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Association Between Unirhinal Olfactory Processing And Self-reported Empathy In Schizophrenia

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ASSOCIATION BETWEEN UNIRHINAL OLFACTORY PROCESSING AND SELF-REPORTED EMPATHY IN SCHIZOPHRENIA

by

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ABSTRACT

Empathy represents one multifaceted component of social cognition that is thought to be significantly impaired in individuals with schizophrenia. Psychophysical tasks of smell identification and hedonic processing of pleasant, neutral, and unpleasant odors share common neural networks involved in empathy. Therefore, we investigated the relationship between odor identification, odor ratings, and self-reported empathy in 25 outpatients with schizophrenia and 25 nonpsychiatric individuals. Group differences on empathy scores and unirhinal smell identification performance (with hedonic and intensity ratings) were examined, along with the relationships between smell identification scores, self-reported empathy, and schizophrenia symptomatology. The preliminary findings suggest that individuals with schizophrenia display significant differences from controls on measures of self-reported empathy, odor identification, and hedonic ratings of odors. Deficits in self-reported global and affective empathy were influenced by group and sex, whereas cognitive empathy was reduced across all patients in comparison to controls. Patients displayed reduced unirhinal odor identification accuracy for pleasant but not neutral or unpleasant odors in comparison to controls. Central to the overall aim of the current study, a robust positive correlation was observed between left- and right-nostril hedonic ratings for pleasant odors and self-reported global and affective empathy scores across all participants. In patients, we also found a statistical trend between affective empathy and left-nostril identification accuracy across all odors. Collectively, the results lend support to the role of olfactory-limbic brain regions in the hedonic processing of odors and suggest that aberrant performance observed in schizophrenia may be related to abnormalities in the anatomical and physiological substrates that also subserve empathy.

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LIST OF ACRONYMS/ABBREVIATIONS

ASPD	Antisocial Personality Disorder
BES	Basic Empathy Scale
BOLD	Blood Oxygen Level Dependent
DS	Deficit Syndrome
dPFC	Dorsolateral Prefrontal Cortex
DSM-IV-TR	Diagnostic and Statistical Manual – 4th edition – Text Revision
fMRI	Functional Magnetic Resonance Imaging
mPFC	Medial Prefrontal Cortex
NDS	Non-deficit Syndrome
OFC	Orbitofrontal Cortex
PET	Positron Emission Tomography
PFC	Prefrontal Cortex
rCBF	Regional Cerebral Blood Flow
SCID-I	Structured Clinical Interview for DSM-IV Axis I Disorders
SCID-II	Structured Clinical Interview for DSM-IV Axis II Disorders
SCID-II-APS	Avoidant, Paranoid, and Schizotypal sections of the SCID-II
SCI-PANSS	Structured Clinical Interview - Positive and Negative Symptom Scale
SPD	Schizotypal Personality Disorder
ToM	Theory of Mind
UPSIT	University of Pennsylvania Smell Identification Test
WRAT-3R	Reading Subtest of the Wide Range Achievement Test – 3rd edition

INTRODUCTION

Imagine you are watching your favorite team play basketball. One player assertively dribbles the ball down the center of the court and jumps in the air to shoot the ball. Suddenly, as though the game is in slow motion, the player appears to lose his footing and collides into a defender in mid-air. As one player falls to the ground, you see the distinctness with which his ankle twists. A grimace of pain erupts on the player's face as he lays in a heap on the floor clutching his ankle in agony. Almost instinctively, you turn your attention to the plight of the player and your face turns into a grimace. You immediately perceive the impact of pain the player is experiencing. A bolt of emotion shoots through you as you actively adopt the player's perspective and internalize the pain the player is feeling. This hardwired capacity to vicariously share and understand the emotional and cognitive state of another individual is referred to as the phenomenological experience of empathy (Decety & Jackson, 2004; Ickes, 1997).

Diverse lines of research in philosophy, developmental psychology, and cognitive neuroscience have been instrumental in defining and operationalizing empathy. Thus far, this research has culminated in the development of a model that denotes human empathy, in its most rudimentary sense, as a multidimensional construct with cognitive, affective, and self-regulatory components (Batson et al., 1991; Decety, 2007; Eisenberg, 2000; Hodges & Wegner, 1997). In a more sophisticated sense, empathy is characterized as a biopsychosocial phenomenon influenced by genetics, neurodevelopment, and environmental factors (Anckarsäter & Cloninger, 2007). Indeed, the natural variations observed in empathy are influenced by a myriad of factors including our attitudes, prejudices, intellectual perspective, intentions, and emotions

(Anckarsäter et al., 2007; Decety et al., 2004). The multi-faceted nature of this construct has made empathy an interesting yet challenging aspect of social cognition to study.

Cross-disciplinary research has illuminated the architecture of human empathy within developing children and healthy adults expanding our understanding of 'natural' variations in human empathy. In recent years, researchers have called upon the study of empathy in individuals who either lack empathy or possess empathy and use it in maladaptive ways, in order to understand *empathic dysfunction* (Decety & Moriguchi, 2007). Accordingly, research on individuals with particular psychiatric and neurological disorders who have difficulty representing or simulating the emotional and mental states of others have been useful in this regard. Thus far, empathy deficits have been observed in autism, antisocial personality disorder, schizophrenia, and in individuals with particular cerebral lesions. These populations have been crucial to understanding the cognitive correlates of empathy and possible brain networks that contribute to empathy deficits.

The presence of impaired empathy has far more implications than one might presuppose. Empathy deficits extend beyond the domain of social interaction and into the realm of metacognition, self-awareness, and social understanding (Hobson, 2007). Indeed, empathy is an active process by which observation, knowledge, memory, and reasoning are used in synchrony to comprehend the mental and affective states of others (Batson et al., 1991; Eisenberg, 2000; Hodges et al., 1997; Ickes, 1997). The study of empathy has powerful indications for current research on genetic and neurodevelopmental mental disorders given its multifaceted nature and its link to specific neuroanatomical structures in the brain. In addition, empathy is affected by neurodevelopment, neuropathology, and mental illness and budding research has found evidence for the heritability of empathy (Hoffman, 2000; Zahn-Waxler, Robinson, & Emde, 1992).

Given its link to positive human interaction and prosocial behavior, the study of empathy has gained interest in mental disorders marked by impaired social cognition and poor social relationships. As such, the study of empathy has received attention in individuals with schizophrenia. Schizophrenia, a chronic and pervasive psychiatric illness, is debilitating given the nature and degree to which deficits in social cognition impair daily functioning. Schizophrenia is often conceptualized as a neurodevelopmental disorder with genetic diathesis (Weinberger, 1987). Markedly poor social interaction and cognitive deficits are core features of the illness that contribute to significant declines in social and cognitive functioning (American Psychiatric Association, 2000). Despite numerous studies documenting the pervasive and devastating nature of these deficits, the cognitive and affective aspects of empathic function and the underlying mechanisms are not fully understood in schizophrenia.

Collectively, the research on empathy within various psychiatric disorders, including schizophrenia, has led to differential findings, suggesting that more research on the neurocognitive correlates of empathy is needed. Thus far, functional neuroimaging and neuropsychological studies have advanced our understanding of the brain-behavior relationships that underlie empathy. Several studies have pointed to areas in the orbitofrontal cortex (OFC) and the amygdala as neuroanatomical structures that underlie empathy (Barrash, Tranel, & Anderson, 2000; Blair & Cipolotti, 2000; Tranel, 1994). In addition, extensive findings have suggested that empathy-related networks (e.g., the OFC and amygdala) are compromised in schizophrenia (Liu, Tam, Xie, & Zhao, 2002; Namiki et al., 2007; Staal et al., 2000). While several cognitive tasks probe integrity of the OFC and amygdala, olfactory identification tasks represent one of the most robust of available measures (Moberg et al., 1999). In addition, the OFC and amygdala are involved in the hedonic processing of odors (Zald & Pardo, 1997).

Based on these findings, the overall objective of the current study was to further understand the neurocognitive correlates of empathy in schizophrenia using a robust measure of brain networks thought to subserve empathic abilities. The following paper will begin with a discussion of the significance of research on social cognitive deficits in schizophrenia. The multidimensionality of empathy and its components will be reviewed, followed by a brief introduction to neuroanatomy relevant to empathy. An in-depth review of recent functional neuroimaging studies in empathy will be presented. Given the role of impaired empathy in several psychiatric disorders, neuropsychological findings in related psychiatric and neurological populations will be examined. In the latter part of this paper, empirical data on empathy and related constructs will be reviewed within schizophrenia. We will discuss these findings in the framework of current knowledge on the neuropathology and course of schizophrenia. Finally, the psychophysical tasks believed to best probe compromise in these areas will be elucidated.

SIGNIFICANCE AND BACKGROUND

Schizophrenia is a chronic and debilitating disorder of brain and behavior marked by significant deficits in social and cognitive functioning (American Psychiatric Association, 2000). Social and cognitive deficits pervade numerous areas of functioning often leading to multiple hospitalizations, increased mortality, and homelessness. Recent estimates suggest that schizophrenia places a large burden on mental health systems, with a total cost estimate of $62.7 billion (Wu et al., 2005). Despite advancements in the research of individuals with schizophrenia and efforts towards their deinstitutionalization, schizophrenia is still ranked within the top ten causes of disability worldwide (Keshavan, 2006). Given the urgent need for effective interventions, research aimed at understanding the abnormal neural substrates that subserve behavioral deficits observed in schizophrenia is of utmost importance.

While numerous deficits contribute to declines in daily functioning, impairments in social cognition are considered one of the most debilitating clinical features of the illness (American Psychiatric Association, 2000). Thus far, poor social cognitive skills have been linked to symptom severity and symptom duration during the active phase of psychosis (Corcoran & Frith, 2003; Corcoran, Mercer, & Frith, 1995; Pickup & Frith, 2001). In addition, research has demonstrated that social cognitive deficits are present during the absence of acute illness, suggesting the enduring nature of these impairments (Edwards, Pattison, Jackson, & Wales, 2001; Herold, Tenyi, Lenard, & Trixler, 2002; Janssen, Krabbendam, Jolles, & van Os, 2003). Impairments in social functioning substantially reduce the potential for effective vocational and interpersonal functioning and are often resistant to treatment intervention (Rosenheck et al.,

2006). Consequently, research is needed to provide a deeper understanding of the brain-behavior relationships that underlie impaired social functioning in schizophrenia.

Social cognition, defined as "the processes and functions that allow a person to understand, act on, and benefit from the interpersonal world" (Corrigan & Penn, 2001, p. 3), appears to be an intuitive avenue with which to explore deficits in social functioning in schizophrenia. Empathy represents a multifaceted construct of social cognition (Decety, 2007). Moreover, Lee (2007) has postulated that impaired empathy may underlie deficits in social functioning as "empathy mediates the understanding of others in social interaction, by representing or simulating other people's thoughts and feelings within the self" (p. 17). Therefore, a better understanding of the multidimensional nature of empathy and its application to schizophrenia research is needed.

Empathy: A Multidimensional Construct

Titchener first introduced the term *empathy* to North America in 1909 (Titchener, 1909). In a later work, he described empathy as a "process of humanizing objects, of reading or feeling ourselves into them" (Titchener, 1924, p. 417). Over the past century, the definition of empathy has evolved considerably. Initially, empathy was defined as a '*predictive accuracy'* by which successful empathic responding implied increased ability to predict others' thoughts and feelings (Dymond, 1949). Alternate approaches to defining empathy focused more on the qualities of sensation and emotional perception. Grief and Hogan (1973) noted that empathy is a sensitivity to the needs and values of others. Similarly, Mehrabian and Epstein (1972) emphasized the affective nature of empathy, noting that the empathic response involves sharing the emotional experience of another. Though these characeristics appeared to embody empathy to a greater

degree than previous predictive accuracy models, these conceptualizations did not fully account for the psychological inference, cognitive flexibility, and reasoning that empathic abilities require (Decety et al., 2004). Indeed, the capacity to appreciate and reason through another's mental state appears to be a necessary component of this process, and involves more than predicting the cognitive and emotional state of another. With this in mind, Eisenberg & Fabes (1998) conceptualized empathy as "an affective response that stems from the apprehension or comprehension of another's emotional state or condition" (p. 702).

A desire to synthesize the varied conceptualizations have led researchers to broad agreement that empathy involves two primary components: 1) an affective response which entails sharing another's emotional state; and 2) the cognitive ability to adopt another's perspective (Davis, 1983; Decety et al., 2004; Ickes, 1997). In recent years, Decety & Jackson (2004) have proposed that a self-regulatory mechanism that monitors the difference between the feelings of the self versus that of another individual are required in empathic abilities. Through these varied definitions, the multidimensionality of empathy becomes evident and a need to further our understanding of its components is apparent.

Cognitive Empathy. Cognitive empathy involves the process of espousing the perspective of another's thoughts, feelings, and actions (Hojat, Mangione, Kane, & Gonnella, 2005). Throughout empathy literature, cognitive empathy has been used interchangeably with the concept of "theory of mind" (ToM) (Shamay-Tsoory, Tomer, Goldsher, Berger, & Aharon-Peretz), or the ability to mentally represent another's emotions, thoughts, and perceptions (Adolphs, 2001). Other researchers have referred to cognitive empathy as 'perspective taking' or 'cognitive role taking' (Gladstein, 1983). Despite differences in nomenclature, there is general consensus that cognitive empathy necessitates understanding, either consciously or

subconsciously, the point of view of another (Davis, 1996; Decety, 2007; Gladstein, 1983). Decety (2007) posits that humans are fundamentally egocentric and that self-perspective is a default mode of the human mind. Further, he suggests that humans use the most parsimonious tool – our own knowledge-base – to comprehend and predict another person's behavior. This knowledge base is a fusion of our own perspectives, judgments, and attitudes about people within our environment. Cognitive empathy is then an active process by which one inhibits the default response of self-perspective and adopts the perspective of another. In this way, cognitive empathy may be best understood as an adaptive tool by which individuals are able to understand people and events around them.

The process of perspective taking while maintaining self-other awareness would suggest a need for cognitive flexibility and self-regulation (Decety et al., 2007). To date, neuropsychological and neuroimaging studies (described in more detail later) have linked cognitive empathy, mental flexibility, and self-regulation to shared neural networks in the brain. In addition, findings from extant literature suggest that several characteristics are more related to cognitive in comparison to affective empathy. These characteristics range from increased self-monitoring and social self-esteem to lower levels of shyness, loneliness, and social anxiety (Davis, 1983; Mill, 1984).

Affective Empathy. Definitions for affective empathy appear most closely related to the way in which empathy is conceptualized in its everyday use. Affective empathy is defined "as an observer's emotional response to the affective state of another" (Baron-Cohen & Wheelwright, 2004, p. 164). Gladstein (1983, p. 468) described empathy as "responding with the same emotion to another's emotion." Similarly, Mehrabian and Epstein (1972) emphasized the notion of "emotional empathy" in which one individual shares the emotions of another. Generally,

definitions of affective empathy typically touch upon a process by which one internalizes the emotional state of another (for a review, see: Duan & Hill, 1996).

Recently, a *perception-action coupling* model has been discussed as a mechanism by which affective empathy occurs (for review, see: Preston & de Waal, 2002). According to this model, perception of another individual's state triggers an individual's representation of the state. Further, this mechanism is thought to be an unconscious and autonomic process of mimicry in which motor representations and somatic responses are generated. Preston and de Waal (2002) have reviewed an array of findings in support of this model and its central role in interpersonal interaction. While the perception-action coupling model has garnered support, future research is needed to fully elucidate the underlying mechanism by which an affective empathic response occurs.

Overall, theories about the facets of empathy have both enthralled and eluded researchers. Consensus among empathy researchers has been difficult due to the number of disciplines and frameworks in which empathy is studied. This research indicates that cognitive and affective empathy dissociate, and that the two concepts are mutually influenced, yet distinct, aspects of empathy. To further test these ideas, researchers have used an array of neuroimaging techniques and neuropsychological testing to understand the nature of empathy in both normal development and in individuals with empathic dysfunction.

Empathy and the Brain

In cognitive neuroscience, the application of functional neuroimaging and neuropsychological approaches has revolutionized our knowledge of the neuroanatomical

correlates of empathy. In addition, studies employing these multiple methods on individuals with observed empathy-related deficits have dissected the multidimensionality of empathy, uncovering interesting findings regarding empathy and its components.

Neuroanatomy of Empathy. Several overlapping, yet isolable, regions in the brain are currently thought to underlie the multidimensionality of human empathy. Broadly, the prefrontal cortex (PFC) is thought to subserve cognitive aspects of empathy, while the affective component of empathy has been linked to emotional processing networks (e.g., amygdala) in the limbic system. The PFC is located in the frontal lobe of the brain and is loosely divided into four major regions including: 1) the orbitofrontal cortex (OFC), 2) medial prefrontal cortex (mPFC), 3) the dorsolateral prefrontal cortex (dFPC), and 4) the anterior and ventral cingulate cortex (Krawczyk, 2002). While these distinctions will become more relevant in later sections, these regions are best understood as prime centers for "executive functioning" faculties. Executive functioning encompasses several abilities including higher-order thinking, decision making, metacognition, planning, organization, self-regulation, set-shifting, and cognitive flexibility (Lezak, Howieson, & Loring, 2004). The OFC, considered central to empathic responding, has direct and reciprocal connections with several other brain structures, including the amygdala, olfactory cortex, cingulate cortex, hippocampus, and dPFC (Price, 2006). Among these connections, the robust and bidirectional connections between the OFC and the amygdala are of direct relevance to the study of empathy. The amygdala has been described as a major component of emotional processing and learning. Specifically, the amygdala is thought to "add affective tone to sensory input and memories" (Kolb & Whishaw, 2008, p. 405) and to be heavily responsible for processing facial expressions of fear (Lezak et al., 2004).

Neuroimaging of Empathy. Functional neuroimaging methods, such as functional magnetic resonance imaging (fMRI) and positron emission tomography (PET), have been used to assess activity in the brain using markers such as regional cerebral blood flow (rCBF) and brain energy metabolism (Farrow et al., 2001). Recently, fMRI has been used to make inferences about brain regions involved in empathy in healthy adults. In one of the first published works to assess the functional neuroanatomy of empathy, Farrow et al. (2001) scanned individuals while they judged the emotional states of others. Empathic responses activated the left frontal, left anterior middle temporal, and orbitofrontal gyri, in addition to the precuneus.

