformation of the variable for these analyses was inappropriate. However, later analyses of the TRT both with and without the outlier were examined.

Distributions of current negative affect scores suggested potential floor effects, and a transformation of the variable was not possible. One outlier in the proband group was detected scoring > 2 standard deviations above the group mean (this was not the same outlying individual identified in the TRT distribution). Non-parametric analyses of NA ratings were conducted in addition to parametric tests in later study analyses, but because of the possible floor effects, caution is warranted in the interpretation of results stemming from the questionnaire.

Age and gender were also examined, to assess whether age or gender should be entered as covariates in later analyses. Spearman rho correlation coefficients were examined between age and each of the study variables. Across all groups and within each sample separately (proband, relative, and control) age was not significantly associated with any of the study variables. However, within controls there was trending association of age with extraversion score on the IPIP, $rho = .35$, $p = .09$. Thus, in subsequent study analyses of controls including the IPIP, age was entered as a covariate.

T-tests and/or Wilcoxon rank sum tests (the latter for comparisons within probands to avoid assuming distributional normality) were conducted to examine differences between males and females within each subject group on each study variable. Within the schizophrenia probands, females (n = 6) scored significantly lower than males (n = 24) on reports of arousal to positive pictures on the SRLT (t [28] = 3.63, p = .001). Males and females within the proband group did not vary on any other study variables. In all later analyses examining the gender-related variable in this group, follow-up analyses were conducted including gender as a covariate. If results differed with and without gender as a covariate, both results were reported.

Within the first-degree relatives of schizophrenia probands, females (n = 22) had significantly elevated scores relative to males (n = 11) on the following variables: TEPS Anticipatory Pleasure (t [31] = 2.24, p = .03), SRLT Liking of positive pictures (t [31] = 2.06, p = .049), and olfactory hedonic ratings (t [16] = 2.19, p = .044). Males and females within the relative group did not vary on any other study variables. In all later analyses examining the gender-related variables in this group, follow-up analyses were conducted including gender as a covariate. If results differed with and without gender as a covariate, both results were reported.

Within the control participants, females (n = 22) had significantly elevated scores relative to males (n = 11) of current NA (t[21] = 1.89, p = .04). There was a trend toward gender differences in scores from the Magical Ideation Scale, with males scoring generally higher than females (*M (SD)* = 4.46 (3.78) and 2.00

(1.83), respectively, p = .08). Males and females within the control participant group did not vary on any other study variables. In all later analyses examining any gender-related variables in this group, follow-up analyses were conducted including gender as a covariate. If results differed with and without gender as a covariate, both results were reported. These supplemental analyses can be found at the end of the Results section with headings entitled "Supplemental Analyses".

Correlations among Anhedonia Measures and with Other Symptoms

Next, I examined correlations among measures of anhedonia. As can be seen in Table 2, the anhedonia interview measures tended to be strongly correlated with each other, as probands with higher anhedonia were less likely to engage in recreational and prosocial activities. In addition, as expected, the SPQ no close friends and constricted affect subscales were highly correlated with each other. In addition, there were some significant correlations between interview anhedonia measures and self-reported anhedonia-like symptoms, although these correlations tended not to be as strong.

As can be seen in Table 3, anhedonia measures were not significantly correlated with another interview rated schizophrenia emotion symptom, flat affect, or a lack of emotional expression. This is consistent with research separating motivational/volitional negative symptoms like anhedonia from expressive negative symptoms such as flat affect (for a review, see Messinger et al., 2011). In contrast, as expected, self-reported anhedonia was strongly correlated with both increased other self-reported social symptoms (social anxiety and suspiciousness) as well as decreased extraversion.

Correlations among Positive Emotion Variables

Next I examined the correlations between the different positive emotion variables in this study in the probands (correlations in the relatives and the controls are in Tables 5-6). As can be seen in Table 4, the picture rating task (PRT) and self-rated liking task (SRLT) measures tended to be strongly correlated with each other. This makes sense, as they both involved ratings of pictures. In contrast, the measure of olfactory liking, the *Sniffin' Sticks* (SS), was not significantly correlated with other measures, although associations tended to be stronger with liking and wanting on the TEPS. In addition, the TEPS wanting and liking scores were strongly correlated with each other and exhibited very similar correlations with other variables, making it unclear to what extent they were measuring unique constructs. In contrast, the TRT which is thought to measure a potentially critical emotion variable, the extent to which people are willing to expend effort for monetary reward (Treadway & Zald, 2011), was unassociated with every other PA variable. Finally, it should be noted that people's current rating of their positive mood was strongly associated with the PRT, the SRLT, and the TEPS.

Hypotheses 1-4: Association of Anhedonia with Positive Emotion Measures

Hypothesis 1. Hypothesis 1 was that anhedonia would be significantly associated with positive affect intensity ratings for picture stimuli on the picture rating task. Specifically, I hypothesized that interviewer-rated anhedonia and as measured by the SANS would be significantly associated with a decrease in PA intensity. Spearman *rhos* are presented in Table 7, showing that contrary to what

was expected, the Anhedonia subscale of the SANS trended toward a positive association with PA intensity for positive pictures on the PRT. In addition, the SFS social and recreational subscales were unassociated with PA intensity.

We also wanted to examine whether associations would be found with another schizophrenia symptom involving emotion. I included SANS Flat Affect associations in the table to illustrate associations with another negative symptom factor . This was also unassociated with PA intensity in the probands.

Next, I examined the association of self-reported anhedonia on the SPQ with ratings of PA intensity. Table 8 examines self-reported anhedonia, social anxiety, and suspiciousness measured by subscales of the SPQ, as well as extraversion as measured by the IPIP. As can be seen in Table 8, there was a trend predicting decreased PA intensity for positive pictures on the PRT from self-reported anhedonia. This finding was consistent with my hypothesis that anhedonia would be associated with decreased PA intensity, but is strikingly different from results obtained by the interview measures of anhedonia. Furthermore, not only was self-reported anhedonia predictive of PA intensity, but associations with self-reported social anxiety and suspiciousness on the SPQ were not significant (*rhos* = -.07 and -.15, respectively). Thus, it appears that the association with PA intensity was specific to anhedonia.

An association between PA intensity and self-reported extraversion in probands was significant, *rho* = .41, p = .02. This is generally consistent with the notion that extraversion reflects increased PA, and that anhedonia reflects decreased PA, and was an expected result. To examine whether variance in extraversion

accounted for a relationship between SPQ anhedonia and PA intensity, I removed the variance accounted for by extraversion and examined the association between anhedonia and PA intensity. Despite a significant overlap between anhedonia and extraversion (*rho* = .50, $p < .05$), accounting for the variance in extraversion still resulted in a significant relationship between self-reported anhedonia and PA intensity (*rho* = -.43, $p < .05$).

Hypothesis 2. Hypothesis 2 was that any association between anhedonia and positive affect intensity would not be accounted for by current depression or affect, as measured by the BPRS and current affect items. Depression as measured by the BPRS was not significantly associated with either interview-rated or self-reported anhedonia. We then examined whether current affect (specifically, positive affect reported by the probands, which was highly associated with PA intensity) might mediate a relationship between self-reported anhedonia and PA intensity.

Mediational analyses of current PA on the relationship between self-reported anhedonia symptoms and positive affect intensity as measured by the PRT were conducted with PRODCLIN for R (Mackinnon et al., 2007). This method, unlike the Sobel test, yields asymmetric confidence intervals for a product of the regression coefficients without any assumption that the regression coefficient products are normally distributed. Because zero fell within both 95% and 99% upper and lower confidence intervals, I concluded that current PA did not mediate the relationship between anhedonia and positive affect intensity.

Partial correlations controlling for variance in NA resulted in highly significant relationships between self-reported no close friends/constricted affect

composite scores and PRT PA intensity (r = -.59, p = .005) and PA frequency (r = -.57, p = .008). When separating the composite anhedonia score into the two independent subscales, partial correlations still showed significant relationships of each of the subscales with the on-line emotion ratings of positive affect.

Hypothesis 3. Hypothesis 3 was that SANS anhedonia would be associated with self- reported positive appraisal of on-line stimuli. To test this, I examined the association of anhedonia in the probands with the "liking" emotion task variables. I hypothesized that interviewer-rated anhedonia as measured by the SANS would be significantly associated with a decrease in pleasure ratings as measured by the SRLT, the olfactory measure, and the TEPS Liking subscale.

Spearman *rhos* for these associations are presented in Table 7. As shown, there were few significant associations between anhedonia on the SANS and "liking" reports. Again, this was counter to the association hypothesized relating to the interview measures of anhedonia.

In contrast, SANS interview-assessed anhedonia was significantly negatively associated with hedonic liking ratings on the nasochemical sensory test (n = 25). This is somewhat inconsistent with results showing that SANS anhedonia is not associated with liking on the picture tasks. In light of the olfactory ratings being unassociated with other PA variables, this association may be interpreted to mean that nasosensory modality of hedonic response is distinct from these other PA measures and associated with interview-rated anhedonia. As can be seen in Table 7, the association between hedonic ratings and anhedonia was not specific to anhedonia, however, as ratings were also associated with the

emotional symptom of flat affect. On the other hand, this smell task was not associated with other negative symptoms on the SANS unrelated to emotion, such as lack of speech and lack of goal-directed activity.

Next, I examined whether the SFS interview measures of social and recreational behaviors might be associated with the liking measures. Similar to the SANS, correlations of SFS social and recreational subscales with liking measures failed to be significant. Specifically, the olfactory ratings were unassociated with SFS interview subscales (both *rhos* $\leq$ .2), though the association was in the expected direction.

I then examined whether self-reported anhedonia as measured by the SPQ was associated with the liking measures. As can be seen in Table 8, self-reported anhedonia trended toward a negative association with SRLT liking, was significantly negatively associated with SRLT arousal for positive pictures, and was significantly negatively associated with TEPS liking. This was consistent with the hypothesis that anhedonia would be associated with liking, but the results are again strikingly different from those of the interview-based measures. I also predicted that the suspiciousness and social anxiety subscales would not reflect anhedonia, thus would not be associated with liking variables. As can be seen in Table 8, consistent with this these SPQ subscales were not significantly associated with any of the liking variables. Lastly, consistent with what was expected, extraversion trended toward a positive association with liking on the TEPS (*rho* = .33, p = .05).

Hypothesis 4. Hypothesis 4 was that anhedonia would be associated with decreased self- reported and behavioral measures of wanting, or anticipatory pleasure. To test this, correlations between anhedonia and anticipatory pleasure measures were conducted. As presented in Table 7, SANS anhedonia was not significantly associated with self-reported TEPS anticipatory pleasure. However, another schizophrenia emotion symptom, flat affect, was significantly associated with TEPS anticipatory pleasure scores. Counter to what was expected, anhedonia was not negatively associated with TRT performance in the proband group (*rho* = .25).

I next examined whether self-reported anhedonia may be associated with decreased wanting in people with schizophrenia. Here, the TEPS Wanting subscale was negatively associated with self-reported anhedonia in the probands. However, similar to the SANS interview rating results, the TRT was not significantly associated with self-reported anhedonia in the probands, if anything being positively associated with anhedonia (rho = .30). The social anxiety and suspiciousness subscales of the SPQ were not significantly associated with TEPS wanting, though extraversion was very highly associated with TEPS wanting scores (rho = .59, p <.001). Finally, analyses examining correlations of SFS social and recreational subscales with both wanting measures failed to be significant.

Hypotheses 5-9: Associations of Hedonic Measures with Phenotypes in First-Degree Relatives and Nonpsychiatric Controls

Hypothesis 5. Hypothesis 5 was that self-reported anhedonia would be significantly associated with positive affect intensity ratings for picture stimuli on the picture rating task in first-degree relatives and in controls. This required examining

Spearman *rho* correlations between anhedonia (from the RSAS and PAS) and the measure of PA intensity for positive pictures from the PRT. Spearman rho correlations of SAE scales with emotion variables in first-degree relatives (*ns* = 29-34) are presented in Table 9. Counter to what was hypothesized, social and physical anhedonia were not associated with decreased PA intensity on the Picture Rating Task in relatives and controls.