It is not surprising that neuroimaging studies reveal activity in several regions within the prefrontal cortex during higher level empathic processes. As empathy is a complex ability that involves functions in both cognitive and affective spheres, separate areas of the prefrontal cortex appear to work as a network in order to execute an empathic response. This would fit with Decety & Moriguchi's (2007) current theoretical model of empathy as a "parallel and distributed computational mechanism with a number of dissociable computational mechanisms" (p. 3). Ultimately, theories such as this have led to further studies attempting to examine the neural bases for the affective and cognitive components of empathy. A recent meta-analysis attempted to parcel out the role of the mPFC by examining an array of neuroimaging studies measuring empathy-related tasks (Seitz, Nickel, & Azari, 2006). Eighty studies (employing fMRI or rCBF with PET) that included the mPFC as a region of interest were included in the analysis. The results revealed that the mPFC was heavily involved in self-awareness and the motivational control of action, two aspects believed to influence the expression of human empathy.

Empirical work by Baron-Cohen et al. (1994) sought to examine the neural basis of Theory of Mind (ToM, also referred to as cognitive empathy) using single photon emission

computerized tomography (SPECT) in healthy adults. Increased cerebral blood flow was reported in the right OFC in comparison to the left frontal-polar region. Extending these findings, Völlm et al. (2006) used fMRI to compare brain activity during tasks measuring ToM (i.e., cognitive empathy) and tasks measuring global empathy. Results revealed shared neural networks including fronto-temporal areas of the brain, including the mPFC and right OFC. Interestingly, empathy tasks additionally recruited emotional processing brain regions which included the paracingulate, anterior/posterior cingulate, and the amygdala. The results of these findings suggest that empathy recruits a broad range of affective and cognitive functions and that these aspects dissociate and are subserved by separate processes in the brain.

Further fMRI investigations have focused on the specific role of the OFC in empathy (Hynes, Baird, & Grafton, 2006). Individuals were scanned while presented with scenarios that involved emotional perspective-taking and conceptual perspective taking. Interestingly, emotionally-laden perspective-taking elicited a stronger hemodynamic response in the OFC than conceptual perspective-taking. Hynes et al. (2006) believed this finding lent support for distinct, yet overlapping, neural systems subserving empathy and its components. The results of their analysis also indicate that the OFC is involved in cognitive empathy but that emotionally-laden cognitive tasks involve additional activity in the OFC after networks involved in emotional processing (e.g., the amygdala) are recruited. This finding has been supported by another neuroimaging study in which researchers suggested a central role of the OFC in making moral appraisals (Moll et al., 2002).

Collectively, neuroimaging studies have revealed a great deal about brain-behavior relationships in empathy and suggest that several regions of the brain are activated during empathic responding in healthy adults. In addition, activated brain regions appear to map onto

the multidimensionality of empathy as both emotional processing and cognitive appraisal networks are recruited.

Neuropsychology of Empathic Dysfunction. An important complement to neuroimaging studies is an examination of neuropsychological functions that are sensitive to empathic dysfunction. The knowledge ascertained during neuropsychological testing is used for the evaluation, treatment, and rehabilitation of individuals with suspected or demonstrated neurological or psychiatric problems. Empathy deficits are associated with a wide range of neurological and psychiatric conditions. However, as Decety et al. (2007) point out, empathy deficits are observed in different ways across these disorders. For example, some disorders are characterized by deficits in affective empathy while others are associated with deficits in cognitive empathy. In these cases, the neuropsychological profile provides insight into the distinct, yet overlapping, neural networks that influence how empathy manifests.

Cerebral and Frontal Lobe Lesions. Generally, individuals with acquired cerebral lesions report significant lower empathy ratings than healthy controls, and these empathy scores remain whether the ratings are provided by the patients or their relatives (Grattan & Eslinger, 1989). Given previous findings linking cognitive flexibility to impaired social relationships, Grattan & Eslinger (1989) examined the correlation between alterations in empathy and cognitive flexibility, which was measured using the Wisconsin Card Sorting Test (WCST; Berg, 1948). The WCST is a task in which the rules for sorting cards of various shapes and colors are changed without notice, requiring cognitive flexibility. Grattan & Eslinger (1989) found a significant relationship between empathy and cognitive flexibility such that higher flexibility was associated with higher empathy scores in a group of brain-injured individuals. This finding holds promise for two main reasons: 1) cognitive flexibility is thought to be linked to executive functioning

abilities in the prefrontal cortex (PFC), and 2) the PFC is a brain region that is thought to be compromised in individuals with schizophrenia and in individuals with other empathy-related disorders.

The above findings led researchers to consider the role of frontal lobe lesions in impaired empathy. In order to investigate the neuropsychological processes that subserve impaired empathic abilities, self-report of empathy was ascertained from a group of individuals with localized lesions in the PFC (PFC group), a group of patients with posterior lesions (PL), and healthy control participants (HC) (Shamay-Tsoory, Tomer, Berger, & Aharon-Peretz, 2003). The PFC group had significant lower empathy scores than both the PL and HC group. Other studies also found that individuals with localized lesions in the PFC displayed significant impairments on measures of cognitive flexibility and affective processing compared to healthy controls (Shamay-Tsoory et al., 2004). In addition, when analysis was limited to lesions in the OFC and medial regions, significantly reduced cognitive and affective empathy scores were found in these groups compared to the HC and PL groups. This finding compelled researchers to hypothesize that the "empathic response requires integration of cognitive and affective processes, and the orbitoprefrontal-medial region of the PFC plays a crucial role in a network mediating empathy" (Shamay-Tsoory et al., 2004, p. 1123).

Among several regions in the PFC, the OFC is considered central to cognitive empathic processing. This is due, in part, to studies demonstrating that individuals with OFC lesions have impaired ToM (Blair et al., 2000; Farrow et al., 2001; Völlm et al., 2006). Though cognitive empathy has been linked to cognitive flexibility, individuals with OFC lesions do not always display deficits in cognitive flexibility (Grattan, Bloomer, Archambault, & Eslinger, 1994). This finding indicates that additional involvement of the dPFC, via projections to and from the OFC,

is necessary for the mental flexibility needed to enhance cognitive empathy. Consistent with this hypothesis, Grattan et al. (1994) found that when groups were delimited by localization of the lesion, individuals with OFC lesions displayed deficits in cognitive empathy, but performed within normal limits on cognitive flexibility tasks. Individuals with dPFC lesions demonstrated deficits in cognitive flexibility and cognitive empathy. In addition, individuals with mPFC lesions showed reduced cognitive flexibility, but scored within normal limits on empathy ratings (Grattan et al., 1994). Collectively, these contrasting profiles of empathy and cognitive flexibility scores in individuals with localized brain lesions have helped parcel out the role of the OFC in empathy. These findings suggest that the OFC is primarily involved in theory of mind aspects of cognitive empathy, while bidirectional connections from the OFC to the mPFC and dPFC are recruited for the mental flexibility components of cognitive empathy.

Empathy and Psychopathology. In addition to neurological populations, substantive evidence now shows that empathy-related impairments appear across several mental illnesses. Autism and psychopathy/antisocial personality disorder (ASPD) are psychiatric disorders most commonly associated with an empathy deficit. This research has explored the way cognitive and affective components of empathy dissociate, as individuals with certain mental illnesses may suffer from a deficit in one aspect of empathy.

Autism. Autism is a pervasive developmental disorder marked by "restricted repetitive and stereotyped patterns of behavior" and significant difficulty communicating and forming social relationships with others (American Psychiatric Association, 2000, p. 75). Impaired empathy is a hallmark of autism and an interesting commentary on its role in autism is presented in the writings of Hobson (2007):

> For anyone who needs to be persuaded of the critical role that empathy plays in human interpersonal engagement, or who wants to learn more about the significance of empathy for early human development – or even, perhaps, one who seeks to understand what empathy *is* – there could be few sources of insight more arresting than the phenomenon of early childhood autism (p. 126).

Among empathy researchers, there is general consensus that children with autism display significant impairment in cognitive empathy. To date, deficits on simple to complex measures of theory of mind (ToM) tasks have been well-documented in autism (for a review see: Baron-Cohen, 2001). In a landmark study, ToM abilities were examined with the false-belief task in groups of children with autism and Down's syndrome, as well as healthy children (Baron-Cohen, Leslie, & Frith, 1985). During the false-belief task (first developed by: Wimmer & Perner, 1983), children were asked to observe a show in which Sally, a puppet character, places a toy in a basket and exits the room. While Sally is gone, another puppet moves the toy to a box. Children were asked where Sally would look for the toy when she returned. Surprisingly, only 20% of children with autistic disorder provided the correct response compared to 85-86% in comparison groups. A subsequent study by Baron-Cohen (1989) reported that the 20% subgroup of children with autism with intact abilities on the false-belief task exhibited deficits on more complex ToM tasks. These studies have been replicated across autism populations and lend considerable insight into the nature of cognitive empathy deficits in autism (c.f. Ozonoff, Pennington, & Rogers, 1991; Sicotte & Stemberger, 1999).

Findings within the realm of affective empathy are less clear. Despite general agreement that children with autism experience reduced emotional empathy, the nature and severity of these deficits is currently debated. Hobson (2007) proposed that empathy deficits in autism arise from their inability to read and respond to emotional content within their social environment. In line with this assertion, several researchers have demonstrated that children with autistic disorder

have difficulty expressing and perceiving emotion (Dawson, Hill, Spencer, Galpert, & Watson, 1990; Sigman, Kasari, Kwon, & Yirmiya, 1992; Snow, Hertzig, & Shapiro, 1987). In contrast, Blair (2008) argued that empathy dissociates in autism and that impaired cognitive empathy predominates their inability to engage in social interaction. Blair (2005) noted methodological limitations of studies reporting emotional deficits in children with autism (e.g., not matching groups for verbal mental age). Moreover, Blair (2005) noted that existing studies suggesting impairment in emotional empathy used "complex 'cognitive' emotions requiring the representation of the mental states of others, such as surprise and embarrassment" (p. 706). It should be noted that methodologically-sound studies have found facial expression recognition differences in high-functioning adults with autism (Humphreys, Minshew, Leonard, & Behrmann, 2007). As such, the findings are difficult to interpret and clouded by confounding variables. In addition, it is possible that the heterogeneity observed in these findings is linked to the heterogeneity of autistic disorder.

Antisocial Personality Disorder and Psychopathy. Antisocial personality disorder (ASPD) and psychopathy are disorders marked by an extreme "disregard for, and violation of, the rights of others" (American Psychiatric Association, 2000, p. 701). Inherent in its name, individuals with ASPD have an inability to form any significant attachment or loyalty to other people, groups, or society. Psychopathy is considered a more severe form of ASPD that accounts for approximately 20% of the ASPD population (Rutherford, Cacciola, & Alerman, 1999). Deceit, manipulation, and empathy deficits are central features of psychopathy, though these traits are not all required for the formal diagnosis of ASPD.

Current conceptualizations suggest that empathy deficits in ASPD and psychopathy result from severe impairment in emotional empathy and self-regulation (Blair, 2005; Decety et al.,

2007). This conceptualization is based on four main theories regarding empathic dysfunction in these populations: 1) individuals with ASPD are able to understand the perspective of others, but do not necessarily *adopt* or *internalize* the perspective of others, 2) individuals with ASPD typically use their ability to understand another's mental state for deceitful gain, 3) individuals with ASPD appear to lack the ability to regulate their emotional reactions, and 4) individuals with ASPD have an impaired emotional response to emotion expression from others.

Results from the literature appear to tentatively support this conceptualization. Research on populations with psychopathy and ASPD have found intact performance on ToM tasks with deficits in emotional processing tasks widely reported (Blair et al., 2000; Dadds et al., 2006; Marsh & Blair, 2008). In a comprehensive study, Dolan & Fullam (2004) examined performance on a social faux pas task[1] and first and second order ToM tasks in individuals with ASPD and healthy controls. In addition, the ASPD sample was differentiated into two groups: those with psychopathy and those without psychopathy. Findings from this study revealed no significant differences in first and second order ToM tasks across the three groups. Interestingly, both ASPD groups showed no deficits in recognizing social faux pas in comparison to controls; however, both ASPD subgroups showed deficits in assessing the mental state of the individual making the faux pas. These authors noted that individuals within both ASPD groups reported an emotional indifference to the impact of faux pas.

Blair (1995) has hypothesized that individuals with psychopathy have difficulties with self-regulation involving disturbance in a violence inhibition mechanism typically generated by

[1] During a social faux pas task, participants are read stories in which an individual has said something they should not have said in a social situation. The task requires that the participant understand the cognitive state of the individual making the faux pas and the emotional state of the receiver (e.g., hurt or insulted). Each participant is asked a series of questions that address detection and understanding of the faux pas, the affective and mental state of the receiver, and the cognitive state of the narrator.

the suffering of others. Decety et al. (2007) have noted that self-regulation is important for emotional development as individuals need to learn how to regulate their emotions during social interactions. Individuals with psychopathy appear to lack the ability to self-regulate, a characteristic that is governed by one's executive functioning abilities. Morgan and Lilienfeld (2000) conducted a meta-analytic review of studies examining neuropsychological measures of executive functioning in samples with ASPD. Thirty-nine studies including over 4,500 participants were analyzed. Interestingly, ASPD groups performed an average of 0.62 standard deviations below comparison groups on executive functioning tests, with medium to large effect sizes reported across studies (Morgan et al., 2000). These findings propose that those with ASPD have difficulties with self-regulation, though the specificity of these findings to violent behaviors is currently unknown.

With regard to emotional empathy, the findings are clearer. Research has consistently found that individuals with psychopathy use their ability to perceive others' intentions for personal gain and show no remorse or guilt when observing the distress of others. In addition, the disruption of emotional recognition and affective responding is thought be linked to a disturbance in emotional processing networks in the brain (Mealey & Kinner, 2002). Research in support of this hypothesis has been promising. Behavioral studies have demonstrated that individuals with psychopathy have difficulty recognizing fear and sadness despite showing intact recognition of other emotions (Blair et al., 2002). In another study, skin conductance was assessed (to infer emotional reactivity) in individuals with psychopathy during the viewing of stimuli divided into three categories: 1) others' distress, 2) threatening, and 3) neutral (Blair et al, 1997). Results revealed that individuals with psychopathy showed a lack of change in skin conductance specific to viewing pictures of others' distress, in comparison to healthy controls.

Meta-analytic research has revealed that individuals with ASPD have deficits specific to the recognition of fearful expressions, which the authors attributed to specific neural substrates (e.g., the amygdala) that are involved in processing fearful faces (Marsh et al., 2008). As the amygdala has a vital role in processing fear faces, Marsh and Blair (2008) have posited that impairment in recognizing fear faces in ASPD is linked to aberrant amygdala response. In a case study of acquired psychopathy, Blair and Cipolotti (2000) conducted a neuropsychological evaluation on an individual with brain damage to the amygdala and the left prefrontal region including bilateral damage to the OFC. The individual presented with significantly reduced recognition of emotional expression as well as social cognition. Results from their assessment revealed markedly impaired performance in recognizing angry and disgusted expressions and an inability to attribute fear, anger, and embarrassment to the story characters.

As outlined above, findings from populations with ASPD and psychopathy lend credence to the idea that several neural mechanisms underlie empathy, including involvement of the OFC and amygdala, and that disruption in one or more of these mechanisms can lead to significant impairments in prosocial behavior and the expression of empathy.

Though research on the neural bases of empathy is in its infancy, data from multiple sources suggests that empathy dissociates into cognitive and emotional components. Thus far, the study of empathy in neurological and psychiatric disorders has been reviewed extensively. This background has helped shape a more specific formulation of how impaired brain function influences empathic dysfunction. Though empathy is better understood in disorders like autism and psychopathy, less is known about this construct in schizophrenia, in which empathy is

observably impaired. Therefore, the application of this modern conceptualization of empathy to schizophrenia research has recently gained increasing interest from researchers.

Schizophrenia: Course, Symptomatology, and Subtypes

Schizophrenia is classified as a psychotic disorder in which thought content, perception, and emotional expression are severely disturbed (American Psychiatric Association, 2000). Characteristic symptoms of schizophrenia are classified as positive or negative depending on the manifestation of the disturbance. Positive symptoms (e.g., hallucinations, delusions, disorganized speech) represent an excess of normal function, while negative symptoms (e.g., anhedonia, alogia, flat affect) represent the loss of normal functions (American Psychiatric Association, 2000). In order to meet a full diagnosis of schizophrenia, the severity of the disturbance must persist for six months (with one month of active symptoms) and must result in impairment in interpersonal, social, or occupational functioning.

Within schizophrenia populations, recent distinctions have been made between individuals with schizophrenia exhibiting a high prevalence of enduring negative symptoms. This has been referred to as the deficit syndrome (DS) and is believed to be a distinct subtype within the broader and heterogeneous disorder of schizophrenia (Kirkpatrick, Buchanan, Breier, & Carpenter, 1993). The deficit syndrome is characterized by symptoms of alogia, blunted affect, and avolition as well as marked social dysfunction and social behavior deficits (Carpenter, Heinrichs, & Wagman, 1988; Kirkpatrick et al., 1993). Further, studies have shown distinction between the DS subtype from non-deficit syndrome using neuroimaging studies, illness outcome, and developmental data (Kirkpatrick, Buchanan, Ross, & Carpenter, 2001; Von Knorring & Lindstrom) schizophrenia patients on a number of domains, including course of illness and risk

factors. Indeed, primary and enduring negative symptoms in patients with DS symptoms have proven to be highly treatment resistant and this has been attributed to a distinct underlying neuropathology associated with the DS condition.

The heterogeneous nature of the symptoms that comprise schizophrenia, coupled with the differential nature of the course and prevalence in subtypes of this disorder, have led some to characterize schizophrenia as a set of disorders with the possibility of multiple and overlapping etiologies. Therefore, it is helpful to review briefly current models of schizophrenia neuropathology and related neuroimaging and genetic studies.

The Neuropathology of Schizophrenia

Despite tremendous advances in clinical psychology and psychiatry and findings from studies on genetics and psychopharmacology, the neuropathology of schizophrenia has not been fully elucidated. Thus far, converging evidence from clinical neuroscience suggests that schizophrenia is a neurodevelopmental disorder with genetic diathesis (Lipska & Weinberger, 2002; Marenco & Weinberger, 2000).

The familial and genetic basis of schizophrenia has been supported by a large selection of studies examining first-degree family members (parents, siblings, and offspring) of persons with schizophrenia (Cadenhead & Braff, 2002). Nonpsychotic relatives of individuals with schizophrenia exhibit similar, yet attenuated, neuropsychological deficits, which appear to increase in severity with the degree of genetic relationship (Cannon et al., 1994; Faraone et al., 2000; Kremen et al., 1994). To date, first-degree relatives have displayed deficits in a number of functions, ranging from olfactory processing (Kopala, Good, Torrey, & Honer, 1998) and eye movement dysfunction (Levy, Holzman, Matthysse, & Mendell, 1993) to abnormalities in

structural brain imaging (Staal, Hulshoff Pol, Schnack, van der Schot, & Kahn, 1998). Despite the apparent role of genetics, the development of schizophrenia involves more than heredity, as concordance rates for monozygotic twins are approximately 48% (Gottesman, 1991). Thus, researchers propose that genetic liability is necessary but not sufficient to develop schizophrenia. As such, there has been an effort to understand the non-genetic factors that influence the probability of developing schizophrenia (Conklin & Iacono, 2002).

A promising "neurodevelopmental" model has been proposed to account for the role of stress and neuropathology in schizophrenia (Weinberger, 1987). In his seminal analysis, Weinberger (1987) postulated that neurodevelopmental abnormalities in schizophrenia are influenced by disruptions in gene expression during early development. Further, he hypothesized that schizophrenia results from abnormal forebrain development, particularly in the prefrontal circuitry (Weinberger, 1987). During the second trimester of pregnancy, neurons migrate to distal portions of the brain and connect with other brain cells. In individuals with schizophrenia, there appears to be a displacement in the organization of neurons in the brain (Akbarian et al., 1996). This suggests a disruption in synaptic pruning, a developmental process by which brain cells reduce the branches of their dendrites. Abnormal synaptic pruning results in too few or too many synapses, an abnormality that is linked to impaired cognitive functioning. The neurodevelopmental model proposes that schizophrenia results from fewer dendrite branches in several keys areas of the brain in the frontal and temporal lobes (McGlashan & Hoffman, 2000). The reduced number of dendrite branches may be a result of: 1) overaggressive pruning of an initially normal number of dendrite branches, or 2) a normal pruning of an initially low number of dendrite branches (McGlashan et al., 2000).

Structural and metabolic abnormalities in the frontal lobes have been well documented in schizophrenia. In a histological study of individuals with schizophrenia, more neurons were found in the deeper levels of the PFC while less neurons were located in the surface white mater of the PFC (Akbarian et al., 1996). As noted previously, the PFC is best understood as a prime center for "executive functioning" faculties. Similar to imaging studies, neuropsychological tasks of executive functioning that probe the integrity of the PFC in schizophrenia have revealed impairments (Bilder et al., 2000). Further, deficits in executive functioning have been documented during the first episode of psychosis suggesting a compromise in the PFC independent of the persistent use of antipsychotic medications, chronicity of psychotic illness, or length of hospitalization duration.

Overall, the neurodevelopmental model takes into account the heterogeneity of schizophrenia and suggests that the etiology of this disorder is influenced by genetics, brain development, and environmental factors. In addition, differing neuropathology may be responsible for the nature of the symptoms (i.e. enduring negative symptoms). Further, the frontal lobes of individuals with schizophrenia may be a central clue into the underlying neural substrates responsible for social impairments in schizophrenia.

Empathy in Schizophrenia

Research on empathy in schizophrenia is currently in its nascent stages, but existing literature has laid a strong foundation for further investigation. Despite measurement challenges, interest in the empathic ability of individuals with schizophrenia occurred as early as the 1950s (Jackson & Carr, 1955). With increasing knowledge of how to operationalize and measure empathy, research on empathy in individuals with schizophrenia has slowly accrued over time.

Evidence of emotional dysfunction in schizophrenia can be traced to the early 1900s. In his observations of patients with schizophrenia, Emil Kraeplin (1919/1989), who first characterized schizophrenia with the Latin name *dementia praecox*, commented on an inability to sympathize or share feelings with others. The social cognitive impairments observed in schizophrenia - such as reduced empathy, anhedonia, and flat affect - have drawn strong comparisons to deficits observed individuals with autism (Lee, 2007). These comparisons led researchers to consider the central role of empathy in understanding social impairment in schizophrenia. Given that empathy requires both comprehending and feeling another's emotional state, impairment in one or both of empathic constructs is thought to explain enduring social deficits observed in individuals with schizophrenia (Shamay-Tsoory, Shur, Harari, & Levkovitz, 2007).

A handful of studies have started to examine empathy and its related cognitive and affective processes in schizophrenia populations. These studies have employed a variety of ways to measure empathy, including self-report measures, computer tasks, neuroimaging studies, or some combination of all three. Assessment of the emotional and cognitive components of empathy using self-report measures has shown conflicting results. One of the most popular self-report measures of empathy is the Interpersonal Reactivity Index (IRI; Davis, 1980), which is composed of two cognitive empathy subscales (perspective taking and fantasy scale) and two affective empathy subscales (personal distress and empathic concern). Thus far, schizophrenia patients have showed differential results on self-reported IRI scores. In one study, both affective and cognitive empathy were significant lower than comparison groups (Shamay-Tsoory et al., 2007). In contrast, Derntl et al. (2009) found that individuals with schizophrenia had discrepant scores on one component of emotional and cognitive empathy (lower fantasy and higher personal

distress scores) while showing similar ratings on the remaining components of empathy (perspective taking and empathic concern). Interestingly, Fujiwara et al. (2008) found a similar discrepancy in patients but in the opposite direction with patients reporting lower personal distress and higher fantasy scores than controls. Montag et al. (2007) found that cognitive but not affective empathy was deficient in schizophrenia. In a recent study, individuals with schizophrenia, their caregivers (relatives or spouses), and community controls were administered an empathy questionnaire (Bora, Gokcen, & Veznedaroglu, 2008). Results revealed a significant discrepancy between patients' self-report of empathy and the report of their spouse or relative. Caregiver ratings of patient's empathy were significantly lower than self-reported control empathy resulting in a large effect size (d = .91). In contrast, no statistically significant differences in empathy scores were evident between patients and controls. Furthermore, caregiver ratings, but not patient self-report ratings, were significantly correlated with negative symptoms of schizophrenia. The authors note that while cognitive deficits accounted for some of the variance in between-group empathy differences, the resulting differences in empathy were still statistically significant. This finding suggests a differential pattern between self and caregiver ratings of empathy in individuals with schizophrenia. However, more research is needed to elucidate if this differential pattern is evident for both cognitive and affective empathy.

Studies examining the cognitive "theory of mind" aspect of empathy in schizophrenia have been difficult to interpret. Studies have supported a general impairment in ToM abilities in schizophrenia. It has been consistently shown that children and adults with schizophrenia display deficits on simple and complex measures of ToM (e.g., the false-belief task described previously) compared to non-psychiatric controls (for a review, see: Lee, Farrow, Spence, & Woodruff, 2004). Recently, Shur, Shamay-Tsoory, & Levkovitz (2008) examined affective and

cognitive ToM tasks in addition to neuropsychological measures related to OFC functioning in schizophrenia patients and controls. They found that schizophrenia patients displayed more errors on the emotional and cognitive ToM tasks compared to controls. Furthermore, neuropsychological measures related to OFC function appeared to account for a significant amount of variance in patients' cognitive but not emotional ToM scores.

However, some have posited that impairment in ToM observed in schizophrenia is related to state (active psychosis) versus trait symptoms. Two independent meta-analyses were conducted to examine ToM abilities in schizophrenia (Brune, 2005; Harrington, Siegert, & McClure, 2005). Both consistently reported that ToM abilities were evident yet noted that findings differed depending on the nature of the schizophrenia group. Some studies suggest that these deficits are most prominent in patients with negative (Frith, 2004; Mazza, De Risio, Surian, Roncone, & Casacchia, 2001) or disorganized symptoms (Greig, Bryson, & Bell, 2004; Langdon, Coltheart, Ward, & Catts, 2002), which may represent a trait marker in schizophrenia (Brune, 2005). In contrast, other studies have demonstrated that ToM abilities are strongly related to delusions and were found to correlate with mental state changes in schizophrenia (Pousa et al., in press). It seems that these conflicting findings may be related to the heterogeneity of the disease in the schizophrenia samples studied. Therefore, more research is needed to elucidate the role of active psychosis in ToM abilities.

Recently, Shamay-Tsoory et al. (2007) found a strong positive relationship between cognitive flexibility and empathy scores in patients with schizophrenia. This is interesting as impairment in cognitive flexibility has been widely reported in schizophrenia (Hartman, Steketee, Silva, Lanning, & Andersson, 2003; Laurent et al., 2001; Scarone, Abbruzzese, & Gambini, 1993). Cognitive flexibility is often measured using the Wisconsin Card Sorting Test

(WCST; Milner, 1963). When an individual continues to match to a particular sort despite feedback that their response is incorrect, the response is deemed *perseverative*. Studies suggest that schizophrenia patients experience reduced performance on the WCST, with increased perseverative errors representing one of the most frequently reported impairments (Koren et al., 1998; Li, 2004).

Although emotional empathy has only been scarcely investigated in schizophrenia, it appears that individuals with schizophrenia experience emotional processing deficits as well (Shamay-Tsoory et al., 2007). A recent study found that emotional recognition accuracy was significantly reduced in individuals with schizophrenia (Kohler, Barrett, Gur, Turetsky, & Moberg, 2007). This finding was primarily driven by deficits in the recognition of fearful and neutral faces and indicates that patients have a severe impairment in their ability to decode the facial affect of others. Interestingly, this deficit has been linked to poor social functioning and increased negative symptoms in schizophrenia (Hooker & Park, 2002; Suslow, Roestel, Ohrmann, & Arolt, 2003). Similarly, reduced affective empathy appears to be significantly related to poor social functioning, including behavioral problems and interpersonal relations. An array of other studies suggest that individuals with schizophrenia have partial gaze avoidance, diminished facial response, and experience a dysregulated vicarious arousal response (Kring & Neale, 1996; Myin-Germeys, Delespaul, & deVries, 2000; Williams, 1974). Furthermore, emotional deficits such as joylessness, interpersonal aversion, and blunted affect are also observed in schizophrenia (Gur et al., 2006; Kayton & Koh, 1975; Montag et al., 2007). As such, impairment in affective empathy may be a result of disruption in one or more of these abilities.

Current conceptualizations of empathy and neuropathology in schizophrenia suggest that disruptions in prefrontal circuitry contribute to reduced empathy in schizophrenia (Eslinger,

1998; Grattan et al., 1994; Grattan & Eslinger, 1992). One study examined self-reported cognitive and affective empathy in relation to set-shifting (probe of dPFC functioning) and reversal (probe of OFC functioning) (Shamay-Tsoory et al., 2007). Their findings suggest that only the cognitive component of empathy was related to OFC functioning in individuals with schizophrenia. The affective component, though reduced in comparison to controls, was unrelated to either task. This study suggests other neuroanatomical regions may be contributing to impaired affective empathy in individuals with schizophrenia. Given the pervasive and enduring nature of deficits in empathy, studies that further our understanding of the underlying brain regions implicated in reduced empathy in schizophrenia are needed.

Olfactory Processing as a Psychophysical Probe

The OFC and amygdala appear to be responsible for overlapping yet distinct functions in the empathic response. Therefore, neuropsychological measures that tap into the OFC and amygdala hold promise for investigating the neural mechanisms subserving empathy in schizophrenia. In recent years, an explosion of research has contributed to an increased understanding of the OFC and the amygdala and their functional contributions to chemosensation, emotional processing, social processing, decision-making, and memory (Zald & Rauch, 2006). As such, the OFC is thought to play a vital role in sensory integration and olfactory processing, as axons to the OFC arise in several components of the olfactory cortex, including the anterior olfactory nucleus and piriform cortex (Rolls, 2006). Additionally, the OFC has direct and reciprocal connections with several other brain structures, including the amygdala, cingulate cortex, hippocampus, and dorsolateral prefrontal cortex (Price, 2006). The amygdala, a

major component of emotional processing, has connections with the primitive olfaction centers and robust and bidirectional connections with the OFC (Lezak et al., 2004; Price, 2006).

Given that the olfactory network has direct connections to the amygdala and OFC, olfactory processing tasks are believed to be a robust and direct measure of integrity in these related pathways. In a recent commentary, Zald (2006) noted that "existing data suggest that [olfactory testing] may actually be among the most sensitive and selective measures of OFC dysfunction" (p. 464). Only a few synapses lie between the receptors in the olfactory epithelium and the primary olfactory complex, establishing one of the most direct connections between the sensory environment and the brain (Moberg et al., 1999). In addition, olfaction is unique from other senses given that primary projections are ipsilateral (e.g., left nostril receptors connect to the left hemisphere of the brain), allowing for the measurement of lateralized deficits in the processing of olfaction and related cognitive and affective domains.

Thus far, it appears that measures of olfactory identification have localization significance to the OFC. Olfactory identification refers to the ability to identify an odor from several alternatives. The University of Pennsylvania Smell Identification Test (UPSIT; Doty, Shamam, & Dann, 1984a) is a widely used measure of olfactory identification. During the task, the subject is asked to scratch a microencapsulated odorant, smell each odor, and pick the one descriptor that best corresponds to the odor out of four choices. In a PET-scan study, Zald and Pardo (1997) found that passively inhaling odors activates both the OFC and amygdala. Additionally, studies have shown that OFC metabolism is reduced in head trauma patients with post-traumatic anosmia (Varney, Pinkston, & Wu, 2001). Jones-Gotman and Zatorre (1988) demonstrated one of the strongest findings in support of the UPSIT's utility in regards to OFC function. In their study, UPSIT performance was examined in a group of 120 individuals with

focalized surgical brain lesions in different areas of the frontal and temporal lobe, and a comparison group of 20 healthy control participants. The results of this study established that impairment after frontal lobectomy was demonstrated only in patients whose frontal-lobe removal invaded the orbital cortex. Another study by Doty et al. (1999) found that fluctuations in task performance on the UPSIT correlated with changes in plaque levels in the inferior frontal lobes including the OFC. These findings were replicated with shorter measures of the UPSIT, indicating that the olfactory identification tasks are sensitive to OFC integrity.

The hedonic processing of odors had also gained attention due to the interrelationship between smell, emotions, and mood and the involvement of overlapping neural substrates. In particular, studies have explored the affective characteristics of odors, as hedonic processing of odors is believed to recruit additional involvement of the amygdala. Affective characteristics of odors in our environment have been described using a number of attributes. Intensity and hedonics of odors have been noted to be two important dimensions of odors that warrant further study. The amygdala's role in olfactory processing is currently debated. Some studies have noted that the amygdala is involved in processing aversive stimuli (c.f. Zald et al., 1997). Other studies have noted the amygdala's involvement in processing unpleasant *and* pleasant stimuli (Hamann, Ely, Grafton, & Kilts, 1999; Hamann, Ely, Hoffman, & Kilts, 2002). In an attempt to rectify these findings, a recent study by Anderson et al. (2003) examined brain activity during the inhalation of high and low concentrations of pleasant and unpleasant odors. Anderson reported amygdala activation during high intensity pleasant and unpleasant odors, while OFC activation occurred during unpleasant and pleasant odors regardless of the intensity. Anderson (2003) interpreted this findings as support for a dissociation of intensity and hedonic dimensions. Others argued against these findings, noting that there was no resolution as to whether the amygdala

"selectively encoded intensity or intensity only with respect to valence extremes" (Winston, Gottfried, Kilner, & Dolan, 2005, p. 8903). To resolve this, Winston et al. (2005) included pleasant, unpleasant, and *neutral* odors at high and low intensities in their analysis and found that activation in the amygdala displayed a concentration by valence interaction during olfactory processing (i.e., the amygdala showed no activation during the processing of intense neutral odors). Interestingly, activity in the OFC was concentration-independent and showed no specificity to the hedonic characteristics of the odors.

Several neuroimaging studies have converged in reporting that dimensions of intensity and pleasantness are processed in separate brain regions (Anderson et al., 2003; Rolls, Grabenhorst, Margot, da Silva, & Velazco, 2008; Winston et al., 2005). In non-clinical samples, intensity of odor stimuli were found to activate the infererior frontal gyrus, while hedonic aspects of odors activate the medial OFC and hypothalamus (Rolls et al., 2008). In another study, Rolls et al. (2003) reported that subjective hedonic but not intensity ratings were significantly correlated with level of activity in the medial OFC. Activity in the medial olfactory areas, including the pyriform and entorhinal cortex, were found to correlate significantly with intensity but not hedonic ratings. These findings appear to clarify the OFC and amygdala's role in hedonic olfactory processing and the role of peripheral olfactory pathways in the processing of odor intensity.

Overall, this research supports the utility of olfactory probes for combined OFC and amygdala function, areas also involved in empathy. In one highly relevant study, the relationship between olfactory identification and empathy was directly assessed in healthy adults (Spinella, 2002). Spinella found a robust relationship between right nostril-assessed smell identification

and a measure of affective empathy, consistent with the right hemispheric dominance of emotional functions. Although olfactory identification probes cannot differentiate between relative deficits in the OFC and amygdala, the use of intensity and hedonic ratings of odors may help determine dissociation between these brain networks, especially in the context of findings in schizophrenia (detailed below).

Olfactory Processing in Schizophrenia

Olfactory Identification. Thus far, numerous studies across a variety of research laboratories have demonstrated deficits on tasks of olfactory identification in individuals with schizophrenia (Brewer et al., 2001; Goudsmit et al., 2004; Houlihan, Flaum, Arnold, Keshavan, & Alliger, 1994; Kohler et al., 2001; Kopala, Good, Martzke, & Hurwitz, 1995; Malaspina et al., 2002; Malaspina et al., 1994; Moberg et al., 1997; Serby, Larson, & Kalkstein, 1990; Stedman & Clair, 1998; Wu, Buchsbaum, & Moy, 1993). These findings have been demonstrated during the first episode of psychosis (Kopala, Clark, & Hurwitz, 1993) and across both nostrils (assessed separately) in male patients with schizophrenia (Rupp et al., 2005b). In a comprehensive meta-analysis, Moberg et al. (1999) found that olfactory identification deficits observed across schizophrenia samples were independent of medication use, sex, and smoking status. Further, research by Kohler et al. (2007) found that *only* right-nostril-assessed olfactory identification was positively related with emotional recognition accuracy in individuals with schizophrenia, particularly when identifying the emotion expressed by sad faces. Interestingly, this association was only found in the schizophrenia group.