Hypothesis 6. Hypothesis 6 was that any association between self-reported anhedonia and PA intensity would not be accounted for by current depression or affect, as measured by the BPRS and the Mood Questionnaire. The lack of association of anhedonia with PA intensity made these analyses unnecessary.

Hypothesis 7. Hypothesis 7 was that anhedonia would be associated with self-reported liking in the first-degree relatives. To test this, correlations between anhedonia and liking ratings on the SRLT, the olfactory measure, and the TEPS were examined. As can be seen in Table 9, social and physical anhedonia were associated with liking as measured by the SRLT. Physical anhedonia, but not social anhedonia, in the relatives was also significantly associated with TEPS liking scores in the relatives.

Enough SPQ pilot data were collected on first-degree relatives that relationships between the SPQ anhedonia composite score and emotion variables could also be examined. Spearman rho correlations in first-degree relatives (*n* = 21) are presented in Table 9. As shown, self-reported anhedonia on the SPQ was significantly associated with decreased liking of positive pictures on the SRLT. Self-reported anhedonia was not significantly associated with the olfactory ratings

or TEPS liking scores. The association of anhedonia with SRLT liking seemed specific to anhedonia--social anxiety, suspiciousness, and extraversion were unassociated with the SRLT in the relatives.

Similar Spearman rho correlations of schizotypy scales with emotion variables were conducted in nonpsychiatric controls (n = 21). No significant associations were observed in the control group (all p values > .2).

Hypothesis 8. Hypothesis 8 was that anhedonia would also be associated with decreased anticipatory pleasure. Social anhedonia in the relatives was not associated with decreased effort for reward on the TRT (*rho* = .05), and was not significantly associated with decreased self-reported wanting as measured by the TEPS (*rho* = -.26). There were no significant associations between physical anhedonia and wanting measures. As shown in Table 9, self-reported anhedonia on the SPQ was not associated with decreased wanting as measured by the TRT or the TEPS.

Similar Spearman *rho* correlations were conducted in nonpsychiatric controls (n = 21). Significant negative associations were observed only between physical anhedonia and TEPS Wanting (*rho* = -.60, p = .005). No other associations were observed (all p values > .2).

Hypothesis 9. If anhedonia had been related to positive affect in at least two of the three subject groups, hypothesis 9 was that the magnitude of any associations between anhedonia and PA intensity would be greatest for patients, then relatives, then controls, respectively. Because associations were not detected in two of the subject groups, these analyses were unnecessary.

Supplemental Analyses: Group Comparisons of Emotion Variable Means

While group comparisons across all tasks are of interest, these analyses come with limitations (as outlined in the Introduction) and are ancillary to the main hypotheses of the research examining relationships between emotion and schizophrenia-spectrum symptoms. Group comparisons on the emotion study variables are presented in Table 10. Given that many of the emotion variables had not been measured in people with schizophrenia previously and heterogeneity of variance was assumed, both non-parametric (Kruskal Wallis) and parametric (ANOVA) analyses were conducted. For significant or trending group effects, follow-up comparisons were conducted to examine individual between-group differences.

Picture Rating Task.

PA and NA affect intensity. For valence intensity of emotion ratings on the PRT, as can be seen in Table 10, there was a significant interaction between valence and group, $F_{2, 84} = 4.21$, $p = .02$, partial $\eta^2 = 0.09$, with sex included as a covariate in the model. I then removed sex as a covariate from the model and the effect remained significant. Follow-up group comparisons of NA and PA affect intensity revealed a significant difference in overall NA and PA ratings between probands and relatives, with probands reporting more NA *and* PA than relatives ($t[63] = 3.30$, $p = .002$, and $t[63] = 2.1$, $p = .04$, respectively). Probands only differed from controls on overall reported NA, however ($t[55] = 3.06$, $p = .003$).

Relatives and controls did not differ significantly on overall NA or PA on the PRT.

When comparing reported high- and low-arousal PA and NA on the PRT between groups, probands reported significantly greater low- and high-arousal NA than relatives and controls (presented in Table 11). In addition, probands reported greater low-arousal PA compared with relatives, but not controls. Relatives and controls did not differ significantly on either high- or low-arousal NA or PA.

We next contrasted groups on NA intensity for negative pictures, and PA intensity for positive pictures. For PA analyses I included performance variables from both the PRT and the SRLT, since the SRLT is a measure of positive affect for positive pictures. First, a between groups analysis of variance revealed a significant group effect for NA for negative pictures on the PRT, $F_{2,86} = 5.42$, $p = .006$. Follow-up t-tests revealed significantly greater NA reported by probands compared with controls ($t[54] = 2.40$, $p = .02$) and relatives ($t[62] = 2.30$, $p = .004$). Relatives did not differ from controls on reports of NA for affectively-congruent picture stimuli. ANOVAs did not reveal significant differences between any of the groups on PA for positive pictures on either the PRT or the SRLT, and follow-up group comparisons confirmed that there were no significant differences between any of the subject groups .

PA and NA affect frequency. For valence frequency of emotion ratings on the PRT, there was not a significant interaction of valence and group with sex entered as a covariate in the model, $F_{2,84} = .95$, $p = .39$, though the model was

somewhat underpowered with a partial $\eta^2 = 0.02$. Removing sex from the model resulted in a nearly significant valence frequency x group interaction, $F_{2,84} = 2.63$, $p = 0.08$, partial $\eta^2 = .06$. Follow-up univariate analyses indicated a significant group effect for NA frequency ($F_{2,88} = 3.99$, $p = .02$) with a significant difference in overall NA frequency ratings between probands and relatives ($t[62] = 2.39$, $p = .02$) and probands and controls ($t[54] = 2.19$, $p = .03$). Univariate analyses with group (proband, relative, control) and gender (male, female) did not reveal any significant interactions of group x gender for any of the variables.

Self-Reported Liking Task. The SRLT, while being a measure of liking of affectively-valenced picture stimuli, also measures general arousal for each picture by eliciting a response on the same 9-point Likert scale for self-reported excitement. As can be seen in Table 10, relatives also differed from controls with significantly greater self-reported arousal for positive pictures. In contrast, probands and relatives did not differ on arousal for positive pictures.

However, there was a significant group x gender interaction for SRLT Arousal for positive pictures. Closer examination of gender in the three groups revealed significant elevations in arousal for positive pictures on the SRLT in female relatives compared with female probands ($t[22] = 4.79$, $p < .001$) and compared with female controls ($t[24] = 2.72$, $p = .01$). So, even though relatives did not report increased liking of positive pictures on the SRLT or PA intensity on the PRT, relatives did report more arousal from positive pictures.

Temporal Experience of Pleasure Scale. Relatives of schizophrenia probands generally scored higher on the TEPS liking self-report than probands or

controls, counter to expectations, though the comparison between relative and proband groups was not significant at $p < .05$. So, even though the relatives reported more current negative affect than controls and did not differ from controls on PA task variables, this group self-reported more liking in daily life. Univariate analyses with group (proband, relative, control) and gender (male, female) did not reveal any significant interactions of group x gender for any of the variables.

Tapping for Reward Task. Tapping for Reward Task scores were significantly associated with group, and when removing a TRT outlier from the proband sample, this group effect remained, $F_{1,97} = 3.49$, $p = .03$. Schizophrenia probands exerted less overall effort for reward than relatives on the this task (SZ mean *(SD)* = 347.9 (94.6) and relative mean *(SD)* = 376.8 (64.6); $p = .14$) and controls (control mean *(SD)* = 399.0 (32.6); $p = .004$). Similarly, relatives exerted less effort on the TRT than controls ($p = .08$). Despite apparent ceiling effects across all groups, there was still an overall group effect with probands exerting less effort than relatives, who exerted less effort than controls. Age and gender were unassociated with TRT performance in any of the three participant groups.

Until now, there have been no behavioral tasks of effort expenditure for reward that have been associated with schizophrenia. This novel finding indicates that when calibrating effort expenditure to the individual's ability, people with schizophrenia choose to expend less effort. If the task measures the construct it intends to measure, this suggests that genetic liability for schizophrenia may be associated with incentive for reward.

Current affect. In univariate analyses of current affect ratings, there was a significant group effect for NA, $F_{2,84}$ = 5.46, p = .006. Probands reported significantly greater NA than controls generally, t[51] = 3.46, p = .002. There was a trend toward higher NA in the probands compared with relatives, t[58] = 1.74, p = .09. Relatives reported significantly more NA than controls, t[51] = 2.01, p = .03.

Group comparisons by affect self-report and by arousal are presented in Table 11. When separating high- from low-arousal negative emotions, probands and relatives both differed significantly from controls in reporting high arousal negative emotion, and probands reported significantly more low arousal negative affect than controls (all p's < .01). Univariate analyses with group (proband, relative, control) and gender (male, female) did not reveal any significant interactions of group x gender for any of the variables.

Schizotypy Symptom Means

Next I examined self-reported schizotypal traits in each group, including schizotypal symptom reports assessed by the SPQ and extraversion on the IPIP. Due to time constraints on the protocol, the relatives and controls provided limited data on this measure (ns presented in Table 13). Schizophrenia proband (n = 31) means and standard deviations are presented in Table 12 for the interpersonal factor and the subscales of the factor. In addition, means and standard deviations of the Extraversion scale of the IPIP are provided in Table 12.

Schizophrenia probands scored significantly higher overall on the SPQ, with significant elevations in the interpersonal factor. Means were elevated

compared with relatives across all subscales of the factor. In addition, probands reported significantly more suspiciousness and less extraversion compared with relatives.

Means and standard deviations of the relatives are compared with those of the probands in Table 12. Nearly the entire sample of relatives and controls completed both the SAE and the IPIP, thus it was possible to conduct all of the planned analyses of schizotypal traits for the purposes of the dissertation. However, first-degree relatives and controls provided limited valid SPQ data, thus only pilot analyses could be completed with these data. 18 relatives and 7 controls provided complete SPQ data, and the remainder of the sample either did not complete the measure due to protocol time restraints (n = 18), invalid responding (n = 2), geographic relocation (n = 6) or attrition due to decreased motivation to complete a last study session (n = 12).

Because there was a large enough sample of relatives completing the SPQ, group comparisons of relatives and probands could be conducted. Repeated measures analysis of the Interpersonal factor subscales yielded an effect of group, $F_{1,45}$ = 6.96, p = .01, but not gender main effects, $F_{1,45}$ = 0.62, p =.44, or an interaction of group x gender, $F_{1,45}$ = 2.48, p = .12.

Next, I compared relatives and controls on self-reported interpersonal traits as measured by the SPQ, SAE, and IPIP Extraversion subscale. Means and

standard deviations, along with group comparison statistics, are presented for selected scales in Table 13.[1]

Repeated measures analysis of the SAE scales yielded an effect of group, $F_{1,46}$ = 5.26, p = .02, but not gender, $F_{1,46}$ = 0.55, p =.46, or interaction of group x gender, $F_{1,46}$ = .19, p = .66. Comparisons of each SAE scale yielded significant group effects for the SAS.

Repeated measures analysis of the SPQ interpersonal factor subscales yielded an effect of group, $F_{1,21}$ = 5.86, p = .03, but the sample was too underpowered to test for gender and group x gender interaction. Comparisons for each subscale yielded group effects for the no close friends and constricted affect subscales (see sample comparisons in Tables 12 and 13).

First-degree relatives reported significantly greater levels of overall schizotypal personality with significantly greater scores on the SPQ interpersonal factor and the RSAS. As expected, increased anhedonia as measured by the RSAS in the relative group was highly significantly associated with increased scores on the no close friends/constricted affect composite score (*rho* = .62, p = .008).