With regard to schizophrenia symptomatology, studies have found that olfactory impairment may be more strongly correlated in individuals with DS schizophrenia (Brewer,

Edwards, Anderson, Robinson, & Pantelis, 1996a; Geddes, Huws, & Pratt, 1991). A study by Goudsmit et al. (2003) found that smell identification deficits were more severe in DS schizophrenia, compared to NDS, and were highly correlated with social dysfunction, a key feature of the deficit syndrome. Even more striking are results from a recent meta-analysis investigating neuropsychological impairment in DS and NDS individuals with schizophrenia (Cohen et al., 2007). The results failed to support a unified pattern of neurocognitive impairment across these subtypes of schizophrenia when neuropsychological measures were grouped into separate cognitive domains. Interestingly, olfactory processes were the most impaired of all neurocognitive domains within DS patients. As noted before, empathy and negative symptoms have also shown a strong positive relationship (Shamay-Tsoory et al., 2007). Therefore, smell identification may hold specific promise for understanding empathy in schizophrenia.

Olfactory identification performance deficits have been demonstrated in unaffected monozygotic twins of individuals with schizophrenia, suggesting contributing genetic factors (Kopala et al., 1998; Ugur, Weisbrod, Franzek, Pfuller, & Sauer, 2005). Consistent with this findings, olfactory deficits have also been observed in individuals at ultra-high risk[2] for developing schizophrenia (Brewer et al., 2003). Interestingly, when participants were reviewed prospectively, those who later developed schizophrenia made significantly more olfactory identification errors than individuals who remained well or developed a different psychotic disorder.

[2] Ultra high-risk was defined based on Phillip's et al. (2002) criteria. Each individual was required to meet at least one criteria: 1) experience of attenuated psychotic symptoms (e.g. magical thinking, perceptual disturbance, or paranoid ideation), 2) experience of trait or state risk factors (e.g. biological family member with psychotic disorder or significant mental status decrease for one month), or 3) brief intermittent symptoms of psychosis (e.g., delusions, hallucinations, unusual thought content, etc.).

Odor Hedonics. Less is known about how individuals with schizophrenia rate odors, including intensity, familiarity, edibility, and hedonic qualities. One of the first studies to investigate odor dimension ratings demonstrated that schizophrenia patients display significantly lower ratings on odor pleasantness, familiarity, and edibility, but showed no between-group differences on odor intensity ratings (Hudry, Saoud, D'Amato, Dalery, & Royet, 2002). This latter finding has been replicated by three separate studies from different research groups (Crespo-Facorro et al., 2001; Hudry et al., 2002; Moberg et al., 2003).

Research on hedonic ratings has gained more attention given the potential for understanding emotional deficits, such as anhedonia and empathy dysfunction, observed in schizophrenia. Moberg et al. (2003) examined hedonic ratings across four low to high suprathreshold concentrations of the same odor (amyl acetate). Compared to male control participants, male patients rated the odor as significantly less pleasant at lower concentrations and as significantly more pleasant at higher concentrations, whereas ratings of the female schizophrenia patients were comparable to female control participants. In two separate but similarly designed studies, Rupp et al. (2005a) found no differences in hedonic ratings between male patients and controls, but later found that a different sample of male patients displayed higher hedonic ratings than male controls (Rupp et al., 2005b). Similar to this latter finding, Doop and Park (2006) reported that schizophrenia patients displayed a restricted (high) range of hedonic ratings, while controls showed more variability in their ratings, resulting in higher mean hedonic ratings in the schizophrenia group. In addition, these findings were more robust in individuals with increased negative symptoms.

In a recent study by Strauss, Allen, Ross, Duke, and Schwartz (2009), community controls and two samples of individuals with schizophrenia (deficit and non-deficit syndrome

subtypes) were administered a brief odor identification measure. In addition, valence ratings were obtained for each of the 12 odors. Findings indicated that deficit patients showed lower total accuracy than controls across all odors. The authors also separately examined odor identification accuracy for pleasant and unpleasant odors and found no differences between the three groups. In contrast, deficit patients displayed lower subjective hedonic ratings for pleasant items in comparison to non-deficit patients and healthy controls. In contrast to the findings of Strauss et al. (2009), results from a study on inpatients with schizophrenia indicated that patients have a reduced olfactory identification accuracy for pleasant, but not unpleasant odors, in comparison to nonpsychiatric participants (Kamath & Bedwell, 2007).

Crespo-Facorro et al. (2001) explored rCBF using PET in response to pleasant and unpleasant odors. Their research group found that individuals with schizophrenia (showing intact hedonic ratings for unpleasant odors) failed to recruit key limbic areas when exposed to unpleasant odors. Instead, individuals with schizophrenia recruited a set of regions in the PFC during exposure to unpleasant odors, which was theorized to be compensating for an underlying deficit in the utilization of limbic regions.

Collectively, these findings suggest that: 1) individuals with schizophrenia have difficulty assigning valence characteristics to pleasant odors, 2) individuals with schizophrenia have an intact ability to assign valence characteristics to unpleasant odors, and 3) a compensatory set of brain areas not normally used for emotional processing of odors are recruited during the experience of unpleasant odors in individuals with schizophrenia. Based on the results of their PET scan study, Crespo-Facorro et al. (2001) theorized that neural substrates needed for experiencing pleasant odors have been usurped for the greater biological need of recognizing aversive and potentially dangerous stimuli. Further, they propose that emotional disturbances in

schizophrenia are a result of these brain abnormalities. While it would be impossible to test this theory empirically, the idea that individuals with schizophrenia have compensatory brain networks for more fundamental needs is an interesting one. It reaffirms the needs to study brain-behavior relationships that underlie empathy as brain networks linked to these deficits may be compromised differently in schizophrenia in comparison to other psychiatric disorders.

Aim and Hypotheses

Despite shared neuroanatomical regions, it appears that the relationship between empathy and olfactory functioning has never been reported in a schizophrenia population. This is surprising given that both are related to functioning in the OFC and amygdala. The cognitive and affective components of olfactory processing make it an ideal task for assessing the neurocognitive underpinnings of empathy in schizophrenia. In addition, assessment of olfactory functioning may be one of the most noninvasive and direct measures of functioning in pathways including the OFC and amygdala (Moberg et al., 1999; Zald, 2006).

The current study was the first to examine the relationship between empathy and olfactory identification in a sample of individuals with schizophrenia. Understanding this relationship could help researchers make inferences regarding the underlying neural mechanisms of impaired empathy. The long-term benefits to research on the neurocognitive basis for reduced empathy in schizophrenia include informing new treatment approaches for this debilitating mental illness. Current psychosocial treatment interventions for schizophrenia have focused on social skills to enhance social functioning and cognitive compensatory strategies to improve brain function in these neural pathways (Reeder, Newton, Frangou, & Wykes, 2004; Wykes et al., 2007). Understanding the neurocognitive basis of empathy could help create psychosocial

treatments and pharmacological interventions that target the specific cognitive functions that have been implicated in poorer social outcome for individuals with schizophrenia. Treatment modalities such as cognitive re-training of social skills related to empathy may aid in the social rehabilitation of individuals with schizophrenia. Researchers have also focused on the development of screening measures to determine severity of symptoms and predict treatment outcome. Previous studies have recommended the use of the UPSIT as a screening measure for individuals at risk for developing persistent negative and disorganized symptoms of schizophrenia (Good, Whitehorn, Rui, Milliken, & Kopala, 2006). In addition, research has demonstrated that the UPSIT may be a premorbid marker of transition to schizophrenia (Brewer et al., 2003). The results of the current study could provide insight into the use of the UPSIT as a tool for the identification of persons with schizophrenia at risk for severe social cognitive impairment.

The overall aim of the current research was to further our understanding of the neurocognitive correlates of impaired empathy in schizophrenia. The proposed research had seven specific aims with matching hypotheses:

1) In order to extend findings suggesting that individuals with schizophrenia have impaired empathy, group differences in self-reported empathy between individuals with schizophrenia and healthy controls were examined. It was hypothesized that individuals with schizophrenia would show a statistically significant reduction in the global empathy score in comparison to control participants.

2) In addition, we examined the cognitive and affective subscales of the self-reported empathy scores in individuals with schizophrenia. It was hypothesized that individuals with schizophrenia

would show statistically significant reduced performance on both the cognitive and affective components of the scale in comparison to healthy control participants.

3) In order to examine previous findings, group differences in olfactory identification performance were explored in individuals with schizophrenia and healthy participants. The olfactory identification task was divided into two parts and completed unirhinally (e.g., one half using the right nostril and the other half with the left nostril). We hypothesized that participants with schizophrenia would display a statistically significant reduction in smell identification accuracy (left and right nostril combined) in comparison to healthy control participants. Given previous findings, we did not hypothesize an interaction of nostril and group.

4) In order to replicate previous findings, participants were asked to subjectively rate the hedonic characteristics (unpleasant to neutral to pleasant) and intensity of each odor on the smell identification task. We hypothesized that schizophrenia patients would report similar intensity ratings across all types of odors and display similar subjective hedonic ratings of unpleasant odors, in comparison to controls. Conversely, it was hypothesized that schizophrenia participants would display a statistically significant decrease in hedonic ratings of pleasant odors in comparison to healthy participants.

5) The relationship between empathy total scores and olfactory identification were explored across both groups. We hypothesized that there would be a statistically significant positive relationship between smell identification performance assessed through the right nostril and total empathy scores. We also hypothesized that left-nostril-assessed olfactory identification would not show a statistically significant relationship with the total empathy score. As the total

olfactory score combines the left and right nostril scores, we expected only a weak relationship between the total olfactory identification score and the empathy score. Further, we hypothesized that the relationship between the smell identification score assessed through the right nostril would show a statistically significant correlation with the cognitive empathy subscale and the affective empathy subscale.

6) The ability to identify pleasant, neutral, and unpleasant odors from the smell identification test was compared between each group. We hypothesized that individuals with schizophrenia would show no significant differences in the identification of unpleasant odors (across both nostrils) in comparison to controls. Conversely, it was hypothesized that individuals with schizophrenia would show a reduced ability to identify pleasant odors with the right nostril in comparison to controls. We hypothesized the subjective hedonic ratings on pleasant odors (identified with the right nostril) would correlate with identification of pleasant odors across both groups. Further, it was hypothesized that the valence ratings of pleasant odors identified with the right nostril would correlate with affective empathy scores across both groups.

7) Finally, the relationships between empathy, olfactory identification ability, and negative symptoms of schizophrenia were explored, as enduring negative symptoms are thought to result from impaired processing in common neural substrates (Weinberger & Berman, 1996). We hypothesized that negative symptoms of schizophrenia would show a statistically significant negative relationship with empathy scores. Further, we hypothesized that right-nostril-assessed olfactory identification scores would show a strong negative correlation with negative symptoms of schizophrenia.

METHODOLOGY

Power Analysis

Previous studies have not examined olfactory performance and empathy within the same sample of individuals with schizophrenia. Separate studies have found large effect sizes for cognitive and affective empathy (Cohen's *d* = 0.74 to 0.91; Shamay-Tsoory et al., 2007). In addition, the average of all effect sizes from seventeen studies examining olfactory identification performance was calculated from a meta-analysis by Moberg et al. (1999), which revealed a large effect size (Cohen's *d* = 1.16) as well. Based on the above studies and Cohen's (1992) recommendations, a power analysis was conducted using G*Power 3 software (Faul, Erdfelder, Lang, & Buchner, 2007), with an alpha of .05, and an estimated *d* of 0.74, in order to estimate the sample size needed to achieve a power level of .80. The estimated total sample size (both groups combined) was suggested as 48. A recent study by Spinella (2002) is the only known study to examine the relationship between olfactory identification ability and emotional empathy in healthy individuals with no known psychiatric diagnosis. This study reported a medium to large effect size (*r* = .46). Based on this study and Cohen's (1992) recommendations, another power analysis was conducted, with an alpha of .05, and an estimated *r* of .46, in order to estimate the sample size needed to achieve a power level of .80. The estimated total sample size (for each group separately) was suggested as 25 (e.g., 50 individuals total). Therefore, the total sample size for the current study (including individuals with schizophrenia and controls) was 50 in order to allow for sufficient power to determine group differences and examine relationships between smell identification abilities and empathy within each group.

Participants

Based on the results of the power analysis, 25 individuals diagnosed with schizophrenia based on criteria set forth by the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision (DSM-IV-TR; American Psychiatric Association, 2000) and 25 nonpsychiatric individuals were recruited from the surrounding community. The schizophrenia sample consisted of outpatients recruited from community mental health facilities, psychiatric hospital units, and the private practices of psychiatrists from the major metropolitan city of Orlando, Florida. Personnel from community mental health facilities listed above provided the schizophrenia outpatients with a flyer that described the study and included contact information for the laboratory where the study was conducted (University of Central Florida, Psychology Building, Room 137). Community controls were recruited using flyers placed in the community (e.g., local grocery stores) and newspaper advertisements. Interested controls were invited to participate based on the need for their particular demographic (based on desire to match these factors to the group of schizophrenia patients). Flyers for both groups mentioned the monetary reimbursement for participation, as described below.

Individuals responding to advertisements, flyers, and referrals from mental health professionals initially participated in a brief phone screening. Individuals were read a series of statements that addressed exclusionary criteria and were asked to answer if they responded "yes" to one or more of the statements. This was used to determine eligibility. During the phone screen, individuals were excluded based on the following criteria: age outside of 18 to 60 years, electroconvulsive therapy in the past 6 months, any history of hospitalization for substance dependence (e.g., detoxification), significant vision (acuity or color) problems, significant hearing problems, significant problems with use of dominant arm, history of significant head

injury (with a loss of consciousness greater than 10 minutes), history of neurological illness (including stroke, seizures, brain tumor, Parkinson's disease), history of certain systematic medical diseases that may affect neurocognitive function (includes active AIDS, lupus, congestive heart disease, insulin-dependent diabetes), history of learning disability or pervasive developmental disorder, or history of nasal/sinus surgery. Additionally, any control participants reporting a diagnosis of schizophrenia or a biological relative diagnosed with schizophrenia or schizoaffective disorder were excluded from the study. An upper age limit was set at 60 years, due to the age-related decline of olfactory ability that occurs over time (Doty et al., 1984b). A lower limit of 18 years was set as the goal of the proposed research was to study adults with schizophrenia. Any individual with schizophrenia who did not report the current use of antipsychotic medication was excluded from the study. Participants were contacted again the day before the research appointment in order to confirm their attendance. In addition, participants were asked to abstain from alcohol or illicit drug use in the 24 hours prior to the study appointment and were asked if they were experiencing nasal congestion in either nostril. Any individual reporting nasal congestion or planned alcohol or illicit drug use was rescheduled to attend a research appointment at a later date when nasal congestion had cleared. Twenty-seven potential controls and nine potential schizophrenia patients did not meet criteria to participate based on the initial phone screen.

Schizophrenia patients had a mean age of 39.61 (SD = 11.92) and healthy controls had a mean age of 39.57 (SD = 11.13). Both groups were composed of 16 males and 9 females. In addition, both groups had relatively equal proportions of individuals who self-identified as Caucasian (each group = 14 individuals), African-American (each group = 7 individuals), Hispanic-Americans (SZ group = 1 individual, HC group = 2 individuals), Asian-Americans (SZ

group = 1 individual, HC group = 0 individuals), and mixed/biracial (each group = 1 individual). With regard to marital status, the schizophrenia group included 16 never married, 2 separated, 2 divorced, 1 widowed, and 3 married. The healthy control group included 13 never married, 0 separated, 4 divorced, 0 widowed, and 8 married. With regard to educational attainment, healthy controls had 14.20 mean years of education (SD = 1.89) and schizophrenia patients had 12.16 mean years of education (SD = 1.77).

Of the patients with schizophrenia, 22 individuals were taking atypical antipsychotic medication, one individual was taking typical antipsychotic medication, and two individuals were taking a combination of both typical and atypical antipsychotic medications at the time of testing. The PANSS scores, measures indicating the severity of positive, negative, and global symptoms of schizophrenia, were as follows: Positive Symptom Scale (mean = 20.36, SD = 5.20), Negative Symptom Scale (mean = 18.08, SD = 4.23), General Psychopathology Scale (mean = 37.08, SD = 6.91), and PANSS Composite score (mean = 2.28, SD = 6.76). Patients reported an average illness duration of 16.17 years (SD = 11.25) and an average age of illness onset of 24.20 years (SD = 11.00).

Measures

Structured Clinical Interview for DSM-IV Axis I Disorders. The Structured Clinical Interview for DSM-IV Axis I Disorders (SCID-I) is a semi-structured clinical interview used to assess whether an individual meets diagnostic criteria in the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision (DSM-IV-TR; American Psychiatric Association, 2000). The interview contains directions for scoring answers in order to derive DSM-IV-TR diagnostic labels. The SCID-I has been shown to be both a reliable measure for

determining if an individual meets criteria for an Axis I DSM-IV-TR diagnosis with excellent inter-rater reliability (kappa = 0.85, range = 0.71 to 0.97) and diagnostic accuracy (82%), when compared with the "gold standard" of consensus diagnosis (Ventura, Liberman, Green, Shaner, & Mintz, 1998).

Structured Clinical Interview for DSM IV Axis II Personality Disorders. The Structured Clinical Interview for DSM IV Axis II Personality Disorders (SCID-II-APS) is a semi-structured clinical interview used to assess whether an individual meets diagnostic criteria for an Axis II Personality Disorder (First, Gibbon, Spitzer, Williams, & Benjamin, 1997). We administered the avoidant, paranoid, and schizotypal personality disorder sections as research has suggested genetic links between these diagnoses and schizophrenia. Items on the SCID-II-APS are scored on a 3-point scale (absent/false = 1, subthreshold = 2, threshold/true = 3). A categorical diagnosis was obtained when the number of "3's" reached the diagnostic threshold according to criteria in the DSM-IV-TR (American Psychiatric Association, 2000).

Structured Clinical Interview for Positive and Negative Symptom Scale. The Structured Clinical Interview for Positive and Negative Symptom Scale (SCI-PANSS; Kay, Opler, & Fiszbein, 1992; Kay, Fiszbein, & Opler, 1987) is a 30-item, seven point rating instrument that assesses negative and positive symptoms in schizophrenia. The SCI-PANSS is a semi-structured interview developed with manualized instructions to be used with the PANSS. The SCI-PANSS contains four subscales: Positive symptoms, Negative symptoms, General Psychopathology, and a Composite scale (Kay et al., 1992). The SCI-PANSS also includes five additional scores for clusters of symptoms including Anergia, Thought Disturbance, Activation, Paranoid/Belligerence, and Depression. Each dimension has distinct criteria in order to rate all 7 levels of symptom severity. The interview is typically conducted in three stages that include a

rapport building stage, the formal interview, and a scoring stage. Each of the 30 items of the SCI-PANSS has a specific definition, and each of these definitions is accompanied by detailed anchor criteria for the seven point rating scale. The seven rating points increase in level of severity (e.g., 1 = Absent, 2 = Minimal, 3 = Mild, 4 = Moderate, 5 = Moderate/Severe, 6 = Severe, 7 = Extreme). Reliability assessments of the PANSS have shown that each item correlated strongly with the appropriate scale total (Kay et al., 1987). Alpha coefficients of single items ranged from .64 to .84 and no gains in alpha coefficients were made by eliminating PANSS items. Inter-rater reliability demonstrated correlations between .89 and .94 (Kay, Opler, & Lindenmayer, 1988; Von Knorring et al., 1995). Assessments of validity have shown strong discriminate, convergent, criterion, predictive, and concurrent validity (Kay et al., 1992). Individuals administering the PANSS received training on this instrument through DVDs and sample forms provided by The PANSS Institute, LLC.

Reading Subtest of the Wide Range Achievement Test – 3rd edition. The Reading Subtest of the Wide Range Achievement Test – 3rd edition (WRAT-3R; Wilkinson, 1993) is a list of 50 words which are ordered by increasing difficulty. The words do not follow the common rules of pronunciation, effectively reducing the likelihood of phonemic decoding as opposed to word recognition. The WRAT-3R has been standardized with the Wechsler Adult Intelligence Scale – 3rd edition (WAIS-III). The WRAT-3R is scored in terms of the number of correctly pronounced words. Using the WRAT-3R manual, a reading scaled score, which also represents an estimate of verbal intelligence, was derived. Research has supported the use of the WRAT-3R Reading scaled score as a reasonable estimate of premorbid IQ (in our case, prior to the onset of schizophrenia), particularly in individuals from the lower range of IQ (Griffin, Mindt, Rankin, Ritchie, & Scott, 2002; Johnstone, Callahan, Kapila, & Bouman, 1996).

Basic Empathy Scale. The Basic Empathy Scale (BES; Jolliffe & Farrington, 2006) is a 20-item self-report measure of cognitive and affective empathy. Participants will be asked to respond to items on a Likert scale (1 = strongly disagree to 5 = strongly agree). The BES was validated with other measures of empathy (Jolliffe et al., 2006). In addition, separate scales for cognitive empathy and affective empathy can be derived which were shown to correlate with each other to only a moderate degree (r = .41), suggesting overlap, yet differentiation, between the two subscales. Confirmatory analysis verified this two-factor solution of cognitive and affective components. Furthermore, the BES was found to have construct and convergent validity (convergent in the expected direction and magnitude) as demonstrated by observed relationships with measures of sympathy, perspective taking, alexithymia, agreeableness, conscientiousness, openness, parental supervision and socioeconomic status.

University of Pennsylvania Smell Identification Test and Odor Ratings. The University of Pennsylvania Smell Identification Test (UPSIT; Doty, Shaman, & Dann, 1984d) is a self-administered odorant test of microencapsulated odors. The measure involves selecting the correct multiple-choice identification out of four possible answers on 40 "scratch 'n' sniff" item. The subject's task is to smell each odor and pick the one descriptor that best corresponds to the odor. The participant must make a selection even if the individual indicates no odor perception. The criteria for item selection and standardization have been described in detail (see Doty et al., 1984c). The internal consistency and 6-month test–retest reliability coefficients were greater than 0.90 (Doty et al., 1984d). Items from the UPSIT were subsequently divided into pleasant, neutral, and unpleasant valence categories using published normative ratings (Doty et al., 1984d). In total, 16 items were categorized as pleasant, 15 items were categorized as neutral, and 9 items were categorized as unpleasant. Pleasant, neutral, and unpleasant valence scores were

standardized into percent correct scores, as there was an unequal distribution of pleasant, unpleasant, and neutral odors within each presentation order.

In addition, participants were asked to rate the intensity and hedonic characteristics of each odor on a 5-point scale. The scales used to acquire odor ratings were adapted from the Self-Assessment Manikin developed by Lang (1985). The Self-Assessment Manikin is a visual representation of each dimension used to measure emotional responses. For the purpose of the current study, *valence* refers to the three odor types of pleasant, neutral, and unpleasant that participants were asked to identify and rate. *Hedonic* refers to a type of pleasantness rating that participants were asked to provide after the odor identification task. Hedonic ratings fell on a 5-point Likert scale from very pleasant to neutral to very unpleasant.

Procedure

This study was conducted with approval from the University of Central Florida's Institutional Review Board (see Appendix). The research appointment occurred in the Clinical Cognitive Neuroscience Laboratory at the University of Central Florida. Any participant who appeared to be under the influence of a substance (e.g., alcohol, cocaine, etc.) was discontinued from participation. The research appointment began with a detailed informed consent procedure. Informed consent was conducted by a clinical psychology doctoral student trained to work with clinical populations. Individuals had the opportunity to ask questions, which were addressed at that time. They were told (written and orally) that they could discontinue participation at any point in the study without negative consequences and that participation was entirely voluntary. In addition, the limits to confidentiality were reviewed with each participant as follows: 1) immediate and/or serious danger to self or others, 2) recent or ongoing child abuse, 3) recent or

ongoing abuse of a dependent adult, 3) diagnosis of disease or condition subject to mandatory public health reporting, and 4) court ordered release of information. All relevant information about the nature of the study was disclosed to participants during the informed consent and debriefing procedures. Participants were asked to sign one copy of the consent form indicating that they agreed to participate. Participants were also provided with a copy of the informed consent.

Following informed consent, individuals were re-read items from the initial phone screen in order to ensure that participants met criteria for participation in the study. No individual was excluded from participation following the re-administration of the screening criteria. Participants were subsequently administered the SCID-I. Any control participant endorsing full diagnostic criteria for current bipolar disorder, psychotic disorder, or substance abuse/dependence were discontinued from participation. Two individuals were discontinued from participation based on these criteria. Any individual referred to the schizophrenia cohort who did not meet full diagnostic criteria for schizophrenia was discontinued from participation. Two individuals were discontinued based on not meeting full diagnostic criteria for schizophrenia.

Following administration of the SCID-I, individuals with schizophrenia were administered the SCI-PANSS while control participants were administered the SCID-II-APS. Any control participant meeting diagnostic criteria for schizotypal, paranoid, or avoidant personality disorder was excluded from participation. Two potential controls were excluded based on meeting full diagnostic criteria for paranoid personality disorder. Participants were administered the WRAT-R3, which provided an estimate of premorbid verbal IQ (for descriptive group comparison and exclusionary purposes). Any individual with an estimated verbal intelligence less than 70 was excluded from the study. No participant was excluded based on this

criterion. Individuals were then asked to fill out paper and pencil tasks that were of interest to various investigators in the lab, which included the empathy scale relevant to this study. During this time, participants were also asked questions regarding their current and past smoking behavior including number of cigarettes smoked per day and number of years smoked. These scores were used to derive two indices of smoking behavior - *smoking status* (current smoker, past smoker, and never smoked) as well as *pack-years* (packs per day x number of years smoked). All participants were administered the UPSIT under supervision, as outlined in the test manual (Doty, McKeown, Lee, & Shaman, 1995). The examiner demonstrated proper scratching of the first odor patch for each participant. Participants were then instructed to scratch, sniff, and identify each scent by choosing one of four typed alternatives. Participants were asked to verbalize their responses and the examiner filled out the appropriate response. In the event that a participant was unable to select a response, they were asked to re-scratch and smell the stimuli. In accordance with standardized procedure of the UPSIT, participants were told to make their best guess regardless of whether they could perceive or identify the odor. Nostril order was counterbalanced within each group. Prior to presenting the UPSIT stimuli, the contralateral nostril was occluded with Durapore™ tape (3M Corporation, Minneapolis, MN) by fitting it over the nostril and columna. According to previous research, this procedure effectively prevents retronasal airflow (Bromley & Doty, 1995) and this technique has been employed in a variety of prior unirhinal olfactory studies with schizophrenia samples (Good, Martzke, Honer, & Kopala, 1998; Good, Martzke, Milliken, Honer, & Kopala, 2002; Kohler et al., 2007; Moberg et al., 2006; Szeszko, Bates, Robinson, Kane, & Bilder, 2004). Following identification of each odor, participants were asked to rate the intensity and hedonic characteristics of the odors on 5-point scales using a visual representation of each dimension.

Participants were also asked to complete other neurocognitive measures that were of interest to other investigators in the laboratory. The average time length of the assessment battery was 3.5 hours for controls and 4 hours for individuals with schizophrenia (including breaks). All participants were compensated at the rate of $8 for each half hour of participation (rounded to the nearest half hour). Any individual meeting DSM-IV-TR diagnosis for an Axis I Disorder was given a referral to the University of Central Florida's (UCF) Psychology Clinic[3], unless the participant reported that he/she was already receiving treatment for that condition.

[3] The UCF Psychology Clinic provides sliding scale psychological services to individuals in the community.

DATA ANALYSIS

Data Screening and Preliminary Analysis

Statistical analyses were conducted in STATISTICA™ (StatSoft® Inc., Tulsa Oklahoma) at an alpha level of .05, unless otherwise noted.

Outliers. Self-reported empathy scores, odor identification scores, and odor hedonic and intensity ratings were screened for outliers, which were defined as scores falling 3.3 SDs above or below the mean. No outliers were found within each group.

Normality. Kolmogorov–Smirnov tests of normality with Lilliefors Significance Corrections were conducted in order to observe departures from normality for all variables of interest separately within the schizophrenia and control group. A conventional and conservative alpha level of .01 was chosen to evaluate significance of the normality tests based on recommendations by Tabachnick and Fidell (2007) for small to moderate sample sizes. As empathy scores, odor identification scores, and odor hedonic ratings were normally distributed within each group, parametric tests were employed. Unirhinal odor identification accuracy scores across each odor valence type were not normally distributed within the schizophrenia group. Therefore, appropriate nonparametric statistics (e.g., Mann-Whitney *U* tests, Friedman's ANOVA, Wilcoxon Tests) were conducted with Bonferroni correction for multiple comparisons.

Sphericity. Assumptions of sphericity were examined for within-subjects analyses in which the repeated-measures had greater than two levels using Mauchly's Test of Sphericity. In cases where the sphericity assumption was violated, degrees of freedom were corrected for using either a Greenhouse and Geisser's (1959) estimate of sphericity (for $\varepsilon < 0.75$) or Huynh and Feldt's (1976) estimate of sphericity (for $\varepsilon > 0.75$) as suggested by Girden (1992).

Homogeneity of Variance. Assumptions of homogeneity of variance between subjects were examined using Levene's (1960) Test of Equality of Error Variances and Brown and Forsythe's (1974a, 1974b) test of homogeneity based on suggestions from Conover, Johnson, & Johnson (1981). In addition, if the tests yielded different decisions on homogeneity, then the result of the Brown-Forsythe test was chosen based on suggestions by Hayes (2005). In cases where the assumption of homogeneity was violated, post-hoc pairwise *t* tests (that estimate variances separately) were performed.

Analysis of Demographic Variables. The schizophrenia patients and nonpsychiatric controls were compared on demographic variables before conducting main analyses. Group differences on age, education, premorbid intelligence (WRAT-3R scores), and pack-years were compared using one-way analysis of variance (ANOVA). Multivariate Hotelling's T^2 test was used to compare differences in maternal and paternal education between patients and controls. Pearson's chi-square (χ^2) tests were used to compare group differences in distributions of all categorical demographic data including race, sex, marital status, and smoking status.

Covariates. As groups differed significantly with respect to smoking behavior (assessed by pack-years and smoking status), pack-years was included as a covariate in each model involving odor identification scores, odor hedonics ratings, and odor intensity ratings due to the potential influence of smoking behavior on olfactory performance. Pack-years was chosen because the variable combines duration of smoking (in years) with current intensity of smoking (packs per day) into one total score, providing the most accurate quantification of smoking out of the two smoking variables. Pack-years were evaluated within each of the models and were not a significant covariate in any olfactory analyses (all p's $> .10$). Therefore, analyses were performed

without covariates in the model in order to preserve power and increase degrees of freedom. Findings are therefore presented with no covariates.

Data Analysis of Study Hypotheses

Group differences in total empathy (BES) scores were examined using ANOVA, with group and sex as the between-subject factors. Items from the BES were subsequently divided into cognitive and affective empathy total scores using instructions provided by the author of the BES (Jolliffe et al., 2006). In total, the cognitive empathy subscale was composed of 11 items and the affective empathy scale was composed of 9 items. Given the unequal distribution of items between the scales, percent total scores were calculated. In order to examine group differences in self-reported cognitive and affective empathy between schizophrenia patients and nonpsychiatric controls, separate ANOVAs were conducted with group (schizophrenia | controls) and sex (male | female) as the between-subject factors and cognitive or affective empathy as the dependent variable. Significant effects were further explored by conducting post-hoc univariate contrasts.

In order to examine whether the effect of diagnosis on unirhinal odor identification score differed as a function of sex, right and left nostril assessed UPSIT scores were submitted to repeated-measures analyses of variance (ANOVA) with group (schizophrenia | control) and sex (male | female) as between-subject factors. Significant effects were further explored by conducting post-hoc univariate contrasts.

In order to examine group differences in unirhinal identification of pleasant, neutral, and unpleasant odors between schizophrenia patients and nonpsychiatric controls, Mann Whitney *U* Tests were conducted. Nonparametric statistics were employed, as all accuracy scores were not

normally distributed. The six left and right-nostril assessed accuracy scores were included as the dependent variables, with group (schizophrenia | control) as the between-subject factor. Differences between males and females in accuracy scores were also examined using Mann Whitney *U* Tests. Within-subject effects for nostril and valence were examined separately using Friedman's Rank Test. Significant effects were followed up with Wilcoxon tests in order to determine significant differences between pairs.

After examining group differences in odor identification ability, group differences in mean hedonic ratings were examined using repeated-measures ANOVAs. Group (schizophrenia | control) and sex (male | female) were between-subject factors, and nostril (right | left) and odor valence (pleasant | neutral | unpleasant) were repeated-measures factors. Significant multivariate effects were further explored using post-hoc univariate contrasts.

Group differences in mean intensity ratings were examined using repeated-measures ANOVAs, with group (schizophrenia | control) and sex (male | female) as between-subject factors, and nostril (right | left) and odor valence (pleasant | neutral | unpleasant) as the repeated-measures factors. Significant multivariate effects were further explored using post-hoc univariate contrasts.

Associations between olfactory valence and intensity judgments, right- and left-nostril assessed odor identification, empathy, and negative symptoms were then examined with correlational analyses. Pearson correlations were conducted, as the indices assessed were normally distributed in the overall sample. The following relationships were explored: 1) unirhinal smell identification performance indices and empathy scores, 2) smell identification performance indices and cognitive and affective empathy subscales, and 3) hedonic and intensity ratings and odor identification scores (separately for pleasant and unpleasant odors). Within the

patient group, the relationship between negative schizophrenia symptoms, empathy (and its subtypes), and olfactory performance indices were also examined.

Coefficients of determination (r^2) and effect sizes – Cohen's *d* and Fisher's correlation ratio (η^2) – were calculated using criteria set forth by Cohen (1988; 1992).

RESULTS

Demographic Variables

Schizophrenia patients (SZ; mean age = 39.61, SD = 11.92) and healthy controls (HC; mean age = 39.57, SD = 11.13) did not differ with regard to *age*, $F(1,48) = .0002$, $p = .99$. Both groups were well-matched with regard to *sex composition*, $\chi^2(1) = 0$, $p > .99$, as there were equal numbers of males and females in each group (16 males and 9 females). In addition, groups did not differ with regard to distribution of *race*, $\chi^2(3) = 1.33$, $p = .86$, as both groups had relatively equal proportions of Caucasians (each group = 14 individuals), African-Americans (each group = 7 individuals), Hispanic-Americans (SZ group = 1 individual, HC group = 2 individuals), Asian-Americans (SZ group = 1 individual, HC group = 0 individuals), and individuals self-identified as mixed/biracial (each group = 1 individual). Both groups did not differ significantly with regard to *marital status*, $\chi^2(4) = 6.23$, $p = .18$ (SZ group: 16 never married, 2 separated, 2 divorced, 1 widowed, and 3 married; HC group: 13 never married, 0 separated, 4 divorced, 0 widowed, and 8 married).

With regard to *educational attainment*, healthy controls (mean years = 14.20, SD = 1.89) had higher years of education compared to schizophrenia patients (mean years = 12.16, SD = 1.77), resulting in a statistically significant group difference, $F(1,48) = 15.47$, $p < .001$. This difference was expected given that the illness itself can affect educational attainment, therefore, maternal and paternal education level was used as a more appropriate estimate of premorbid educational expectation as recommended by Resnick (1992). Schizophrenia patients and nonpsychiatric controls did not differ significantly with regard to *maternal and paternal education*, Hotelling's $T^2 = .19$, $F(2,37) = 0.09$, $p = .92$.