Hierarchical regression analyses predicting RSAS scores were conducted to determine whether variance in the RSAS was accounted for by group status allowing for extraversion and current affect. When adding group (relative vs. control) to the model, current NA remained significant (p <.05) but group status

[1] To minimize skew and kurtosis in the PAS, logarithmic transformation of the variable was conducted and analyses with and without the transformation were examined. There were no notable differences between analyses of the PAS and analyses of the PAS transform.

improved the model significantly, $\Delta F_{1,42} = 4.17$, $\Delta R^2 = .08$. Thus, relative group status predicted social anhedonia even when accounting for extraversion and current NA and PA.

Supplemental Analyses: Ambivalence

One emotion construct previously unexamined in probands and relatives is ambivalence. Though ambivalence has long been thought an important emotional symptom of schizophrenia, recent analyses of data from another study (Docherty et al., in review) suggest that conflicting negative and positive emotions, self-reported in people with psychotic disorders, is associated with mood rather than with schizophrenia. Thus, I decided to examine behavioral evidence of ambivalence as a separate emotion trait in this study, to examine whether ambivalence is associated with anhedonia.

Ambivalence as a construct was described by Bleuler as one of the four primary symptoms of schizophrenia, and was defined by "positive and negative [emotions] at one and the same time" (Bleuler, 1911/1950, p. 53; Raulin, 1993). Despite the potential importance of this construct for schizophrenia, there are arguably no clearly validated measures of ambivalence for use with people schizophrenia. There was some evidence that ambivalence should be studied in these samples. In this study, self-reported negative emotions in the probands was actually positively associated with PA intensity for positive pictures. Interview-rated negative mood was negatively associated with PA intensity. These results suggested a possible decrease in emotional clarity in probands, or an increase in emotional ambivalence. To examine this further, I experimentally created

ambivalence scores by examining both NA for positive pictures and PA for negative pictures on the PRT.

We compared groups on ratings of conflicting affect to see whether people with schizophrenia and their relatives reported more ambivalence. Average NA intensity for positive pictures on the PRT was examined across all subject groups, with a significant overall group effect ($F_{2,91} = 7.01$, $p = .002$) and follow-up group comparisons indicated that probands reported significantly greater NA for positive pictures than relatives ($t[63] = 2.78$, $p = .007$) and controls ($t[55] = 2.99$, $p = .002$). There was also a significant group effect of PA for negative pictures on the PRT, $F_{2,91} = 4.82$, $p = .01$. Despite reporting more negative affect than other groups overall, the proband group reported increased PA for negative pictures on the PRT compared with both relatives and controls. Univariate analyses with group (proband, relative, control) and gender (male, female) indicated no significant interactions of group x gender for any of the variables. Figure 1 presents ambivalence variable by group, with notation for significant between group comparisons.

Given the group effects, one important question to consider was whether ambivalent responses might be disproportionately influenced by current affect in the probands. If current affect is associated with ambivalence, this might explain why previous findings suggested ambivalence to be more related to negative mood than to schizophrenia. Ambivalence scores were examined relative to current affect in the schizophrenia probands. Results are presented in Table 14. As shown, current NA was associated with increased NA for positive pictures, and

current PA was associated with increased PA for negative pictures. So overall, current affect did seem to show a meaningful association with ambivalence variables in the proband group. In looking at these correlations, there are some strikingly large associations, although it is not readily clear what they mean. One interpretation is that *if* probands are generally more emotional than other groups (as suggested by current affect ratings) they may have less emotional clarity when viewing emotional pictures, or they may have increased non-specific emotional reactivity to emotional stimuli.

4. DISCUSSION

This research examined emotion traits as potential phenotypes for anhedonia in genetic liability for schizophrenia. Overall, this study provided novel information about positive affect intensity, liking, and effort expenditure in genetic liability to schizophrenia, examining on-line emotional experience. There was a general lack of association between interview anhedonia and many of the PA variables, coupled with a lack of group differences on the PA variables. However, there was general evidence of association between self-reported anhedonia (in both probands and relatives) with many of the PA variables. In addition, there was an association of olfactory liking with interview symptoms, yielding a curious result. Furthermore, significant group differences on a novel behavioral measure of wanting, the TRT, were detected. Last, significant group differences in a behavioral task measuring ambivalence were detected, and results suggesting that ambivalence may be more associated with affect than with schizophrenia.

Positive Affect Intensity, Liking, and Wanting in Anhedonia

Results suggested that PA intensity, liking, and arousal for positive pictures are somewhat associated with self-reported anhedonia in patients and in relatives, despite a generally intact reporting of liking in each group. Relationships appeared specific to anhedonia and were not found when examining other schizotypal traits of social anxiety and suspiciousness. However, effects were only present relative to self-report symptom measures, and were not generally found when examining interview ratings of anhedonia. This presents questions about potential methodological differences between interview ratings and self-reported anhedonia. One reason for discrepancy could be the amount of information collected by the interviewer for the SANS. Another reason could be the more limited range of time reflected in the SANS--in this interview, symptom severity is rated for the last month, different from self-report measures which are designed to collect stable, trait information. While interview ratings are based on the behaviors and relationships people report, questionnaires also tend to tap how people tend to *feel* about relationships and pleasurable activities.

Another question is whether the SPQ subscales actually tap anhedonia directly in people with schizophrenia. While these subscales measure facets of anhedonia, they may also tap other constructs. Hence, it is possible that our results with patients could be re-interpreted as reflecting broader social and emotional deficits than specifically reflecting anhedonia. It should be noted, however, that results for the SPQ subscales and for more direct anhedonia measures in relatives were roughly similar. At the same time, we also found strikingly different results

between interview and self-report methods of measuring anhedonia, and this may be an important methodological piece to studying the nature of anhedonia and whether it is associated with deficits in either liking or wanting.

Some previous literature has found little association between anhedonia and liking in people with schizophrenia. Horan et al. (2006) found anhedonia to be unassociated with measures of liking. Gard et al. (2007) found anhedonia in probands to be associated with wanting but not liking as measured by TEPS self-report. Other research found that neural activation associated with wanting specifically, but not liking, was related to anhedonia in 23 people with schizophrenia (Ursu et al., 2011). One recent literature review posits that anhedonia stems from a deficit in source memory or access to emotional knowledge of non-current feelings (Strauss & Gold, 2012; also see Brebain et al., 2012). In this study, consistent with previous research, interviewer-rated anhedonia was not associated with PA intensity in probands.

There is reason to posit that methodological factors account for some inconsistency across studies. The use of two behavioral measures of liking and affect in this study (with good convergent validity) suggests that decreased PA *is* associated with *self-reported* anhedonia in people with genetic liability for schizophrenia. This would be consistent with previous studies of anhedonia in college student samples (Kerns et al., 2008), finding an association of PA intensity, as measured by the PRT, with self-reported anhedonia. These findings in college students were present whether anhedonia was examined as a continuous

trait, or whether extreme-scoring college students were tested against both non-schizotypal and schizotypal control groups.

Future studies using both clinical and self-report measures of anhedonia with a larger cohort could offer clarity. More recently, a new structured interview specifically for negative symptoms (the CAINS; Horan et al., 2011) has been validated for use with probands and may be useful in elucidating discrepancies in the literature. For example, it is possible that the range of anhedonia scores rated by SANS interview was too small (0-5) to generate significant effects in this study, or it could be that the range of SANS anhedonia in the probands and relatives electing to participate was limited. The CAINS has a broader range of scores and may more systematically assess important facets of anhedonia that are not systematically measured with the SANS. Also, future research assessing PA intensity with a greater number of picture stimuli may be beneficial--one difference between the SRLT and the PRT relates to the smaller number of positive pictures presented in the PRT. A smaller range of scores on the PRT could lead to limited findings regarding associations, especially between anhedonia in relatives and the PRT (or between anhedonia on the SANS and the PRT).

Olfactory Hedonic Ratings

This research piloted a new olfactory hedonic response task on a subsample of individuals in order to examine sensory modality of liking. An exception to the associations with self-reported anhedonia was this task, which was significantly related to interview-rated anhedonia, but was not related to self-

reported anhedonia in the probands. Olfactory hedonic ratings were also significantly related to social anhedonia in the relatives. While these preliminary results are promising, it is unclear why this olfactory task was not associated with other liking tasks, and why it did not correlate with self-reported anhedonia in the probands.

One possibility is that olfactory hedonic ratings could potentially tap different mechanisms of emotion response. Previous research on olfaction and emotion has found the smells are potent elicitors of emotion, able to produce changes in mood without awareness of a change in smell (Haviland-Jones & Wilson, 2008). In addition, smells seem capable of producing strong affective responses that might be less influenced by social information, as in pictures, that cue participants to how they should respond to the stimulus. At the same time, olfactory information is relayed directly to the amygdala and the orbitofrontal cortex, regions critically involved in emotion, suggesting that smells might be more likely to result in activation of critical neural regions involved in emotion than are non-personally relevant picture stimuli (Haviland-Jones & Wilson, 2008). Furthermore, there is evidence that olfaction can be a marker for neural damage as smell deficits are found early in disorders such as Alzheimer's and Parkinson's and loss of olfaction also associated with emotion changes such as severe depressed mood. This suggests that olfaction might be an important way to assess emotion functioning in schizophrenia. Consistent with this, I found that interview-assessed anhedonia as well as flat affect were both associated with decreased liking of positive smells.

Some previous schizophrenia research has also suggested that olfaction might be impaired in the disorder. In one previous study (Crespo-Faccoro et al., 2001), people with schizophrenia showed impairment in the subjective experience of pleasant odors relative to controls. However, limbic and paralimbic activation was comparable across groups for the pleasant but not unpleasant odors (insular cortex, nucleus accumbens, and parahippocampal gyrus), for which patients recruited a compensatory set of frontal regions. Another study of people with schizophrenia found a reduced accuracy for identifying pleasant odors relative to unpleasant odors (Kamath et al., 2011). While in our study odor identification performance was not tested, it may be that odor valence was reduced in the patient sample and that consequently levels of hedonic response were reduced. Thus future research on this sensory modality, examining valence and accuracy in a larger cohort, is warranted.

Tapping for Reward Task

This study also involved the design and implementation of a new cognitive task paradigm to measure effort expenditure for reward in schizophrenia. The Tapping for Reward Task was designed to demand effort expenditure while controlling for individual differences in physical ability--each participant completed a uniquely calibrated task that based its demands on the baseline tapping speed of the individual. This allowed the experimenter to control for factors such as medication or age that might influence tapping speed. This also controlled for any association of dopamine with baseline finger-tapping speed (which has also been found in nonpsychiatric controls; Volkow et al., 1998).

Not only did people with schizophrenia exert significantly less effort for monetary incentive than controls, but first-degree relatives also exerted less effort than controls. The overall group effect was significant *despite* the presence of apparent ceiling effects in each group, suggesting that if the monetary reward is modified to reduce the ceiling effects, the power to detect group effects may be stronger. Until now researchers have had little success in designing reward incentive tasks for use with schizophrenia samples, and none to our knowledge have shown such behavioral effects in patients and relatives.

Effort expenditure for reward has been associated with anhedonia in at least one sample of anhedonic college students (Treadway et al., 2009) and has been directly linked to dopamine signaling in left striatum and ventrolateral prefrontal cortex (Treadway et al., 2012). However, effort expenditure for reward has never been examined in relation to anhedonia in genetic liability for schizophrenia. Based on the previous research of Treadway and colleagues, one might expect effort for reward to be associated with anhedonia (and/or striatal dopamine signaling) in our schizophrenia and relative sample. While I was able to detect a group effect with the TRT, performance was unrelated to schizophrenia symptoms in the patients, and was unrelated to schizotypal traits in the relatives.

There are several possible reasons that the TRT was not associated with anhedonia in probands or relatives. One possibility is that the ceiling effects found on the TRT minimized the range of scores and reduced power to detect associations. One way to address this question would be to examine larger cohorts and to recalibrate the TRT reward to maximize the range of effort elicited.

Another possibility is that the levels of anhedonia in probands and relatives were lower than that of other samples. The sample in previous research by Treadway et al had a mean RSAS score of 19.5 because the sample was selected for a large range of anhedonia--elevated compared with our relative sample mean of 13.0 and our control sample mean of 9.8.

Previous research has found that dopamine function predicts willingness to expend effort for greater rewards, and underlies individual differences in cost/benefit decision making (Treadway et al., 2012). While first-degree relatives and people with schizophrenia exhibit behavior consistent with differential cost/benefit appraisal, it would be worthwhile for future research to examine whether COMT (largely effecting prefrontal dopamine) moderates a relationship between anhedonia and TRT performance. There is growing literature on the elevations of anhedonia in first-degree relatives, and growing evidence that COMT is related to the presence of anhedonia in relatives (Docherty et al., 2008) and in college samples. It may be that as a group, relatives do not present with levels of anhedonia relevant to TRT performance, but that subgroups without valine to methionine substitutions at the relevant locus would show reduced effort.

The TRT results are seemingly inconsistent with one recent study of passive response to anticipated reward cues, in which fMRI activation was not specific to group status (schizophrenia versus control) but was associated with anhedonia across both groups (Dowd & Barch, 2012). However, this may be due to the effort expenditure required by the TRT; while the previous study measured

brain activation relative to passive anticipation, the TRT behaviorally measured effort people would be willing to spend to receive reward.

Ambivalence

Last, these studies involved the measurement of incongruent emotion for standardized visual stimuli, and allowed for an analogue computation of ambivalence. Ambivalence has long been considered a core facet of schizophrenia, yet to date there is only one study to our knowledge that has measured ambivalence with a behavioral task (Tremeau et al., 2009b). In addition, recently self-reported ambivalence has been associated with mood rather than with schizophrenia symptoms (Docherty et al., in review). In the current study, I found group differences in ambivalence and was able to examine ambivalence as it relates to current affect and schizophrenia symptoms. While schizophrenia patient elevations in ambivalence were consistent with one previous behavioral study of ambivalence (Tremeau et al., 2009b), I also found that ambivalence was significantly associated with current positive and negative affect in probands, but not in relatives or controls.

Elevations in ambivalence were not associated with schizophrenia symptoms in the proband group, and were only associated with current affect. These results are consistent with the recent findings that self-reported ambivalence in schizophrenia-spectrum patients is more associated with current mood symptoms, and with a diagnosis of bipolar disorder or schizoaffective disorder over that of schizophrenia (Docherty et al., in review). Because current affect appears to predict both behavioral and self-report ambivalent responding, it

is possible that ambivalence as a construct may be more associated with mood than with schizophrenia.

Limitations

Two of the most important limitations of the study are the limited sample size and the lack of psychometrically-matched liking and wanting tasks. As data continue to be collected, sample sizes will increase and this may result in effects undetected in these analyses. Specifically, larger control and relative samples may provide needed power to detect group effects for some of the emotion measures. This would be somewhat expected, given the association of the emotion measures with schizotypal traits in the current sample. In addition, the lack of group effects for the liking tasks may be an artifact of measures that do not psychometrically match those of the wanting tasks.

Some additional methodological limitations were unforeseen. First, study administrators observed a general decrease in motivation to participate over the study protocol due to the demands of multiple tasks and questionnaires. And while probands and controls were often motivated by the monetary compensation to participate in the study, relatives had less monetary incentive to participate. Though relatives were also compensated, they were generally motivated by the desire to advance mental health research or to share in an experience with their proband family member. There was one relative participant who verbalized a desire to "compete" with siblings on the tasks involved in the study. However, despite these potential confounds, relatives still exhibited decreased performance on the TRT compared with controls.

In addition, decreased emotional investment, fatigue, or defensiveness in the relatives could have contributed noise to the findings in this study. Last, the increase in anhedonia in relatives and patients is found in individuals who choose to participate in research studies; however, those with very high levels of anhedonia presumably would not wish to participate. To this end, while we still detect increased anhedonia in relatives and patients, any research studying these samples will always be limited to the range of anhedonia in the individuals who are willing to come to the hospital, interact with a protocol administrator, and share personal information.

A last potential confound relates to the relatives sharing genetic material with the probands, which could potentially lead to similarities between groups that are not associated with schizophrenia-spectrum pathology. One way I expect to overcome this confound is to collect larger samples in order to obtain the power to model the effect of family membership on group differences.

REFERENCES

Abi-Dargham, A., & Moore, H. (2003). Prefrontal DA transmission at D1 receptors and the pathology of schizophrenia. *Neuroscientist, 9*(5), 404-416.

Andreasen, N. C. (1984). Scale for the assessment of positive symptoms (SAPS). Iowa City: University of Iowa College of Medicine.

Andreasen, N. C. (1984). Scale for the assessment of negative symptoms (SANS). Iowa City: University of Iowa College of Medicine.

Alves Fda, S., Figee, M., Vamelsvoort, T., Veltman, D., & de Haan, L. (2008). The revised dopamine hypothesis of schizophrenia: evidence from pharmacological MRI studies with atypical antipsychotic medication. *Psychopharmacology Bulletin, 41*(1), 121-132.

Avramopoulos, D., Stefanis, N. C., Hantoumi, I., Smyrnis, N., Evdokimidis, I., & Stefanis, C. N. (2002). Higher scores of self reported schizotypy in healthy young males carrying the COMT high activity allele. *Molecular Psychiatry, 7*(7), 706-711.

Barnett, J. H., Heron, J., Goldman, D., Jones, P. B., & Xu, K. (2009). Effects of catechol-O-methyltransferase on normal variation in the cognitive function of children. *American Journal of Psychiatry, 166*(8), 909-916.

Barrett, L. F. (2004). Feelings or words? Understanding the content in self-report ratings of experienced emotion. *Journal of Personality and Social Psychology, 87,* 266–281.

Berenbaum, H., Boden, M. T., Baker, J. P., Dizen, M., Thompson, R. J., & Abramowitz, A. (2006). Emotional correlates of the different dimensions of schizotypal personality disorder. *Journal of Abnormal Psychology, 115*(2), 359-368.

Berenbaum, H., Kerns, J. G., Vernon, L. L., & Gomez, J. J. (2008). Cognitive correlates of schizophrenia signs and symptoms: II. Emotional disturbances. *Psychiatry Research, 159*(1-2), 157-162.

Berenbaum, H., & McGrew, J. (1993). Familial resemblance of schizotypic traits. *Psychological Medicine, 23*(2), 327-333.

Berenbaum, H., & Oltmanns, T. F. (1992). Emotional experience and expression in schizophrenia and depression. *Journal of Abnormal Psychology, 101*(1), 37-44.

Berlin, I., Givry-Steiner, L., Lecrubier, Y., & Puech, A. J. (1998). Measures of anhedonia and hedonic responses to sucrose in depressive and schizophrenic patients in comparison with healthy subjects. *European Psychiatry, 13*(6), 303-309.

Berridge, K. C. (2007). The debate over dopamine's role in reward: the case for incentive salience. *Psychopharmacology (Berl), 191*(3), 391-431.

Berridge, K. C., & Robinson, T. E. (1998). What is the role of dopamine in reward: hedonic impact, reward learning, or incentive salience? *Brain Research: Brain Research Review, 28*(3), 309-369.

Berridge, K. C., Venier, I. L., & Robinson, T. E. (1989). Taste reactivity analysis of 6-hydroxydopamine-induced aphagia: implications for arousal and

anhedonia hypotheses of dopamine function. *Behavioral Neuroscience, 103*(1), 36-45.

Bilder, R. M., Volavka, J., Lachman, H. M., & Grace, A. A. (2004). The catechol-O-methyltransferase polymorphism: relations to the tonic-phasic dopamine hypothesis and neuropsychiatric phenotypes. *Neuropsychopharmacology, 29*(11), 1943-1961.

Bishop, S. J., Cohen, J. D., Fossella, J., Casey, B. J., & Farah, M. J. (2006). COMT genotype influences prefrontal response to emotional distraction. *Cognitive Affective Behavioral Neuroscience, 6*(1), 62-70.

Blanchard, J. J., Gangestad, S. W., Brown, S. A., & Horan, W. P. (2000). Hedonic capacity and schizotypy revisited: a taxometric analysis of social anhedonia. *Journal of Abnormal Psychology, 109*(1), 87-95.

Bleuler, E. (1950). *Dementia praecox*. New York,: International Universities Press.

Blood, A. J., & Zatorre, R. J. (2001). Intensely pleasurable responses to music correlate with activity in brain regions implicated in reward and emotion. *Proceedings of the National Academy of Sciences U S A, 98*(20), 11818-11823.

Braff, D. L., Freedman, R., Schork, N. J., & Gottesman, II. (2007). Deconstructing schizophrenia: an overview of the use of endophenotypes in order to understand a complex disorder. *Schizophrenia Bulletin, 33*(1), 21-32.

Buckholtz, J. W., Sust, S., Tan, H. Y., Mattay, V. S., Straub, R. E., Meyer-Lindenberg, A., et al. (2007). fMRI evidence for functional epistasis between COMT and RGS4. *Molecular Psychiatry, 12*(10), 893-895, 885.

Byrne, M., Clafferty, B. A., Cosway, R., Grant, E., Hodges, A., Whalley, H. C., et al. (2003). Neuropsychology, genetic liability, and psychotic symptoms in those at high risk of schizophrenia. *Journal of Abnormal Psychology, 112*(1), 38-48.

Canli, T., Qiu, M., Omura, K., Congdon, E., Haas, B. W., Amin, Z., et al. (2006). Neural correlates of epigenesis. *Proceedings of the National Academy of Sciences U S A, 103*(43), 16033-16038.

Cannon, T. D., Cornblatt, B., & McGorry, P. (2007). The empirical status of the ultra high-risk (prodromal) research paradigm. *Schizophrenia Bulletin, 33*(3), 661-664.

Carlsson, A., & Lindqvist, M. (1963). Effect of Chlorpromazine or Haloperidol on Formation of 3methoxytyramine and Normetanephrine in Mouse Brain. *Acta Pharmacologica Toxicol (Copenh), 20*, 140-144.

Cicero, D.C., Becker, T.M., Docherty, A.R., Martin, E.A., & Kerns, J.G. (2009). Prefrontal cortex and anterior cingulate cue-related activity during a cognitive control task. Presented at the Annual meeting of the Organization for Human Brain Mapping, San Francisco, CA.

Clementz, B. A., Grove, W. M., Katsanis, J., & Iacono, W. G. (1991). Psychometric detection of schizotypy: perceptual aberration and physical

anhedonia in relatives of schizophrenics. *Journal of Abnormal Psychology, 100*(4), 607-612.

Cohen, A. S., Leung, W. W., Saperstein, A. M., & Blanchard, J. J. (2006). Neuropsychological functioning and social anhedonia: results from a community high-risk study. *Schizophrenia Research, 85*(1-3), 132-141.

Crespo-Facorro, B., Paradiso, S., Andreason, N. C., O'Leary, D. S., Watkins, G. L., Ponto, L. L., & Hichwa, R. D. (2001). Neural mechanisms of anhedonia in schizophrenia: a PET study of response to unpleasant and pleasant odors. *Journal of the American Medical Association, 286*, 427-435.

Depue, R. A., & Collins, P. F. (1999). Neurobiology of the structure of personality: dopamine, facilitation of incentive motivation, and extraversion. *Behavior and Brain Sciences, 22*(3), 491-517; discussion 518-469.

Docherty, A. R., & Sponheim, S. R. (2008a). Anhedonia as a phenotype for the Val158Met COMT polymorphism in relatives of patients with schizophrenia. *Journal of Abnormal Psychology, 117*(4), 788-798.

Docherty, A. R., & Sponheim, S. R. (2008b). Anhedonia and the Val158Met COMT polymorphism in relatives of patients with schizophrenia. Presented at the Annual meeting of the Society for Research in Psychopathology.

Docherty, A. R. & Kerns, J. G. (2012). Self-reported ambivalence in schizophrenia and associations with negative mood. Manuscript in review.

Docherty, A. R., Berenbaum, H., & Kerns, J. G. (2011). Differential patterns of verbal fluency performance in alogia and formal thought disorder. *Journal of Psychiatric Research*, 45, 1352-1357.