Schizophrenia patients exhibited a higher degree of smoking behavior and a higher composition of smokers than healthy controls when smoking was examined as a categorical variable of *smoking status* (current smoker, past smoker, never smoked), $\chi^2(2) = 9.98$, $p = .01$, or when examined as a continuous variable of *pack-years* (packs per day multiplied by number of years smoking), $F(1,48) = 8.05$, $p = .01$ (see Table 1).

Empathy Analyses

Total Empathy Scores. Group differences in global empathy scores were analyzed using an ANOVA, with total BES score as the dependent variable and group and sex as the between-subject factors. Contrary to our hypothesis, no main effect of group was observed, $F[1,46] = 0.93$, $p = .34$. However, the analysis revealed a statistically significant main effect of sex, $F[1,46] = 5.47$, $p = .02$, $\eta^2 = .09$, with females reporting higher levels of empathy than males. In addition a statistically significant group-by-sex interaction was observed, $F[1,46] = 11.38$, $p = .002$, $\eta^2 = .18$ (see Figure 1 and Table 2). Post-hoc contrast analyses (with a Bonferroni-corrected alpha of .013 for 2 comparisons) revealed that female controls reported significantly higher empathy scores in comparison to females with schizophrenia, $F[1,46] = 7.34$, $p = .01$, $\eta^2 = .14$, and male controls, $F[1,46] = 16.31$, $p < 0.001$, $\eta^2 = .26$. Male patients also reported a higher empathy total score compared to male controls, $F[1,46] = 16.31$, $p = .05$, though this difference did not survive Bonferroni correction. No statistically significant differences in total empathy scores were observed between males and females with schizophrenia, $F[1,46] = 16.31$, $p = .47$.

Cognitive and Affective Empathy Subscales. In order to examine group differences in self-reported empathy subscales, separate ANOVAs were conducted, with group and sex as the between-subject factor and cognitive or affective empathy scores as the dependent variable. For

cognitive empathy, the analysis revealed a statistically significant main effect of group, $F[1,46] = 7.82$, $p = .01$, $\eta^2 = .13$, with schizophrenia patients endorsing significantly fewer cognitive empathy items compared to control participants (see Table 2 and Figure 2). No statistically significant main effect of sex, $F[1,46] = 2.49$, $p = .12$, or group-by-sex interaction, $F[1,46] = 2.27$, $p = .14$, was observed.

For self-reported affective empathy scores, no main effect of group ($F[1,46] = 0.38$, $p = .54$) was observed. A main of effect of sex approached statistical significance, ($F[1,46] = 3.88$, $p = .06$), with females reporting higher affective empathy scores compared to males. A statistically significant group-by-sex interaction was observed, $F[1,46] = 11.25$, $p = .002$, $\eta^2 = .18$. Therefore, males and females were analyzed separately in the post-hoc contrasts with a Bonferroni-corrected alpha of .01 for 4 comparisons. Results revealed that affective empathy scores were significantly higher in male patients compared to male controls, $F[1,46] = 10.96$, $p = .002$, $\eta^2 = .19$, while differences between female controls and female patients approached statistical significance, $F[1,46] = 2.92$, $p = .09$ (see Table 2 and Figure 3). In addition, affective empathy scores were significantly higher in female controls compared to male controls, $F[1,46] = 14.17$, $p < 0.001$, $\eta^2 = .24$, with no statistically significant differences between female patients compared to male patients, $F[1,46] = 0.96$, $p = .33$.

Unirhinal Odor Identification Accuracy Analyses

Unirhinal Odor Identification Scores. Results of the ANOVA revealed that patients demonstrated a statistically significant deficit in UPSIT performance across both nostrils relative to controls, $F[1,46] = 9.20$, $p = .004$, $\eta^2 = .17$ (see Figure 4 and Table 3). No main effect was seen for sex ($F[1,46] = 0.22$, $p = .64$) and no group-by-sex interaction ($F[1,46] = 0.09$, $p = .77$)

was observed. No main effect was seen for nostril (F[1,46] = 1.25, p = .27) and no other significant interactions were observed (all p's > .21; see Table 4).

Odor Identification Scores by Odor Valence Types. Group differences in unirhinal odor identification accuracy were analyzed using Mann-Whitney *U* Tests with Bonferroni correction, as variables were not normally distributed. Left and right-nostril assessed odor identification scores across each odor valence subtype were included as the dependent variables, with group as the between-subject factor. The resulting analysis revealed statistically significant differences between the groups on right-nostril (U = 192.5, p = .02) and left-nostril (U = 163.5, p = .003) assessed accuracy for pleasant odors (See Table 5 and Figure 5). These results survived the Bonferroni corrected alpha of .01 for 6 comparisons. Group differences for right-nostril and left-nostril accuracy for neutral (U = 278.5, p = .51, and, U = 274.0, p = .46) and unpleasant odors (U = 239.5, p = .16, and U = 288.5, p = .64) did not approach statistical significance. Rank sums are presented in Table 5 and means and standard deviations are presented in Table 3.

Differences between males and females in unirhinal identification accuracy across pleasant, neutral, and unpleasant odors were also analyzed using Mann-Whitney *U* Tests. The resulting analysis revealed no statistically significant differences between the males and females on right-nostril assessed intensity ratings for pleasant, U = 275.0, p = .80, neutral, U = 226.0, p = .22, and unpleasant odors, U = 245.5, p = .39. Furthermore, group differences between males and females for left-nostril assessed intensity ratings for pleasant, U = 194.5, p = .06, neutral, U = 210.5, p = .12, and unpleasant odors, U = 234.5, p = .28, were not statistically significant, though differences in left-nostril identification accuracy of pleasant odors approached statistical significance (see Table 5).

In order to examine within-subject differences in odor valence accuracy, a Friedman's Rank Test was conducted separately in patients and controls, with identification accuracy for pleasant, neutral, and unpleasant odors as the dependent variables. Results of the Friedman's ANOVA revealed a statistically significant difference by odor valence in patients, $\chi^2(2) = 7.76$, $p = .02$, and controls, $\chi^2(2) = 10.35$, $p < .01$. In order to determine which valence pairs were significantly different, post-hoc Wilcoxon tests were conducted using a Bonferroni-corrected p-value of .016 for 3 comparisons. Results of the Wilcoxon tests revealed that all patients displayed no significant differences between (1) pleasant and neutral odors, $T(25) = 99.00$, $Z = 1.71$, $p = .09$, (2) unpleasant and neutral odors, $T(25) = 98.50$, $Z = 1.72$, $p = .09$, and (3) pleasant and unpleasant odors, $T(25) = 129.00$, $Z = 0.90$, $p = .37$. For controls, results of the Wilcoxon tests revealed that controls displayed (1) higher identification accuracy for pleasant odors compared to neutral odors, $T(25) = 33.00$, $Z = 3.34$, $p < .001$, (2) no significant differences between pleasant odors compared to unpleasant odors, $T(25) = 109.00$, $Z = 1.17$, $p = .24$, and (3) no significant differences between identification accuracy for neutral and unpleasant odors, $T(25) = 111.00$, $Z = 1.39$, $p = .17$.

Analyses of Hedonic and Intensity Ratings of Odors

Odor Hedonic Ratings. Group differences in mean unirhinal hedonic ratings were analyzed using an ANOVA, with nostril and odor valence as the within-subject factors, and group and sex as the between-subject factors. According to Mauchly's test, the assumption of sphericity was violated for valence, $\chi^2(2) = 15.11$, $p < .001$. Therefore, degrees of freedom and p-values were adjusted using Huynh-Feldt estimates of sphericity as all ε values were greater than 0.75 (ε values are reported below). Results of the adjusted ANOVA revealed a statistically

significant valence-by-group-by-sex interaction (F[1.7,78.5] = 3.29, p = .05, ε = 0.85). In addition, a main effect of odor valence (F[1.7,78.5] = 138.43, p < .0001, ε = 0.85) was observed. No other statistically significant main effects or interactions were observed (all p's > .08; see Table 6). Means and standard deviations are presented in Table 3.

As the valence-by-group-by-sex interaction was statistically significant, patients and controls were analyzed separately in the subsequent analyses (see Figure 6). We found a statistically significant main effect of valence (F[2,46] = 105.52, p < 0.001) and valence-by-sex interaction (F[2,46] = 6.72, p = .003) in controls, whereas patients only showed a main effect of valence (F[2,46] = 50.33, p < 0.001) with no valence-by-sex interaction (F[2,46] = 0.14, p = .87). Univariate contrast analyses were conducted in the control group in order to decompose the valence-by-sex interaction. Results revealed no significant differences in hedonic ratings between male and female controls for pleasant (F[1,23] = 0.49, p = .49) or neutral odors (F[1,23] = 0.08, p = .76), with differences in ratings of unpleasant odors approaching statistical significance (F[1,23] = 4.06, p = .06). In addition, female controls displayed a larger difference in hedonic ratings than male controls between pleasant and unpleasant odors (F[1,23] = 9.73, p = .005), as well as between neutral and unpleasant odors (F[1,23] = 5.08, p = .03). Differences in hedonic ratings between pleasant and neutral odors were not statistically significant, F[1,23] = 2.76, p = .11.

Given the statistically significant main effect of valence, within-subject analyses of hedonic ratings across odor valence types were examined across the entire sample. The analysis revealed that, across both groups, higher mean hedonic ratings were observed for pleasant odors compared to neutral odors, F[1,46] = 89.11, p < .001, and unpleasant odors, F[1,46] = 187.57, p

< .001. In addition, individuals had higher hedonic ratings for neutral compared to unpleasant odors across both groups, $F[1,46] = 93.03$, $p < .001$.

Odor Intensity Ratings. Group differences in mean intensity ratings were analyzed using an ANOVA, with nostril and odor valence as within-subject factors, and group and sex as between-subject factors. According to Mauchly's test, the assumption of sphericity was violated for valence, $\chi^2(2) = 9.50$, $p = .01$. Therefore, degrees of freedom were adjusted using Huynh-Feldt estimates of sphericity ($\varepsilon = 0.93$). The resulting analysis revealed a significant main effect for valence, $F[1.85,85.12] = 8.83$, $p < .001$, with all participants displaying higher intensity ratings for pleasant items compared to neutral ($F[1,46] = 27.40$, $p < .001$) and unpleasant odors ($F[1,46] = 3.99$, $p = .05$). In addition, differences between neutral and unpleasant odors across all participants approached statistical significance, $F[1,46] = 3.49$, $p = .08$. The main effect of group approached statistical significance with patients rating odors at higher intensity levels compared to controls, $F[1,46] = 3.72$, $p = .06$. No main effect of nostril, $F[1,46] = 0.35$, $p = .56$, sex, $F[1,46] = 0.34$, $p = .56$, or group-by-sex interaction, $F[1,46] = 0.20$, $p = .66$, was observed. In addition, no other main effects or interactions were observed (all p's > .14; see Table 7). Means and standard deviations are presented in Table 3.

Relationship Between Odor Identification, Odor Ratings, and Empathy

Next, relationships between right- and left-nostril assessed odor identification performance, self-reported empathy, and odor valence and intensity ratings were examined in the entire sample. No statistically significant linear relationships were observed between empathy indices and unirhinal UPSIT identification accuracy scores (all p's > .09). Furthermore, correlations between empathy indices and individual UPSIT identification accuracy scores for

pleasant, neutral, and unpleasant odors did not approach statistical significance (all *p*'s > .17, see Table 8).

Mean right-nostril assessed hedonic ratings for pleasant odors showed a statistically significant positive relationship with total empathy scores ($r(50) = .33$, $p = .02$) and affective empathy scores ($r(50) = .35$, $p = .01$). Left-nostril assessed hedonic ratings for pleasant odors also showed a statistically significant positive relationship with total empathy scores ($r(50) = .42$, $p = .002$) and affective empathy scores ($r(50) = .44$, $p = .001$). These latter relationships between left-nostril assessed hedonic ratings for pleasant items and empathy indices were the only correlations to survive the Bonferroni corrected alpha of 0.002 for 18 comparisons (see Table 9). Relationships between empathy scores and intensity ratings were also explored and no correlations were statistically significant (all *p*'s > .10; see Table 9).

Across the entire sample, the relationship between odor identification accuracy and odor hedonic ratings were examined. A statistically significant positive relationship between left-nostril identification accuracy for unpleasant odors and left-nostril hedonic ratings for pleasant odors was observed, $r(50) = .33$, $p = .02$. This relationship did not survive the Bonferroni corrected alpha of .001 for 48 correlations. No other statistically significant relationships were observed (all *p*'s > .08, see Table 10).

Examination of relationships between odor identification accuracy indices and odor intensity ratings revealed that left-nostril identification accuracy for unpleasant odors had a statistically significant positive relationship with intensity ratings for right-nostril intensity ratings for pleasant, $r(50) = .32$, $p = .02$, and unpleasant odors, $r(50) = .30$, $p = .03$, as well as with left-nostril intensity ratings for neutral, $r(50) = .32$, $p = .02$, and unpleasant odors, $r(50) = .37$, $p = .01$. These relationships did not survive Bonferroni correction (alpha = .001 for 48

correlations). All other relationships were not statistically significant (all p's > .08; see Table 10).

Relationship Between Negative Symptoms, Empathy, and Odor Identification in Patients

The relationships between negative symptoms, empathy indices, and odor identification ability were examined. A statistically significant inverse relationship between negative symptoms and global, ($r(25) = -.43$, $p = .03$) and cognitive ($r(25) = -.42$, $p = .04$) empathy was observed (see Table 11 and Figure 7). These relationships did not survive the Bonferroni-corrected alpha of .02 for three comparisons; however, the r^2 value of .18 indicated a large effect size.

In patients, a statistically significant inverse relationship between affective empathy and left-nostril identification scores was observed, $r(25) = -.41$, $p = .05$. Despite the fact that this relationship did not survive the Bonferroni-corrected alpha of .01 for 6 comparisons, the large effect size ($r^2 = .17$) suggested that this relationship may be more robust in a larger sample.

No relationships between negative symptoms and unirhinal odor identification scores were observed (all p's > .15, see Table 12). A statistically significant negative relationship was observed between negative symptoms and right-nostril accuracy for pleasant odors, $r(25) = -.42$, $p = .03$. However, this relationship also did not survive the Bonferroni-corrected alpha of .01 for 6 comparisons.

Lastly, the relationship between negative symptoms and odor valence ratings were examined and no statistically significant relationships were observed (all p's > .11, see Table 13).

DISCUSSION

The overall purpose of the current study was to broaden our understanding of the relationship between empathy and olfactory performance in individuals with schizophrenia and demographically-matched healthy controls. Despite previous research suggesting a robust relationship between olfactory identification and self-reported empathy in healthy individuals, as well as research suggesting shared neuroanatomical substrates underlying olfactory and empathic processing, it appears that the current study was the first to examine the relationship between empathy and olfactory functioning in schizophrenia. We also examined group differences in self-reported global empathy, cognitive empathy, and affective empathy in individuals with schizophrenia and healthy controls. Group differences in unirhinal olfactory identification, odor hedonic ratings, and odor intensity ratings were also examined. Finally, we explored the relationship between olfactory and empathic indices across our entire sample, as well as separately in individuals with schizophrenia.

Empathy

Contrary to our hypothesis, individuals with schizophrenia did not display global deficits in self-reported empathy. Instead, our findings suggest that differences in self-reported empathy were influenced by the sex of the participant. We found that females with schizophrenia had significantly lower global empathy scores compared to female controls. Differences between males with schizophrenia and male controls were statistically significant but did not survive Bonferroni correction for multiple comparisons. Interestingly, when we examined these interactions in self-reported empathy subtypes, we found a differential influence of sex. Affective empathy was influenced by sex. Differences on affective empathy between female

patients and female controls were not statistically significant. Conversely, male patients reported significantly higher affective empathy compared to male controls. A visual inspection of the scatter plot suggested that the group differences were not driven by outliers or extreme scores. For cognitive empathy, we found that, irregardless of the individual's sex, schizophrenia patients reported significantly lower levels of perspective-taking and understanding of another's feelings compared to healthy controls.

While the influence of sex on self-reported empathy has not been well-studied in schizophrenia, a substantial body of literature on empathy in non-clinical populations has consistently reported sex differences in self-reported empathy scores. For example, results of a meta-analytic review found a consistent female advantage in studies employing self-report questionnaires and ratings of empathy (Eisenberg & Lennon, 1983). Findings involving facial, gestural, or physiological measures of empathy were more mixed and no consistent pattern of sex differences emerged. Thus, the authors concluded that sex differences in empathy are heavily influenced by the way in which empathy is defined and assessed. Operationalization of empathy appears to have a significant impact on the results. Until the past decade, there was little consensus in the empirical literature on the multifaceted nature of empathy and the differences that exist between constructs such as empathy, sympathy, emotional appraisal, and perspective-taking. Therefore, we examined a study employing the same measure of empathy used in the current study (Basic Empathy Scale). In a study using a non-clinical sample, Jolliffe et al. (2006) found that females displayed higher levels of self-reported global, affective, and cognitive empathy than males, with larger effect sizes reported for global and affective empathy compared to cognitive empathy. In our small sample of male and female controls, we replicated the results of Joliffe et al. (2006) as we also found a more robust effect size for global (d = 2.16) and

affective empathy (d = 1.95) compared to cognitive empathy (d = 1.17) between males and females, irregardless of diagnosis.

Our findings within patients are more difficult to compare to prior studies given that this is the first known study to examine self-report on the Basic Empathy Scale in schizophrenia. Prior studies examining self-report ratings of empathy in schizophrenia have employed different measures, including the Interpersonal Reactivity Index (IRI; Davis, 1980) and the Questionnaire Measure of Emotional Empathy (QMEE; Mehrabian et al., 1972). The IRI is the most well-studied empathy measure in schizophrenia despite the fact that it may not adequately tap into the current conceptualization of empathy (Jolliffe et al., 2006). Studies using the IRI have shown inconsistent results within the schizophrenia literature. One study found deficits in global and cognitive empathy in patients while showing intact affective empathy compared to controls (Shamay-Tsoory et al., 2007). Other researchers have reported deficient scores on either cognitive or empathy subscales (Derntl et al., 2009; Fujiwara et al., 2008; Montag et al., 2007). With regard to the QMEE, a recent study found that patients reported lower scores compared to controls (Cohen's d = .74) (Shamay-Tsoory et al., 2007). While the authors did not examine the interaction of group and sex, they did note that sex was not a statistically significant covariate in the analysis.