Dowd, E. C., Barch, D. M. (2012). Pavlovian reward prediction and receipt in schizophrenia: relationship to anhedonia. *PLoS One*, 7, e35622.

Dreher, J. C., Kohn, P., & Berman, K. F. (2006). Neural coding of distinct statistical properties of reward information in humans. *Cerebral Cortex, 16*(4), 561-573.

Egan, M. F., Goldberg, T. E., Kolachana, B. S., Callicott, J. H., Mazzanti, C. M., Straub, R. E., et al. (2001). Effect of COMT Val108/158 Met genotype on frontal lobe function and risk for schizophrenia. *Proceedings of the National Academy of Sciences U S A, 98*(12), 6917-6922.

Etain, B., Roy, I., Henry, C., Rousseva, A., Schurhoff, F., Leboyer, M., et al. (2007). No evidence for physical anhedonia as a candidate symptom or an endophenotype in bipolar affective disorder. *Bipolar Disorders, 9*(7), 706-712.

Fanous, A., Gardner, C., Walsh, D., & Kendler, K. S. (2001). Relationship between positive and negative symptoms of schizophrenia and schizotypal symptoms in nonpsychotic relatives. *Archives of General Psychiatry, 58*(7), 669-673.

Faraone, S. V., Seidman, L. J., Kremen, W. S., Pepple, J. R., Lyons, M. J., & Tsuang, M. T. (1995). Neuropsychological functioning among the

nonpsychotic relatives of schizophrenic patients: a diagnostic efficiency analysis. *Journal of Abnormal Psychology, 104*(2), 286-304.

Fenton, W. S., & McGlashan, T. H. (1991). Natural history of schizophrenia subtypes. I. Longitudinal study of paranoid, hebephrenic, and undifferentiated schizophrenia. *Archives of General Psychiatry, 48*(11), 969-977.

Freedman, R. (2003). Schizophrenia. *New England Journal of Medicine, 349*(18), 1738-1749.

Gard, D. E., Gard, M. G., Kring, A. M., & John, O. P. (2006). Anticipatory and consummatory components of the experience of pleasure: A scale development study. *Journal of Research in Personality, 40,* 1086-1102.

Gard, D. E., Kring, A. M., Gard, M. G., Horan, W. P., & Green, M. F. (2007). Anhedonia in schizophrenia: distinctions between anticipatory and consummatory pleasure. *Schizophrenia Research, 93,* 253-260.

Gard, D. E., & Kring, A. M. (2009). Emotion in the daily lives of schizophrenia patients: Context matters. *Schizophrenia Research*, 115, 379-380.

Goghari, V. M., & Sponheim, S. R. (2008). Differential association of the COMT Val158Met polymorphism with clinical phenotypes in schizophrenia and bipolar disorder. *Schizophrenia Research, 103*(1-3), 186-191.

Goghari, V., Silberschmidt, A., Docherty, A. R., MacDonald, A. & Sponheim, S. R. (2008). Anhedonia as a phenotype for the Val158Met COMT polymorphism in relatives of patients with schizophrenia. Presented at the Annual meeting of the Society for Research in Psychopathology.

Gooding, D. C., & Braun, J. G. (2004). Visuoconstructive performance, implicit hemispatial inattention, and schizotypy. *Schizophrenia Research, 68*(2-3), 261-269.

Gooding, D. C., & Tallent, K. A. (2003). Spatial, object, and affective working memory in social anhedonia: an exploratory study. *Schizophrenia Research, 63*(3), 247-260.

Gottesman, II, & Gould, T. D. (2003). The endophenotype concept in psychiatry: etymology and strategic intentions. *American Journal of Psychiatry, 160*(4), 636-645.

Heckers, S., Rauch, S. L., Goff, D., Savage, C. R., Schachter, D. L., Fischman, A. J., et al. (1998). Impaired recruitment of the hippocampus during conscious recollection in schizophrenia. *Nature Neuroscience, 1*(4), 318-323.

Heerey, E. A., & Gold, J. M. (2007). Patients with schizophrenia demonstrate dissociation between affective experience and motivated behavior. *Journal of Abnormal Psychology, 116*(2), 268-278.

Henry, J. D., Green, M. J., de Lucia, A., Restuccia, C., McDonald, S., & O'Donnell, M. (2007). Emotion dysregulation in schizophrenia: reduced amplification of emotional expression is associated with emotional blunting. *Schizophrenia Research, 95*(1-3), 197-204.

Henry, J. D., Rendell, P. G., Green, M. J., McDonald, S., & O'Donnell, M. (2008). Emotion regulation in schizophrenia: affective, social, and clinical

correlates of suppression and reappraisal. *Journal of Abnormal Psychology, 117*(2), 473-478.

Hikida, T., Jaaro-Peled, H., Seshadri, S., Oishi, K., Hookway, C., Kong, S., et al. (2007). Dominant-negative DISC1 transgenic mice display schizophrenia-associated phenotypes detected by measures translatable to humans. *Proceedings of the National Academy of Sciences U S A, 104*(36), 14501-14506.

Ho, B. C., Wassink, T. H., O'Leary, D. S., Sheffield, V. C., & Andreasen, N. C. (2005). Catechol-O-methyl transferase Val158Met gene polymorphism in schizophrenia: working memory, frontal lobe MRI morphology and frontal cerebral blood flow. *Molecular Psychiatry, 10*(3), 229, 287-298.

Hong, J., Shu-Leong, H., Tao, X., & Lap-Ping, Y. (1998). Distribution of catechol-O-methyltransferase expression in human central nervous system. *Neuroreport, 9*(12), 2861-2864.

Horan, W. P., Brown, S. A., & Blanchard, J. J. (2007). Social anhedonia and schizotypy: the contribution of individual differences in affective traits, stress, and coping. *Psychiatry Research, 149*(1-3), 147-156.

Horan, W. P., Blanchard, J. J., Clark, L. A., & Green, M. F. (2008a). Affective traits in schizophrenia and schizotypy. *Schizophrenia Bulletin, 34*(5), 856-874.

Horan, W. P., Reise, S. P., Subotnik, K. L., Ventura, J., & Nuechterlein, K. H. (2008b). The validity of Psychosis Proneness Scales as vulnerability

indicators in recent-onset schizophrenia patients. *Schizophrenia Research, 100*(1-3), 224-236.

Horan, W. P., Kring, A. M., Gur, R., Reise, S., & Blanchard, J. J. (2011). Psychometric evaluation of the Clinical Assessment Interview for Negative Symptoms (CAINS) in a large outpatient schizophrenia sample. *Schizophrenia Research, 132*, 140-145.

Horvitz, J. C., Stewart, T., & Jacobs, B. L. (1997). Burst activity of ventral tegmental dopamine neurons is elicited by sensory stimuli in the awake cat. *Brain Research, 759*(2), 251-258.

Juckel, G., Schlagenhauf, F., Koslowski, M., Filonov, D., Wustenberg, T., Villringer, A., et al. (2006). Dysfunction of ventral striatal reward prediction in schizophrenic patients treated with typical, not atypical, neuroleptics. *Psychopharmacology (Berl), 187*(2), 222-228.

Kamath, V., Bedwell, J. S., Compton, M. T. (2011). Is the odour identification deficit in schizophrenia influenced by odour hedonics? *Cognitive Neuropsychiatry, 16*, 448-460.

Kegeles, L. S., Abi-Dargham, A., Zea-Ponce, Y., Rodenhiser-Hill, J., Mann, J. J., Van Heertum, R. L., et al. (2000). Modulation of amphetamine-induced striatal dopamine release by ketamine in humans: implications for schizophrenia. *Biological Psychiatry, 48*(7), 627-640.

Kendler, K. S., & Diehl, S. R. (1993). The genetics of schizophrenia: a current, genetic-epidemiologic perspective. *Schizophrenia Bulletin, 19*(2), 261-285.

Kendler, K. S., Thacker, L., & Walsh, D. (1996). Self-report measures of schizotypy as indices of familial vulnerability to schizophrenia. *Schizophrenia Bulletin, 22*(3), 511-520.

Kerns, J. G., Docherty, A. R., & Martin, E. A. (2008). Social and physical anhedonia and valence and arousal aspects of emotional experience. *Journal of Abnormal Psychology, 117*(4), 735-746.

Kring, A. M., Barrett, L. F., & Gard, D. E. (2003). On the broad applicability of the affective circumplex: representations of affective knowledge among schizophrenia patients. *Psychological Science, 14*(3), 207-214.

Kumari, V., Mitterschiffthaler, M. T., Teasdale, J. D., Malhi, G. S., Brown, R. G., Giampietro, V., et al. (2003). Neural abnormalities during cognitive generation of affect in treatment-resistant depression. *Biological Psychiatry, 54*(8), 777-791.

Kwapil, T. R. (1998). Social anhedonia as a predictor of the development of schizophrenia-spectrum disorders. *Journal of Abnormal Psychology, 107*(4), 558-565.

Laruelle, M., Abi-Dargham, A., Gil, R., Kegeles, L., & Innis, R. (1999). Increased dopamine transmission in schizophrenia: relationship to illness phases. *Biological Psychiatry, 46*(1), 56-72.

Lawrie, S. M., Whalley, H., Kestelman, J. N., Abukmeil, S. S., Byrne, M., Hodges, A., et al. (1999). Magnetic resonance imaging of brain in people at high risk of developing schizophrenia. *Lancet, 353*(9146), 30-33.

Lawrie, S. M., Whalley, H. C., Abukmeil, S. S., Kestelman, J. N., Donnelly, L., Miller, P., et al. (2001). Brain structure, genetic liability, and psychotic symptoms in subjects at high risk of developing schizophrenia. *Biological Psychiatry, 49*(10), 811-823.

Le Pen, G., Gaudet, L., Mortas, P., Mory, R., & Moreau, J. L. (2002). Deficits in reward sensitivity in a neurodevelopmental rat model of schizophrenia. *Psychopharmacology (Berl), 161*(4), 434-441.

Levy, J., Heller, W., Banich, M. T., & Burton, L. A. (1983). Asymmetry of perception in free viewing of chimeric faces. *Brain and Cognition, 2*(4), 404-419.

Li, W., Zhou, Y., Jentsch, J. D., Brown, R. A., Tian, X., Ehninger, D., et al. (2007). Specific developmental disruption of disrupted-in-schizophrenia-1 function results in schizophrenia-related phenotypes in mice. *Proceedings of the National Academy of Sciences U S A, 104*(46), 18280-18285.

Lotta, T., Vidgren, J., Tilgmann, C., Ulmanen, I., Melen, K., Julkunen, I., et al. (1995). Kinetics of human soluble and membrane-bound catechol O-methyltransferase: a revised mechanism and description of the thermolabile variant of the enzyme. *Biochemistry, 34*(13), 4202-4210.

Mandelli, L., Serretti, A., Marino, E., Pirovano, A., Calati, R., & Colombo, C. (2007). Interaction between serotonin transporter gene, catechol-O-methyltransferase gene and stressful life events in mood disorders. *International Journal of Neuropsychopharmacology, 10*(4), 437-447.

Martin, E. A., Docherty, A. R., & Kerns, J. G. (2008). Social and physical anhedonia and valence and arousal aspects of emotional experience. Presented at the Annual meeting of the Society for Research in Psychopathology.

Martin, E. A., Cicero, D. C., Becker, T. M., Docherty, A. R. & Kerns, J. G. (2009). Associations between schizotypy facets and attention to positive versus negative emotion. Presented at the Annual meeting of the Society for Research in Psychopathology.

McCabe, S. B., & Gotlib, I. H. (1995). Selective attention and clinical depression: performance on a deployment-of-attention task. *Journal of Abnormal Psychology, 104*(1), 241-245.

McDonald, C., Grech, A., Toulopoulou, T., Schulze, K., Chapple, B., Sham, P., et al. (2002). Brain volumes in familial and non-familial schizophrenic probands and their unaffected relatives. *American Journal of Medical Genetics, 114*(6), 616-625.

McGlashan, T. H., Zipursky, R. B., Perkins, D., Addington, J., Miller, T., Woods, S. W., et al. (2006). Randomized, double-blind trial of olanzapine versus placebo in patients prodromally symptomatic for psychosis. *American Journal of Psychiatry, 163*(5), 790-799.

McIntosh, A. M., Job, D. E., Moorhead, T. W., Harrison, L. K., Lawrie, S. M., & Johnstone, E. C. (2005). White matter density in patients with schizophrenia, bipolar disorder and their unaffected relatives. *Biological Psychiatry, 58*(3), 254-257.

McIntosh, A. M., Job, D. E., Moorhead, W. J., Harrison, L. K., Whalley, H. C., Johnstone, E. C., et al. (2006). Genetic liability to schizophrenia or bipolar disorder and its relationship to brain structure. *American Journal of Medical Genetics B: Neuropsychiatric Genetics, 141B*(1), 76-83.

Meyer, K. D., & Morris, J. A. (2009). Disc1 regulates granule cell migration in the developing hippocampus. *Human Molecular Genetics, 18*(17), 3286-3297.

Miller, T. J., McGlashan, T. H., Rosen, J. L., Cadenhead, K., Cannon, T., Ventura, J., et al. (2003). Prodromal assessment with the structured interview for prodromal syndromes and the scale of prodromal symptoms: predictive validity, interrater reliability, and training to reliability. *Schizophrenia Bulletin, 29*(4), 703-715.

Moreau, J. L., Borgulya, J., Jenck, F., & Martin, J. R. (1994). Tolcapone: a potential new antidepressant detected in a novel animal model of depression. *Behavioral Pharmacology, 5*(3), 344-350.

Overall, J. E., & Gorham, D. R. (1962). The Brief Psychiatric Rating Scale. *Psychological Reports*, 10, 799–803.

Phillips, M. L., Drevets, W. C., Rauch, S. L., & Lane, R. (2003). Neurobiology of emotion perception II: Implications for major psychiatric disorders. *Biological Psychiatry*, *54*(5), 515-528.

Pizzagalli, D. A., Iosifescu, D., Hallett, L. A., Ratner, K. G., & Fava, M. (2008). Reduced hedonic capacity in major depressive disorder: evidence from a probabilistic reward task. *Journal of Psychiatric Research, 43*(1), 76-87.

Pizzagalli, D. A., Jahn, A. L., & O'Shea, J. P. (2005). Toward an objective characterization of an anhedonic phenotype: a signal-detection approach. *Biological Psychiatry, 57*(4), 319-327.

Pletnikov, M. V., Ayhan, Y., Nikolskaia, O., Xu, Y., Ovanesov, M. V., Huang, H., et al. (2008). Inducible expression of mutant human DISC1 in mice is associated with brain and behavioral abnormalities reminiscent of schizophrenia. *Molecular Psychiatry, 13*(2), 173-186, 115.

Pletnikov, M. V., Ayhan, Y., Xu, Y., Nikolskaia, O., Ovanesov, M., Huang, H., et al. (2008). Enlargement of the lateral ventricles in mutant DISC1 transgenic mice. *Molecular Psychiatry, 13*(2), 115.

Posner, J., Russell, J. A., & Peterson, B. S. (2005). The circumplex model of affect: an integrative approach to affective neuroscience, cognitive development, and psychopathology. *Developmental Psychopathology, 17*(3), 715-734.

Prata, D. P., Mechelli, A., Fu, C. H., Picchioni, M., Toulopoulou, T., Bramon, E., et al. (2009). Epistasis between the DAT 3' UTR VNTR and the COMT Val158Met SNP on cortical function in healthy subjects and patients with schizophrenia. *Proceedings of the National Academy of Sciences U S A, 106*(32), 13600-13605.

Puglisi-Allegra, S., Carletti, P., & Cabib, S. (1990). LY 171555-induced catalepsy and defensive behavior in four strains of mice suggest the involvement of different D2 dopamine receptor systems. *Pharmacology and Biochemistry of Behavior, 36*(2), 327-331.

Puglisi-Allegra, S., Kempf, E., & Cabib, S. (1990). Role of genotype in the adaptation of the brain dopamine system to stress. *Neuroscience and Biobehavioral Reviews, 14*(4), 523-528.

Raine, A. (2006). Schizotypal personality: neurodevelopmental and psychosocial trajectories. *Annual Review of Clinical Psychology, 2*, 291-326.

Robinson, T. E., & Berridge, K. C. (1993). The neural basis of drug craving: an incentive-sensitization theory of addiction. *Brain Research: Brain Research Reviews, 18*(3), 247-291.

Roffman, J. L., Gollub, R. L., Calhoun, V. D., Wassink, T. H., Weiss, A. P., Ho, B. C., et al. (2008). MTHFR 677C --> T genotype disrupts prefrontal function in schizophrenia through an interaction with COMT 158Val --> Met. *Proceedings of the National Academy of Sciences U S A, 105*(45), 17573-17578.

Rolls, E. T., Loh, M., Deco, G., & Winterer, G. (2008). Computational models of schizophrenia and dopamine modulation in the prefrontal cortex. *Nature Reviews Neuroscience, 9*(9), 696-709.

Salamone, J. D., Correa, M., Farrar, A., & Mingote, S. M. (2007). Effort-related functions of nucleus accumbens dopamine and associated forebrain circuits. *Psychopharmacology (Berl), 191*(3), 461-482.

Schenkenberg, T., Bradford, D. C., & Ajax, E. T. (1980). Line bisection and unilateral visual neglect in patients with neurologic impairment. *Neurology, 30*(5), 509-517.

Schurhoff, F., Szoke, A., Chevalier, F., Roy, I., Meary, A., Bellivier, F., et al. (2007). Schizotypal dimensions: an intermediate phenotype associated with the COMT high activity allele. *American Journal of Medical Genetics B: Neuropsychiatric Genetics, 144B*(1), 64-68.

Seamans, J. K., & Yang, C. R. (2004). The principal features and mechanisms of dopamine modulation in the prefrontal cortex. *Progress in Neurobiology, 74*(1), 1-58.

Seeman, P. (1987). Dopamine receptors and the dopamine hypothesis of schizophrenia. *Synapse, 1*(2), 133-152.

Seeman, P., & Kapur, S. (2000). Schizophrenia: more dopamine, more D2 receptors. *Proceedings of the National Academy of Sciences U S A, 97*(14), 7673-7675.

Seidman, L. J., Faraone, S. V., Goldstein, J. M., Kremen, W. S., Horton, N. J., Makris, N., et al. (2002). Left hippocampal volume as a vulnerability indicator for schizophrenia: a magnetic resonance imaging morphometric study of nonpsychotic first-degree relatives. *Archives of General Psychiatry, 59*(9), 839-849.

Smyrnis, N., Avramopoulos, D., Evdokimidis, I., Stefanis, C. N., Tsekou, H., & Stefanis, N. C. (2007). Effect of schizotypy on cognitive performance and its tuning by COMT val158 met genotype variations in a large population of young men. *Biological Psychiatry, 61*(7), 845-853.

Snitz, B. E., Macdonald, A. W., 3rd, & Carter, C. S. (2006). Cognitive deficits in unaffected first-degree relatives of schizophrenia patients: a meta-analytic

review of putative endophenotypes. *Schizophrenia Bulletin, 32*(1), 179-194.

Sponheim, S.R., Docherty, A.R., Kreuger, R.F., Tackett, J.L. (2009). Paper Presentation. Positive and Negative Schizotypy as Indicators of Biological Vulnerability to Schizophrenia and Bipolar Disorder. Oral presentation at the Annual meeting of the Society for Research in Psychopathology.

Stefanis, N. C., Van Os, J., Avramopoulos, D., Smyrnis, N., Evdokimidis, I., Hantoumi, I., et al. (2004). Variation in catechol-o-methyltransferase val158 met genotype associated with schizotypy but not cognition: a population study in 543 young men. *Biological Psychiatry, 56*(7), 510-515.

Strauss, G. P. & Gold, J. M. (2012). A new perspective on anhedonia in schizophrenia. *American Journal of Psychiatry*, 169, 364-373.

Suslow, T., Dannlowski, U., Lalee-Mentzel, J., Donges, U. S., Arolt, V., & Kersting, A. (2004). Spatial processing of facial emotion in patients with unipolar depression: a longitudinal study. *Journal of Affective Disorders, 83*(1), 59-63.

Szendi, I., Kiss, M., Racsmany, M., Boda, K., Cimmer, C., Voros, E., et al. (2006). Correlations between clinical symptoms, working memory functions and structural brain abnormalities in men with schizophrenia. *Psychiatry Research, 147*(1), 47-55.

Tan, H. Y., Chen, Q., Sust, S., Buckholtz, J. W., Meyers, J. D., Egan, M. F., et al. (2007). Epistasis between catechol-O-methyltransferase and type II

metabotropic glutamate receptor 3 genes on working memory brain function. *Proceedings of the National Academy of Sciences U S A, 104*(30), 12536-12541.

Tan, H. Y., Callicott, J. Y., Weinberger, D. R. (2009). Prefrontal cognitive systems in schizophrenia: towards human genetic brain mechanisms. *Cognitive Neuropsychiatry, 14,* 277-298.

Tomppo, L., Hennah, W., Miettunen, J., Jarvelin, M. R., Veijola, J., Ripatti, S., et al. (2009). Association of variants in DISC1 with psychosis-related traits in a large population cohort. *Archives of General Psychiatry, 66*(2), 134-141.

Treadway, M. T., Buckholtz, J. W., Schwartzman, A. N., Lambert, W. E., & Zald, D. H. (2009). Worth the 'EEfRT'? The effort expenditure for rewards task as an objective measure of motivation and anhedonia. *PLoS One, 4*(8), e6598.

Ursu, S., Kring, A. M., Germans Gard, M., Minzenberg, M., Yoon, J., Ragland, D., Solomon, M., & Carter, C. S. (2011). Prefrontal cortical deficits and impaired cognition-emotion interactions in schizophrenia. *American Journal of Psychiatry*, *168*, 276-285.

Watson, D. & Clark, L. (1994). *Manual for the Positive and Negative Affect Scale - Extended Form.* Iowa City, IA: University of Iowa.

Worden, L. T., Shahriari, M., Farrar, A. M., Sink, K. S., Hockemeyer, J., Muller, C. E., et al. (2009). The adenosine A2A antagonist MSX-3 reverses the effort-related effects of dopamine blockade: differential interaction with

D1 and D2 family antagonists. *Psychopharmacology (Berl), 203*(3), 489-499.

Yoon, K. L., Joormann, J., & Gotlib, I. H. (2009). Judging the intensity of facial expressions of emotion: depression-related biases in the processing of positive affect. *Journal of Abnormal Psychology*, *118*(1), 223-228.

Table 1

Demographic Characteristics: Schizophrenia Probands, First-Degree Relatives, and Controls

	SZ	REL	NC
N	35	35	29
Age (Years)	44.3 (10.3)	50.4 (16.8)[b]	43.1 (13.1)
Gender (% Female)	18[a]	64	35
Race (*n*)			
Caucasian	26	30	25
African American	10	4	1
Latino/a	1	1	1
Native American	3	2	3
Asian	0	0	0
Relative Status			
% Mother	n/a	5	n/a
% Father	n/a	4	n/a
% Sister	n/a	16	n/a
% Brother	n/a	8	n/a
% Offspring	n/a	3	n/a
GAF[c]	53.4 (12.2)	76.5 (9.5)	86.2 (4.5)
DIGS Parental Education Score	4.5 (1.4)	4.4 (1.2)	4.8 (1.1)
DIGS Birth Complications (*n*)	5	4	2

Note. SZ = schizophrenia patients, REL = first degree relatives, NC = non-psychiatric controls; GAF = Global Assessment of Functioning, DIGS = Diagnostic Interview for Genetics Studies. Mean (standard deviation).
[a] $p < .05$, X^2 comparison with relative participant group
[b] $p < .10$, age compared with both probands and controls
[c] $p < .001$, all between group GAF score comparisons

Table 2

Spearman Correlations among Self-Report and Interview Measures of Negative Symptoms: Participants with Schizophrenia

	1	2	3	4	5
1) SANS Anhedonia					
2) SFS Prosocial Activity	-.70****				
3) SFS Recreational Activity	-.38†	.48**			
4) SPQ No Close Friends	.42†	-.46*	-.10		
5) SPQ Constricted Affect	.27	-.38†	-.23	.54**	
6) SPQ Anhedonia Composite	.37	-.47*	-.21	.90****	.84****

Note. SPQ = Schizotypal Personality Questionnaire, SANS = Scale for the Assessment of Negative Symptoms, SFS = Social Functioning Scale.
† $p < .10$.
* $p < .05$.
** $p < .01$.
**** $p < .001$.