The discrepant role of sex in affective but not cognitive empathy observed in the current study is interesting. Current neuroimaging studies of empathy suggest that cognitive empathy is heavily influenced by self-regulation and cognitive flexibility and recruits fronto-temporal areas of the brain, including the mPFC and right OFC. In contrast, affective empathy recruits additional involvement of the paracingulate, anterior and posterior cingulate, and the amygdala (Völlm et al., 2006). Several studies examining the amygdala and ACC have suggested that the

brain volume of this region is heavily influenced by sex, illness, and brain laterality (Fujiwara et al., 2008; Kopelman, Andreasen, & Nopoulos, 2005; Niu et al., 2004). Studies on amygdala volume in schizophrenia have reported sexually dimorphic changes, with male patients displaying smaller amygdala volume compared to male controls, and female patients displaying larger amygdala volume compared to female controls (Gur et al., 2000). Frazier et al. (2008) also reported smaller amygdala volume in male, but not female, patients, which they attributed to abnormal hormone levels in males with schizophrenia. Other studies have found smaller right, but not left, amygdala volume in female patients compared to female controls (Gibbs et al., 2008). The same discrepancy for females amygdala volume was reported by Niu et al. (2004); however, they also found that males patients displayed bilaterally reduced amygdala volume in comparison to male controls.

Studies on ACC volume have been even more inconsistent. One study reported that patients displayed a reduction of thickness in the ACC with comparable grey matter volume between patients and controls (Calabrese et al., 2008; Fornito et al., 2008), while another reported a higher volume in males patients only (Kopelman et al., 2005). In addition, a recent study by Fujiwara et al. (2008) examined structural abnormalities in the ACC and its relationship to self-reported cognitive, affective, and global empathy scores. Results revealed a significant sex-by-diagnosis interaction of ACC size, with female patients exhibiting decreased bilateral ACC volume in comparison to male patients and male and female controls. In female patients, lower left ACC volume was strongly correlated with higher scores on the affective empathy subscale (personal distress). Prior findings suggesting that males and females with schizophrenia display pervasive deficits in cognitive flexibility, self-regulation, and perspective-taking would align with our finding of lower self-reported cognitive empathy scores for patients, regardless of

sex. In contrast, self-reported affective empathy is differentially influenced in males and female patients. Therefore, global and affective empathy may depend largely on the heterogeneity in the underlying neuropathology leading to aberrant brain volume or on other factors which have shown to be different in males and females with schizophrenia such as illness course, hormone levels, negative symptom severity, affective symptoms, and premorbid functioning (for a review, see: Leung & Chue, 2000).

Odor Identification and Odor Valence

As hypothesized, outpatients with schizophrenia showed significantly reduced unirhinal olfactory identification across both nostrils in comparison to demographically-matched controls. Consistent with prior research (Good et al., 1998; Good et al., 2002; Moberg et al., 1997; Rupp et al., 2005b), we found that sex, nostril, and smoking behavior did not interact significantly with group membership on unirhinal odor identification performance. In order to explore the influence of odor valence on odor identification accuracy, odors were divided into pleasant, neutral, and unpleasant categories. Though discrepancies have been reported in the existing literature, we hypothesized that schizophrenia outpatients would show a reduced accuracy for right-nostril identification of pleasant odors with intact accuracy for unpleasant odors in comparison to controls. The results of the current study supported this hypothesis as we found that odor valence differentially influenced odor identification accuracy in schizophrenia patients and controls. We found that patients displayed reduced left- and right-nostril odor identification accuracy for pleasant odors. Contrary to our expectation, this result was more robust in left-nostril assessment. As hypothesized, there were no significant between-group differences in identification accuracy for unpleasant and neutral odors.

The differential identification accuracy for pleasant and unpleasant odors observed in the current study coincides with previous findings from our group indicating that schizophrenia inpatients displayed similar birhinal identification accuracy for unpleasant but not pleasant odors compared to controls (Kamath, Bedwell, & Compton, 2009). The results of the current study expand on these findings and indicate that even when nostrils are assessed in isolation, there is a differential influence of odor valence on identification accuracy. Given the predominance of emotional processing in the right hemisphere and research by Zatorre, Jones-Gotman, Evans, and Meye (1992) indicating activation of the right OFC during olfactory stimulation, we hypothesized that individuals with schizophrenia would displayed a particular deficit of right-nostril assessed identification accuracy for pleasant odors. However, a more consistent pattern of neuroimaging research on lateralization of odor valence processing has suggested that unpleasant odors are predominantly processed in the right hemisphere while the processing of pleasant odors occurs primarily in the left hemisphere (Henkin & Levy, 2001). In addition, a study by Kim and Watanuki (2003) found that processing of odor valence may be more bilaterally processed for unpleasant odors with a left hemisphere advantage for the processing of pleasant odors. Interestingly, prior studies have suggested that olfactory deficits in schizophrenia correlate significantly with lower verbal memory (Compton et al., 2006; Good et al., 2002) and general verbal ability (Seckinger et al., 2004) - cognitive functions associated with left-hemispheric processing in most individuals.

In addition to hemispheric differences in the processing of odor valence, fMRI studies have also found that pleasant odors, but not unpleasant odors, activate the medio-rostral OFC (Rolls et al., 2003). Activation of the medial-OFC during processing of pleasant odors was also reported in another study (Grabenhorst, Rolls, Margot, da Silva, & Velazco, 2007). Furthermore,

pleasant and unpleasant odors were also reported to activate the middle of the ACC (Rolls et al., 2003) and the amygdala (Winston et al., 2005; Zald et al., 1997). These general neurogimaging findings coincide with several reports indicating that individuals with schizophrenia display deficits on psychophysical probes of the OFC (Lee et al., 2007; Shamay-Tsoory et al., 2007; Shurman, Horan, & Nuechterlein, 2005) as well as reduced OFC volume (Nakamura et al., 2008). The role of the OFC in processing pleasant but not unpleasant odors, as well as neuroimaging and psychophysical studies suggesting abnormal OFC processing in schizophrenia, indicate that aberrant processing in the underlying OFC circuitry may result in the differential pattern of identification accuracy for pleasant and unpleasant odors observed. In addition, reduced left-nostril assessed identification accuracy for pleasant odors may be largely influenced by aberrant functioning in *left hemisphere* OFC circuitry in schizophrenia.

Why did patients display intact identification accuracy for unpleasant odors? An examination of previous studies on odor valence processing in schizophrenia is somewhat inconsistent. Based on the results of their chemosensory event-related potentials (ERP) analysis of pleasant and unpleasant odors, Pause, Hellmann, Goder, Aldenhoff, and Ferstl (2008) noted that individuals with schizophrenia display increased processing speed for unpleasant odors, and proposed that individuals with schizophrenia have an advantage for processing negative, and potentially threat-related, stimuli. These results appear to coincide with findings from a PET study reporting that individuals with schizophrenia displayed intact pleasantness ratings for unpleasant but not pleasant odors (Crespo-Facorro et al., 2001). The authors noted that, when exposed to unpleasant odors, schizophrenia patients failed to recruit key limbic regions, and instead recruited regions in the prefrontal cortex. In contrast, Strauss, Allen, Ross, Duke, and Schwartz (2009) examined birhinal identification accuracy of pleasant and unpleasant odors in

community controls and two samples of individuals with schizophrenia (deficit and non-deficit syndrome subtypes). In contrast to our current findings, they did not observe a differential pattern of identification accuracy for pleasant and unpleasant odors between deficit and non-deficit schizophrenia patients and controls. Instead, they reported a main effect of group and valence, with all patients performing worse than controls on the olfactory identification measure and all participants displaying higher identification accuracy for pleasant compared to unpleasant odors. The discrepancy between our results and that of Strauss et al.'s (2009) may be largely due to differences in sample size, sample characteristics, and length of olfactory identification test (40-item UPSIT vs. 12-item B-SIT). In addition, we assessed olfactory identification unirhinally compared to the birhinal method employed by Strauss et al. (2009). It is possible that testing each nostril in isolation made the task of identifying unpleasant nostrils easier for patients and even allowed for a greater degree of compensatory brain functions for identification of unpleasant odors. Research comparing unirhinal versus birhinal odor presentation is mixed. Some studies have reported that birhinal testing is easier than unirhinal tests, though this study was limited to testing of odor memory (Bromley et al., 1995). Other studies have indicated that birhinal assessment requires additional interaction of both hemispheres compared to unirhinal presentation (Cain, 1977), which may make it easier to identify odors when nostrils are testing in isolation (Doty, Bromley, Moberg, & Hummel, 1991; Turetsky, Moberg, Arnold, Doty, & Gur, 2003). Therefore, it is possible that patients may have some degree of compensation for negative (and potentially threat-related) odors due to compensatory brain networks which, combined with unirhinal identification and other sample characteristics, allows for patients to display identification accuracy of unpleasant odors comparable to controls.

Odor Intensity and Hedonic Ratings

Similar to prior research, we examined mean intensity and hedonic ratings of pleasant, neutral, and unpleasant odors in patients and controls. We hypothesized that patients would display similar intensity ratings to controls while showing significantly lower hedonic ratings for pleasant but not unpleasant odors. As hypothesized, differences in mean intensity ratings between patients and controls were not statistically different. With regard to hedonic ratings, we found a statistically significant valence-by-group-by-sex interaction. Further examination of the three-way interaction revealed a sex-by-valence interaction in controls but not in patients. A significant main effect of valence was observed with pleasant odors receiving higher hedonic ratings than neutral items, and neutral odors receiving higher hedonic ratings compared to unpleasant odors. No statistically significant main effect of group or interaction of group and sex was found for hedonic ratings.

The lack of statistically significant between-group differences on mean intensity ratings observed in the current study coincides with a number of prior schizophrenia studies (Crespo-Facorro et al., 2001; Hudry et al., 2002; Moberg et al., 2003). However, prior research on hedonic ratings has been more mixed. One of the first studies to thoroughly compare patient ratings on a wide variety of odor dimensions found that schizophrenia patients displayed significantly lower ratings on odor pleasantness, familiarity, and edibility compared to controls (Hudry et al., 2002). Moberg et al. (2003) found a significant group-by-sex interaction with male patients rating an odor as significantly less pleasant at lower concentrations and as significantly more pleasant at higher concentrations compared to female patients and male and female controls. In two separate but similarly designed studies, Rupp et al. (2005a) initially found no differences in hedonic ratings between male patients and controls, but later found that a different

sample of male patients displayed higher hedonic ratings than male controls (Rupp et al., 2005b). Similar to this latter finding, Doop and Park (2006) reported that schizophrenia patients displayed a restricted (high) range of hedonic ratings, while controls showed more variability in their ratings, resulting in higher mean hedonic ratings in the schizophrenia group. In the current study, we found that patients did not display the sexual dimorphism that we observed in controls. Female controls tended to rate unpleasant odors as significantly more unpleasant compared to male controls and displayed a larger difference between ratings of odor valence types. Conversely, female patients were comparable to male patients in ratings for each odor valence type and in mean differences in hedonic ratings between each odor valence.

As we found no main effect of group and no group by sex interaction on hedonic ratings, our results stand in contrast to studies reporting differences in odor hedonic ratings primarily in male patients with schizophrenia (Crespo-Facorro et al., 2001; Moberg et al., 2003; Rupp et al., 2005b). This discrepancy may be due to differences in patient characteristics (e.g., illness onset and duration of illness), sample sizes, and methods of assessments employed. For example, Strauss et al. (2009) found that only patients with the deficit subtype displayed lower subjective hedonic ratings for pleasant items in comparison to non-deficit patients and healthy controls. This suggests a need to consider patient symptom characteristics when examining hedonic ratings. Although the current study did not differentiate between deficit and non-deficit patients, no suggestion of an association between level of negative symptoms (from PANSS interview) and hedonic ratings for *pleasant* odors was observed. Instead, we found a linear relationship between a higher level of negative symptoms and lower mean hedonic ratings for *unpleasant* odors (r = -.33). This correlation did not reach statistical significance in our small sample (p = .11); however, the correlation represented a medium effect size that is likely meaningful. As a

result, more research is needed to elucidate the interaction of sex, symptom ratings, and valence on hedonic ratings.

Relationships Between Olfaction and Empathy Scores

Contrary to our expectation and to a study by Spinella (2002), we failed to find a relationship between self-reported empathy scores and left- and right-nostril olfactory identification performance across the entire sample. Instead, we found a statistically significant positive relationship between left-nostril assessed hedonic ratings for pleasant odors and global and affective empathy scores (r^2 = .18 and .19, respectively). We also found less robust correlations between right-nostril assessed hedonic ratings for pleasant odors and global and affective empathy scores (r^2 = .11 and .12, respectively). These results appear to coincide with several studies reporting a greater left hemisphere participation in the emotional processing of olfactory stimuli (Royet & Plailly, 2004) with participation of the right OFC also reported to a lesser degree (Zatorre et al., 1992). In fact, we noted previously that an earlier study showed that subjective hedonic but not intensity ratings were significantly correlated with level of activity in the medial OFC, particularly for pleasant odors (Rolls et al., 2003). Therefore, our results of a strong positive relationship between empathy scores and left-nostril identification accuracy for pleasant (but not unpleasant or neutral) odors coincide directly with these prior findings.

There are several explanations for why we did not replicate Spinella's (2002) results within our control group. First, Spinella (2002) used a very small convenience sample of undergraduate students that was predominantly female. In contrast, our sample consisted of demographically-matched community controls with a higher number of males. We also employed a different measure of empathy. Interestingly, while Spinella (2002) reported a strong

relationship between right-nostril assessed identification and affective empathy in a non-clinical sample, we found a positive trend between left-nostril identification and affective empathy scores in patients (r^2 = .17, large effect size).

With regard to the relationship between olfactory performance indices and positive and negative symptoms, previous studies have consistently reported a negative relationship between odor identification ability and negative symptoms (Brewer, Edwards, Anderson, Robinson, & Pantelis, 1996b; Brewer et al., 2001; Goudsmit et al., 2003). We found no statistically significant relationships between negative symptoms of schizophrenia and olfactory identification performance. Instead, we found that individuals with a higher degree of negative symptoms (e.g., flat affect and anhedonia) displayed reduced right-nostril accuracy for pleasant odors (r^2 = .18, large effect size). This finding coincides with results from Strauss et al. (2009) who reported that deficit patients displayed reduced hedonic ratings for pleasant but not unpleasant odors in comparison to the non-deficit patients and healthy controls.

Limitations

Several limitations were apparent in the current research. The central measure of empathy employed in the current study is a relatively understudied measure in the schizophrenia literature. This made it difficult to compare our findings to other schizophrenia studies investigating self-reported empathy. The benefit of employing such a measure was our belief that it best captured the current conceptualization of empathy. The current study did not have clinicians or caregivers rate their perceptions of empathy. Previous findings have suggested that schizophrenia patients tend to underreport empathy or may have a lack of insight into the full nature of their empathy deficits (Bora et al., 2008). As such, caregiver ratings have been used to compare ratings

between family members and self-report. Caregiver ratings would have been a useful comparison to patient's ratings, in order to examine differences in insight between patients and caregivers. Furthermore, the current study lacked other measures of empathy, including photorealistic images or cognitive paradigms, which may have had better construct validity than the self-report measure employed.

Another limitation of our study was that all individuals with schizophrenia were taking antipsychotic medications during study participation. It is unclear what influence long-term antipsychotic use has on self-reported empathy and olfactory perception. Prior studies have indicated that odor identification deficits are independent of medication status (Moberg et al., 1999) and have noted that medicated schizophrenia patients perform worse on olfactory measures even when compared to other psychiatric populations on neuroleptics (Hurwitz, Kopala, Clark, & Jones, 1988). In addition, olfactory identification deficits have been observed in neuroleptic-naïve patients with schizophrenia (Brewer et al., 2001; Kopala, Clark, & Hurwitz, 1992; Sirota et al., 1999) and in "ultra-high risk" individuals who later developed the illness (Brewer et al., 2003). Nevertheless, little is known about the influence of neuroleptic use on hedonic and intensity ratings as well as identification accuracy across particular odor valence subtypes. Future studies examining the current findings in neuroleptic-naïve schizophrenia patients with first episode psychosis would greatly improve our understanding of empathic and olfactory functioning without the influence of prolonged medication use.

The current study was also limited by the odors used for assessment. Odors are typically described across a variety of dimensions including pleasantness, edibility, familiarity, and intensity. Using discrepant odors that potentially vary greatly on a number of these dimensions may have influenced hedonic and intensity ratings in our sample. Therefore, analyzing these

variables in future studies would be an important step in furthering our understanding of odor hedonic processing in schizophrenia. In addition, batteries that involve equal numbers of pleasant, neutral, and unpleasant odors at high and low intensities would greatly increase our understanding of how intensity, valence, and the interaction of intensity and valence influence odor processing and odor ratings.

Finally, the current study would be improved with a larger sample size, particularly for the number of females in our sample. Using a much larger sample with a balanced number of males and females would allow us to better generalize the current findings. It would also allow us to examine relationships between variables of interest separately in male and female patients.

Future Directions

The results of our study clearly warrant a follow-up study that refines the methodology employed, addresses the limitations of the current research, and expands upon the current findings. One interesting way to build upon the current findings would be to examine performance on a photorealistic task of empathy in first-episode schizophrenia patients and controls while examining blood-oxygen-level-dependent (BOLD) effects during fMRI. For example, Dziobek et al. (2008) developed a photorealistic measure of empathy called the "Multifaceted Empathy Test." The task is divided into cognitive and affective components where participants are asked to judge pictures of individuals in different situations. Individuals are asked to rate how they think the individual is feeling based on four alternative choices (cognitive empathy). Individuals also rate the arousal, intensity, and their subjective experiences of each photo (affective empathy). For the follow-up study, BOLD effects would be measured in a counterbalanced order during the observation and rating of pleasant, neutral, and unpleasant

photorealistic stimuli in patients and controls. The relationship between areas of significant brain activation and the individual's subjective ratings of the stimuli and cognitive empathy accuracy scores could also be examined. Participants and their caregivers/family members could also fill out self-report measures of empathy in order to compare the individual's performance on the photorealistic empathy measure to their own self-report and to that of their caregivers and family members.