Table 3

Divergent Validity of Anhedonia Measures with Other Measures of Negative Symptoms and Personality: Participants with Schizophrenia

	1	2	3	4	5	6	7
1) SANS Anhedonia							
2) SFS Prosocial Activity	-.70****						
3) SFS Rec. Activity	-.38†	.48**					
4) SPQ Anhedonia	.37	-.47*	-.21				
5) SANS Flat Affect	.07	-.14	-.29	.28			
6) SPQ Social Anxiety	-.02	-.18	-.15	.53**	-.12		
7) SPQ Suspiciousness	.12	-.17	-.10	.64***	.13	.31	
8) IPIP Extraversion	.22	.13	.18	-.50**	-.22	-.53**	-.36†

Note. SANS = Scale for the Assessment of Negative Symptoms, SFS = Social Functioning Scale, Rec. = Recreational, SPQ = Schizotypal Personality Questionnaire, IPIP = International Personality Item Pool.

† $p < .10$.

* $p < .05$.

** $p < .01$.

**** $p < .001$.

Table 4

Spearman Correlations Among Affect Measures: Participants with Schizophrenia

	1	2	3	4	5	6	7
1) PRT PA Intensity							
2) SRLT Liking	.64****						
3) SRLT Arousal	.42*	.53**					
4) SS Total	-.12	-.06	-.36				
5) TEPS Liking	.28	.40*	.19	.24			
6) TRT Effort	.02	-.03	.02	.03	.01		
7) TEPS Wanting	.39*	.36†	.16	.33	.78****	.09	
8) Current PA	.67****	.49**	.43*	-.15	.45**	-.15	.54**

Note. PRT = Picture Rating Task, PA = positive affect, SRLT = Self-Reported Liking Task, SS = Sniffin' Sticks, TEPS = Temporal Experience of Pleasure Scale, TRT = Tapping for Reward Task.

† $p < .10$.

* $p < .05$.

** $p \leq .01$.

*** $p \leq .005$.

**** $p \leq .001$.

Table 5

Spearman Correlations Among Affect Measures: First-Degree Relatives

	1	2	3	4	5	6	7
1) PRT PA Intensity							
2) SRLT Liking	.27						
3) SRLT Arousal	.27	.24					
4) SS Total	-.18	.64*	.43				
5) TEPS Liking	.20	.32	.26	.09			
6) TRT Effort	.11	-.19	.07	.20	-.08		
7) TEPS Wanting	.38*	.53**	.03	.20	.48**	-.12	
8) Current PA	.27	-.09	.10	-.10	.03	.40*	-.12

Note. PRT = Picture Rating Task, PA = positive affect, SRLT = Self-Reported Liking Task, SS = Sniffin' Sticks, TEPS = Temporal Experience of Pleasure Scale, TRT = Tapping for Reward Task.

† $p < .10$.

* $p < .05$.

** $p \leq .01$.

Table 6

Spearman Correlations Among Affect Measures: Nonpsychiatric Controls

	1	2	3	4	5	6	7
1) PRT PA Intensity							
2) SRLT Liking	.39†						
3) SRLT Arousal	-.28	.29					
4) SS Total	.38	.60†	-.45				
5) TEPS Liking	.39†	.13	-.32	.72**			
6) TRT Effort	.08	.48*	.35	-.21	-.46*		
7) TEPS Wanting	.21	.26	-.22	.84****	.70**	-.40†	
8) Current PA	.51*	.22	-.22	.06	.15	.03	-.04

Note. PRT = Picture Rating Task, PA = positive affect, SRLT = Self-Reported Liking Task, SS = Sniffin' Sticks, TEPS = Temporal Experience of Pleasure Scale, TRT = Tapping for Reward Task.

† $p < .10$.

* $p < .05$.

** $p \leq .01$.

*** $p \leq .005$.

**** $p \leq .001$.

Table 7

Associations between Interview Ratings of Negative Symptoms and Hedonic Liking and Wanting Measures in the Schizophrenia Probands

	Anhedonia	SFS	Flat Affect
PRT PA Intensity	.29	.07	.01
SRLT Liking	.15	.06	-.23
SRLT Arousal	.29	.21	.27
SS Liking	-.42*	.22	-.45*
TEPS Liking	.17	.16	-.26
TRT Effort	.25	-.13	-.01
TEPS Wanting	-.28	.31	-.39*

Note. SFS = SFS recreational and social composite score, PRT = Picture Rating Task, PA = Positive Affect, SRLT = Self-Reported Liking Task, SS = Sniffin' Sticks Hedonic Rating, TEPS = Temporal Experience of Pleasure Scale.
* $p < .05$.

Table 8

Associations between Self-Reported Symptoms, Personality and Hedonic Liking and Wanting Measures in the Schizophrenia Probands

	SPQ Anhedonia	Social Anxiety	Suspicious	Extraversion
PRT PA Intensity	-.36†	-.07	-.15	.41*
SRLT Liking	-.33†	.14	-.08	.37*
SRLT Arousal	-.43*	-.23	-.25	.30
SS Liking	-.29	-.14	-.24	.33
TEPS Liking	-.42*	-.04	-.22	.33†
TRT Effort	.30	.26	.30	.16
TEPS Wanting	-.43*	<.01	-.22	.59****

Note. SPQ Anhedonia = no close friends and constricted affect composite score, Suspicious = Suspiciousness subscale, PRT = Picture Rating Task, PA = Positive Affect, SRLT = Self-Reported Liking Task, SS = Sniffin' Sticks Hedonic Rating, TEPS = Temporal Experience of Pleasure Scale.

† $p < .10$.

* $p < .05$.

**** $p < .001$.

Table 9

Correlations of Hedonic Liking and Wanting Measures with Self-Reported Schizotypal Traits in First-Degree Relatives

	No Close Friends/ Constricted Affect	Social Anhedonia	Physical Anhedonia
PRT PA/Pos. Pictures	.16	.13	.04
SRLT Liking/Pos. Pictures	-.61*	-.46*	-.40*
SRLT Arousal/Pos. Pictures	.29	-.22	-.38†
SS Liking Rating	.03	-.28	-.16
TEPS Liking	-.24	-.19	-.44*
TRT Effort	-.15	.05	.33†
TEPS Wanting	-.41†	-.26	-.32†

Note. PRT = Picture Rating Task, PA = Positive Affect, SRLT = Self-Reported Liking Task, Pos. = Positive, SS = Sniffin' Sticks Hedonic Rating, TEPS = Temporal Experience of Pleasure Scale.
† $p \leq .15$.
* $p < .05$.

Table 10

Comparisons of Emotion Variable Means

Measure	SZ	REL	Control
PA Intensity for Positive Pictures	10.20 (3.7)	8.88 (2.8)	9.54 (3.2)
PA Frequency for Positive Pictures	81.25 (29.7)	72.72 (20.5)	75.92 (24.5)
SRLT Arousal for Positive Pictures[†]	5.49 (1.2)	5.53 (0.8)[a]	4.99 (0.8)
SRLT Liking of Positive Pictures	6.54 (0.9)	6.61 (1.0)	6.73 (0.7)
SS Liking Rating	69.5(18.9)	73.5(14.7)	75.8(11.6)
TEPS Liking[†]	32.14 (7.3)	35.70 (8.7)[a]	31.44 (5.4)
TEPS Wanting	43.06 (8.4)	43.87 (6.7)	44.28 (6.3)
Current Negative Affect[*]	15.0(6.6)[b]	12.6(4.1)[a]	10.8(1.2)
Current Positive Affect	33.9(9.6)	32.93(8.1)	33.0(6.7)

Note. SZ = schizophrenia sample, REL = first-degree relative sample, PA = positive affect, SRLT = Self-Reported Liking Task, SS = Sniffin' Sticks, TEPS = Temporal Experience of Pleasure Scale.
[a] = different from controls, $p < .05$.
[b] = different from controls, $p < .005$.
[†] = between groups comparison, $p < .10$.
[*] = between groups comparison significant, $p < .01$.

Table 11

Intensity of Positive Affect (PA) and Negative Affect (NA) by Arousal Level and by Measure Across Groups

Measure	Probands	Relatives	Controls
PANAS-X Items			
PA, High Arousal	15.93 (4.98)	15.17 (4.89)	14.78 (4.08)
PA, Low Arousal	18.00 (5.07)	17.40 (4.08)	18.21 (3.32)
NA, High Arousal*	7.43 (3.50)[a]	6.17 (1.70)[a]	5.30 (0.77)
NA, Low Arousal*	7.60 (3.33)[a]	6.40 (2.51)	5.48 (0.73)
Picture Rating Task			
PA, High Arousal	12.02 (5.28)	9.85 (3.91)	10.12 (3.40)
PA, Low Arousal	12.75 (5.89)[b]	10.24 (3.20)	11.15 (3.53)
NA, High Arousal*	10.73 (5.11)[a,b]	7.55 (3.80)	7.43 (3.63)
NA, Low Arousal*	7.56 (4.60)[a,b]	4.04 (2.95)	4.15 (2.31)

Note. Standard deviations appear in parentheses. PANAS-X = Positive and Negative Affect Schedule - Extended Form.
* = between groups analysis of variance significant, $p \leq .01$.
[a] = significantly different from controls, $p \leq .01$.
[b] = significantly different from relatives, $p < .01$.

Table 12

Comparisons of Self-Reported Interpersonal Traits in Probands and Relatives

	SZ	REL
SPQ Total	24.4(14.4)*	14.6(7.9)
SPQ Interpersonal Factor	12.2(7.1)*	7.7(4.7)
SPQ No Close Friends	3.4(2.3)	2.5(1.9)
SPQ Constricted Affect	2.4(1.9)	1.6(1.2)
SPQ Social Anxiety	3.9(2.4)†	2.5(2.5)
SPQ Suspiciousness	2.5(2.1)*	1.1(1.3)
IPIP Extraversion[a]	6.3(4.4)*	9.0(4.0)

Note. SZ = schizophrenia sample, REL = first-degree relative sample, SPQ = Schizotypal Personality Questionnaire, IPIP = International Personality Item Pool.
[a] A larger sample of probands and relatives provided these data (probands $n = 35$, relatives $n = 30$).
† $p < .10$ comparison with relatives.
* $p < .05$ comparison with relatives.

Table 13

Comparisons of Self-Reported Interpersonal Traits in Relatives and Controls

	REL	NC
SPQ Total	14.6(7.9)**	5.6(4.1)
SPQ Interpersonal Factor	7.7(4.7)*	3.4(2.9)
SPQ No Close Friends	2.5(1.9)*	0.9(0.9)
SPQ Constricted Affect	1.6(1.2)*	0.6(0.5)
SPQ Social Anxiety	2.5(2.5)	1.9(2.3)
SPQ Suspiciousness	1.1(1.3)†	0.1(0.4)
RSAS[a]	13.0(5.0)**	9.8(3.3)
PAS[a]	13.5(6.3)	13.1(6.3)
IPIP Extraversion[b]	9.0(4.0)	10.5(3.9)

Note. REL = first-degree relative sample, NC = non-psychiatric control sample, SPQ = Schizotypal Personality Questionnaire, RSAS = Revised Social Anhedonia Scale, PAS = Physical Anhedonia Scale, IPIP = International Personality Item Pool.
[a] relatives $n = 34$, controls $n = 21$.
[b] relatives $n = 30$, controls $n = 25$.
† $p < .10$.
* $p < .05$.
** $p < .01$.

Table 14

Associations between Ambivalence in Hedonic Behavioral & Self-Report Measures and Affect in Schizophrenia Probands

	Current NA	Current PA
Ambivalence Variable		
PRT NA/Positive Pictures	.37*	.20
PRT PA/Negative Pictures	.23	.48**
General Affect Variable		
PRT Total NA/All Pictures	.44*	.28
PRT Total PA/All Pictures	.37†	.69****

Note. NA = negative affect, PA = positive affect, SRLT = Self-Reported Liking Task.
† $p < .10$.
* $p < .05$.
** $p < .01$.
**** $p < .001$.

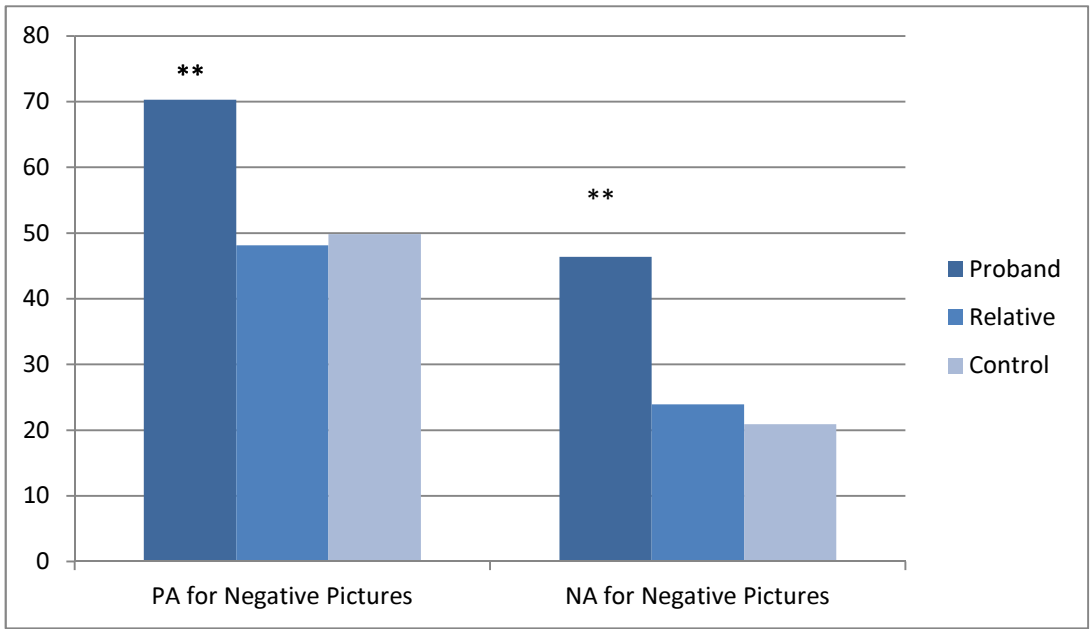

Figure 1. Comparison of ambivalence means across groups. Greater scores indicate greater ambivalence.

**all *p*s ≤ .02 compared with both relatives and controls.

APPENDIX

I. DNA COLLECTION METHODS

I will collect DNA from subjects for genetic analyses. In the Sponheim lab, a research assistant and I will acquire 8 milliliters of blood and two buccal cell samples from each subject participating in the study. Blood will be drawn through venous puncture by trained medical VA staff. About 2 milliliters of whole blood will be used to fill four FTA blotter cards. The swab procedure entails the participant swabbing the inside of each cheek 40 times with each of four swabs. The remaining blood and buccal cell samples will be frozen and stored in the Minneapolis VA laboratory freezer with a subject number but no personally identifying information.

Genotyping

DNA extraction and genotyping of COMT and DISC1 will be completed in the molecular genetics laboratory of the General Clinical Research Center (GCRC) at the University of Minnesota. Again, all samples will be de-identified prior to transporting. Dr. Sponheim's collaborator, Dr. Matthew McGue, is currently using the GCRC laboratory for genotyping samples from a large family study of substance use, thus the mechanism for obtaining genotype data is known and used. Genomic DNA will be prepared from either blood samples or buccal swabs. DNA fragments containing selected SNPs will be amplified using the appropriate primers. After amplification, genotyping will be performed with a DNA sequencer contained in the GCRC molecular genetics laboratory. Because it is prudent to attempt to obtain SNP data for several gene loci at once, given the

usefulness of the data in future studies, additional functional polymorphisms are determined for AKT1, KCNH2, NRG1, and DTNBP1.

NRSA Data Analysis

To test my hypothesis that COMT polymorphism is related to anhedonia in relatives of patients but not in controls, a repeated measures ANOVA will be performed examining group, COMT, and the interaction between group and COMT. Planned follow-up univariate analyses will compare groups and COMT polymorphisms on each Wisconsin Schizotypy scale. One hypothesis of the NRSA research is that the relationship between anhedonia and PA intensity on the picture rating task will be enhanced in relatives with the val allele of the COMT gene at codon 158. To test this hypothesis, I will examine COMT as a moderator of associations between anhedonia and PA intensity, expecting a COMT x PA intensity interaction predicting scores of anhedonia in a regression analysis. Another hypothesis is that DISC1 polymorphism is related to anhedonia in relatives of patients but not in controls, and a repeated measures ANOVA will be performed examining group, DISC1, and the interaction between group and DISC1. Planned follow-up analyses will compare groups and DISC1 polymorphisms on each Wisconsin Schizotypy scale. Another hypothesis is that a relationship of anhedonia with PA intensity will be moderated in relatives by DISC1 polymorphism. To test this hypothesis, I will examine DISC1 as a potential moderator of correlations between anhedonia and performance on the each task.

To maximize power in the COMT and DISC1 analyses, analyses will focus on continuous phenotypes. Each participant group will be examined to

ensure Hardy-Weinberg Equilibrium, and t-tests will be conducted to examine group differences in age and gender. To examine association between genotype and each index of schizotypy (i.e., social anhedonia) we will carry out a mixed model ANOVA for each dependent variable with all available subjects included, diagnosis and genotype as fixed effects, and family membership as a random effect. Structuring the ANOVAs in this manner reduces and models the nonindependence of observations stemming from studying members of the same family (Sponheim, 2009). Consultants Drs. Daniel Weinberger, Deborah Levy, and Ian Gizer will advise on genotyping, association, and transmission analyses.

Power Analysis

When analyzing the two separate 2 (schizophrenia relatives versus controls) by 3 (COMT or DISC1 polymorphism) within-subjects ANOVAs, to have a power of .80 in the current study, the comparison would need a moderate effect size (*Cohen's d* = .32). In a previous study, (Docherty & Sponheim, 2008), effect sizes ranged from C*ohen's d* = .30-.40 for the effect of group and COMT on the anhedonia measures (n = 95 relatives and n = 35 controls). With a sample size of 75 relatives and 75 controls, we would have a power of 0.9 to detect this effect.

Protection of Human Subjects

Subjects will be asked for a blood sample taken from the arm (about 8 mils) or small samples of cheek cells collected with a soft swab (buccal swab) rubbed on the inside of the mouth. For blood draws, the subject may experience some pain when the blood draw is completed. Possible side effects from blood

draw include faintness, inflammation of the vein, bruising, or bleeding at the site of the puncture. There is a slight possibility of infection. For cheek buccal swabs, the subject may experience slight discomfort when the swab is used on the subject's cheek. Participants are informed of all of these risks during the informed consent process. During the course of the study, the subject will have access to medical center facilities should the subject require medical attention.

The blood is drawn by Dr. Scott Sponheim's trained laboratory technician with the applicant present in the room. Dr. Sponheim, Co-Sponsor of the grant proposal, has worked with whole blood samples in DNA collection for several years at the Minneapolis Veterans Affairs Medical Center and has mentored the applicant on protection of human subjects. Dr. Sponheim has received funding for his research with DNA from NIH and he continues to practice under established HIPAA guidelines for protection of PHI. The applicant has been trained at the VA for HIPAA compliance and human subject protection.

The consent form used for the study, approved by the IRBs at the Minneapolis Veterans Affairs Medical Center and the University of Minnesota, includes an option for the subject to express whether they would like their DNA sample to be stored for future research. The subject will not receive information about the results from genetic analyses of his/her specific DNA sample.

First, we will collect the sample and the applicant will put a subject ID and a date of collection on the sample. The applicant will then carry the sample directly to a secure specimen freezer at the Minneapolis VA Medical Center.

Blood and cheek cell samples will be stored temporarally at this secure specimen freezer.

This freezer is kept in a locked biomedical laboratory alotted to Dr. Sponheim. The DNA sample will only be used for research purposes and in accordance to the subjects wishes as specified on the consent form. Dr. Sponheim's laboratory technician, Tricia Bender, maintains an inventory of frozen specimens at the VA in this secure research area (once again, there is no identifying information on these specimens).

Tricia Bender prepares plates of samples at the VA for genotyping at the University Biomedical Genomics Center (BMGC). She has been trained in HIPAA procedures and protection of human subjects. The plates that are transported to the VA personally by Tricia Bender have no PHI on them and the technicians at the University of Minnesota analyze the samples using a Sequenom (described in the grant), a highly automated process.

In rare instances, we may have the BMGC maintain the DNA material that was in the plate that was not entirely used in the first analysis, if we are concerned about the reliability of DNA reading and we require follow-up genotyping. This will be a short-term maintenance of the material up to the point where the material is used in follow-up genotyping.

II. OLFACTORY HEDONIC RATING FORM

Smell Test and Hedonic Response Measure

Subject ID _____ Rater:___ Date: _____

Task Notes:

Threshold number:_____

Administrator: *We would like to have you rate the pleasantness of certain smells. "Pleasantness" refers to how much you like the smell, vs. how much you dislike the smell. There are no right or wrong answers—just rate how much you like or dislike each smell. When prompted, you should give a rating for how much you like the current smell. You can make your ratings from 1 to 9.*

****

1	2	3	4	5	6	7	8	9
Extremely Unpleasant				**Average**				**Extremely Pleasant**

1. 1 2 3 4 5 6 7 8 9

2. 1 2 3 4 5 6 7 8 9

3. 1 2 3 4 5 6 7 8 9

4. 1 2 3 4 5 6 7 8 9

5. 1 2 3 4 5 6 7 8 9

6. 1 2 3 4 5 6 7 8 9

7. 1 2 3 4 5 6 7 8 9

8. 1 2 3 4 5 6 7 8 9

9. 1 2 3 4 5 6 7 8 9

10. 1 2 3 4 5 6 7 8 9

11. 1 2 3 4 5 6 7 8 9

12. 1 2 3 4 5 6 7 8 9

13. 1 2 3 4 5 6 7 8 9

14. 1 2 3 4 5 6 7 8 9

15. 1 2 3 4 5 6 7 8 9

16. 1 2 3 4 5 6 7 8 9

III. CURRENT AFFECT RATING LIST

Negative Affect	Positive Affect
Afraid	*Active*
Ashamed	*Alert*
Distressed	*Attentive*
Guilty	*Determined*
Hostile	*Enthusiastic*
Irritable	*Excited*
Jittery	*Inspired*
Nervous	*Interested*
Scared	*Proud*
Upset	*Strong*

VITA

Anna Docherty was born in Prince George, British Columbia and was educated in Greenfield, Massachusetts and New Haven, Connecticut. She then attended Oberlin College and earned a Bachelor of Arts degree in English. She was admitted to the University of Missouri-Columbia, where she earned her doctorate in clinical psychology and developed expertise in the assessment, treatment, and research of psychotic disorders under the mentorship of Dr. John Kerns. She is completing her residency at the Minneapolis Veterans Affairs Health Care System, where she is receiving additional training in the assessment and treatment of serious and persistent mental health conditions. She has completed a predoctoral training grant from the National Institutes of Mental Health examining the genetics of schizophrenia signs and symptoms.