To understand further the relationship between empathy and olfactory processing, the BOLD effects could also be measured as participants were delivered high and low intensity pleasant, neutral, and unpleasant odors via unilateral stimulation using an olfactometer. In addition, participants would be asked to rate the hedonic characteristics, familiarity, intensity, and edibility of each odor while inside the scanner in order to compare group differences as done in the current study.

Brain activations could subsequently be compared to see areas of overlap during olfactory stimulation and empathic responding. This study would allow for a more direct assessment of whether common neuroanatomical substrates subserve empathy and olfactory processing, and whether this relationship is influenced by the neuropathology of schizophrenia, hemispheric lateralization, stimuli intensity and valence, as well as participant's sex.

The advantages of this follow-up study would include better control of odor dimensions such as intensity and valence, the use of a photorealistic measure of empathy and caregiver ratings, the use of neuroleptic-naïve patients, and the use of neuroimaging techniques to understand further the brain-behavior relationships that subserve empathy and olfactory processing.

Conclusions

The preliminary findings from this study add to the growing body of literature suggesting that individuals with schizophrenia display significant differences from controls on measures of self-reported empathy. Previous schizophrenia studies have typically neglected to examine the influence of sex on empathic responding, especially with regard to empathy subtypes. Our results suggest that sex is an important variable of consideration especially with respect to self-reported global and affective empathy scores. We found that male patients reported higher levels of affective empathy and female patients reported lower levels of global empathy, in comparison to sex-matched controls. In contrast, self-reported cognitive empathy was not influenced by sex, but was significantly lower in patients.

With regard to olfactory identification and judgments, our results indicate that individuals with schizophrenia have a specific deficit for identifying pleasant odors, with intact identification accuracy for neutral and unpleasant odors. Previous research on odor identification typically combines all odor valences into one analysis. These results indicate that separately examining identification accuracy for pleasant, neutral, and unpleasant odors may be informative for future studies.

With regard to odor ratings, we replicated prior research suggested no significant group differences in intensity ratings. Our results propose an added complexity to differences in hedonic ratings in patients and controls. An observation of a diagnosis-by-sex interaction in odor processing is atypical in schizophrenia; however, as Moberg et al. (2003) pointed out, hedonic and intensity ratings of odors may more specifically measure the parts of the brain where emotion and olfactory processing converge. As such, sex differences in schizophrenia, including

differences in sex hormones, brain development, and socialization, may be central to understanding how male and female patients and controls differ on ratings of odor dimensions.

Central to the overall aim of the current study, we found a robust relationship between left- and right-nostril hedonic ratings for pleasant odors and global and affective empathy scores across all participants. In patients, we also found a meaningful linear relationship between affective empathy and left-nostril identification accuracy. Collectively, our findings provide further evidence for the role of olfactory-limbic brain regions in the hedonic processing of odors and suggest that disruptions in hedonic processing seen in schizophrenia may be related to abnormalities in the anatomical and physiological substrates that also subserve empathy and emotional processing.

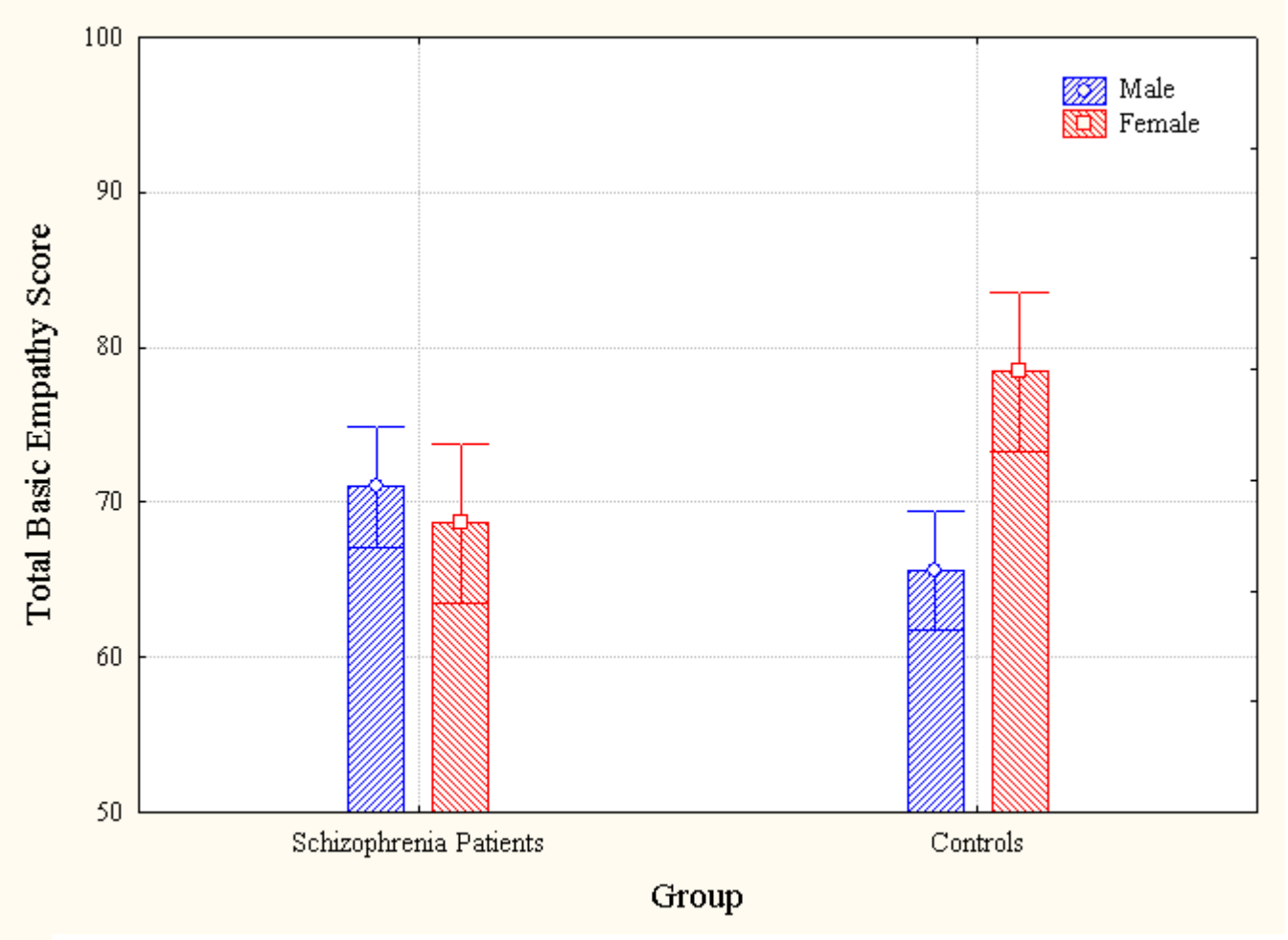

Figure 1: Means and SEs of Total Empathy Scores

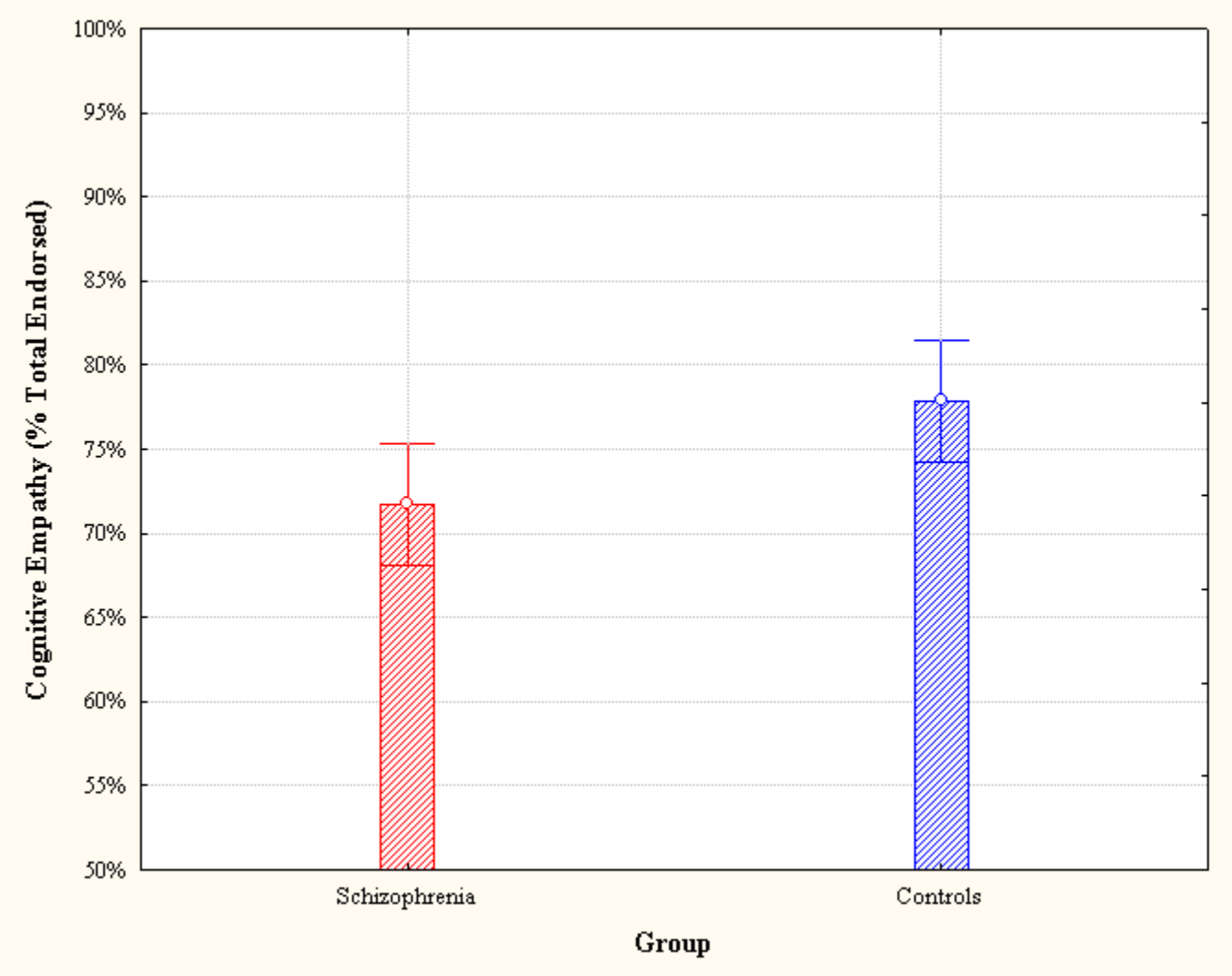

Figure 2: Mean and SEs of Cognitive Empathy Percent Scores

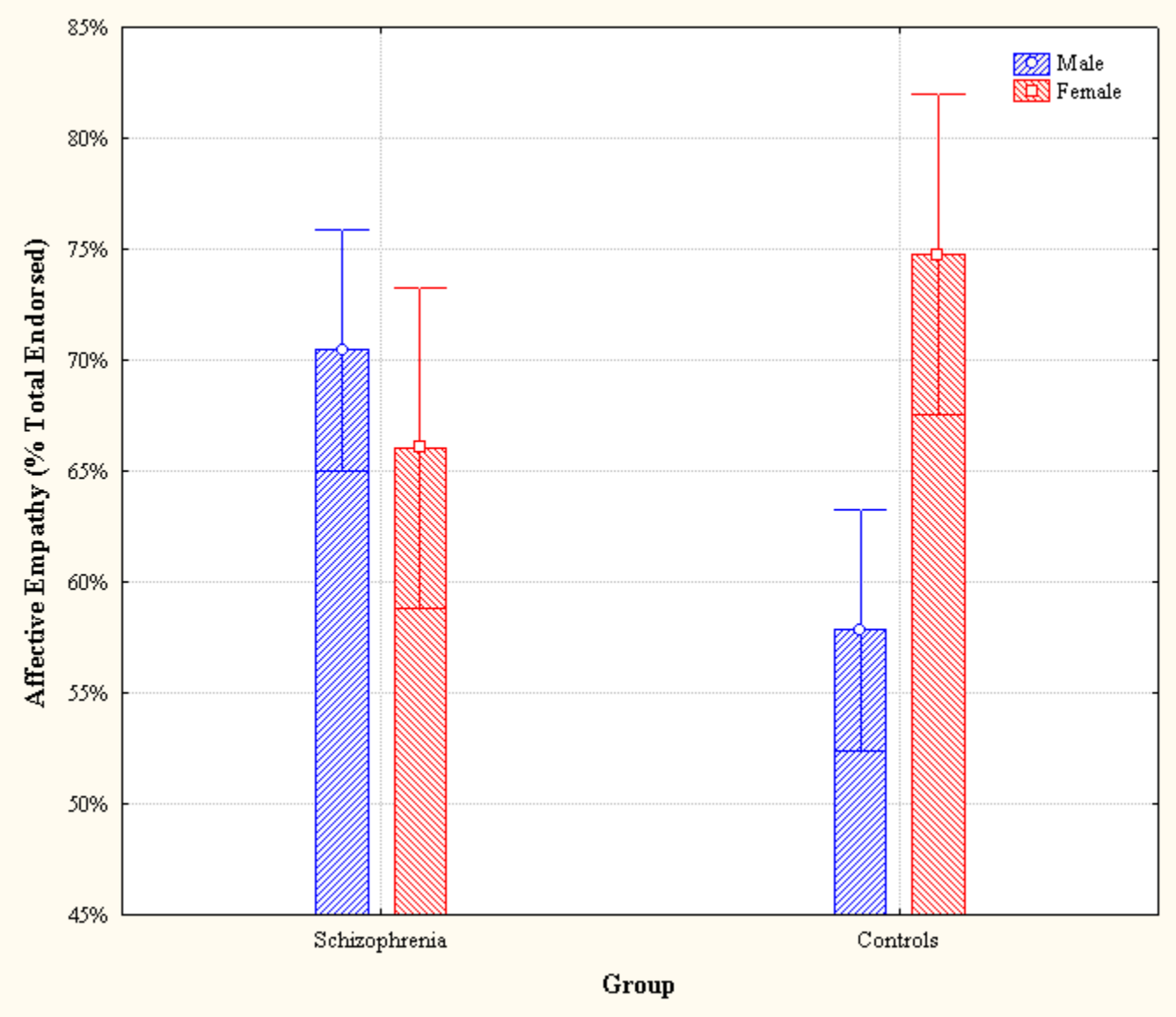

Figure 3: Means and SEs of Affective Empathy Percent Scores

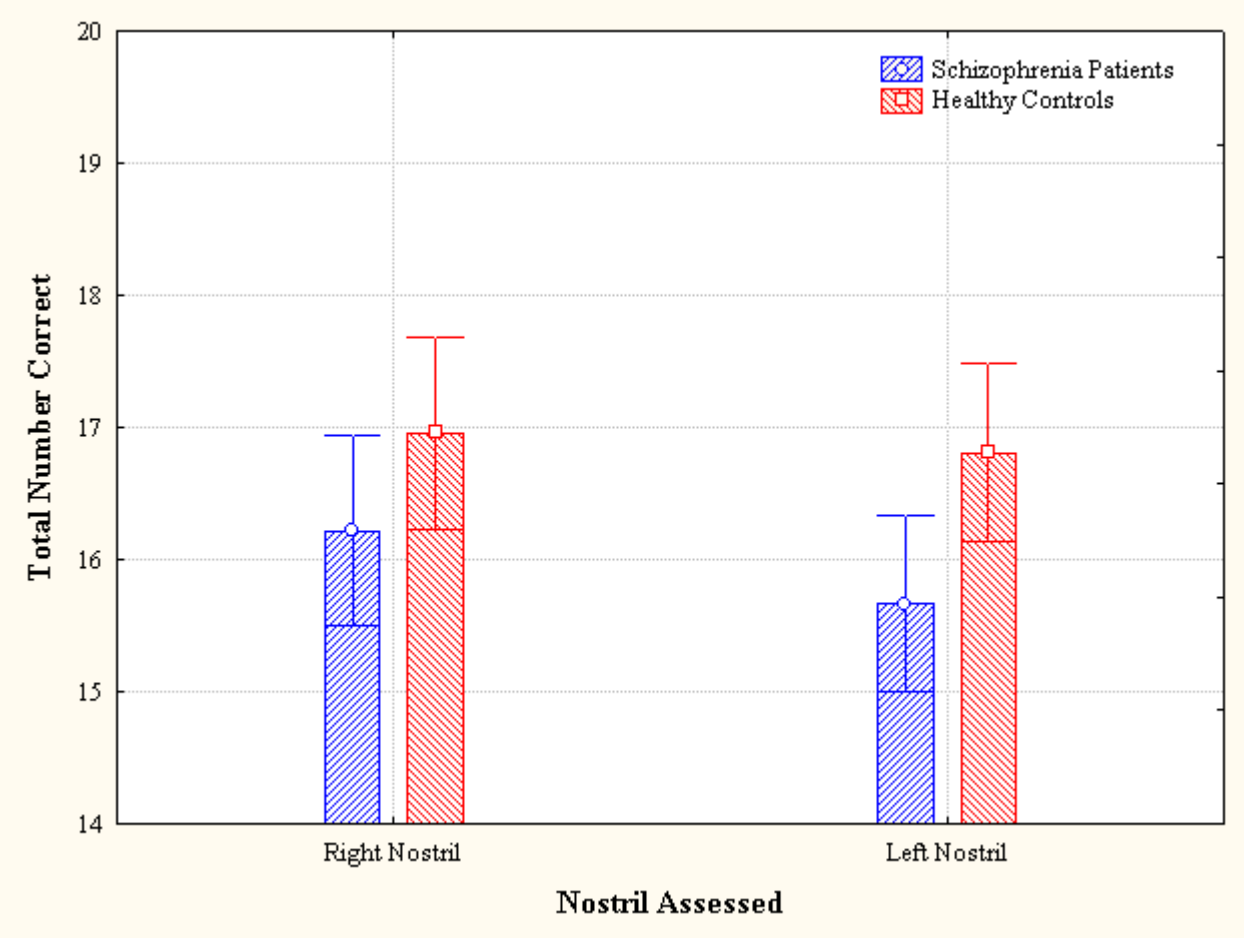

Figure 4: Means and SEs of Left and Right Nostril Odor Identification Scores

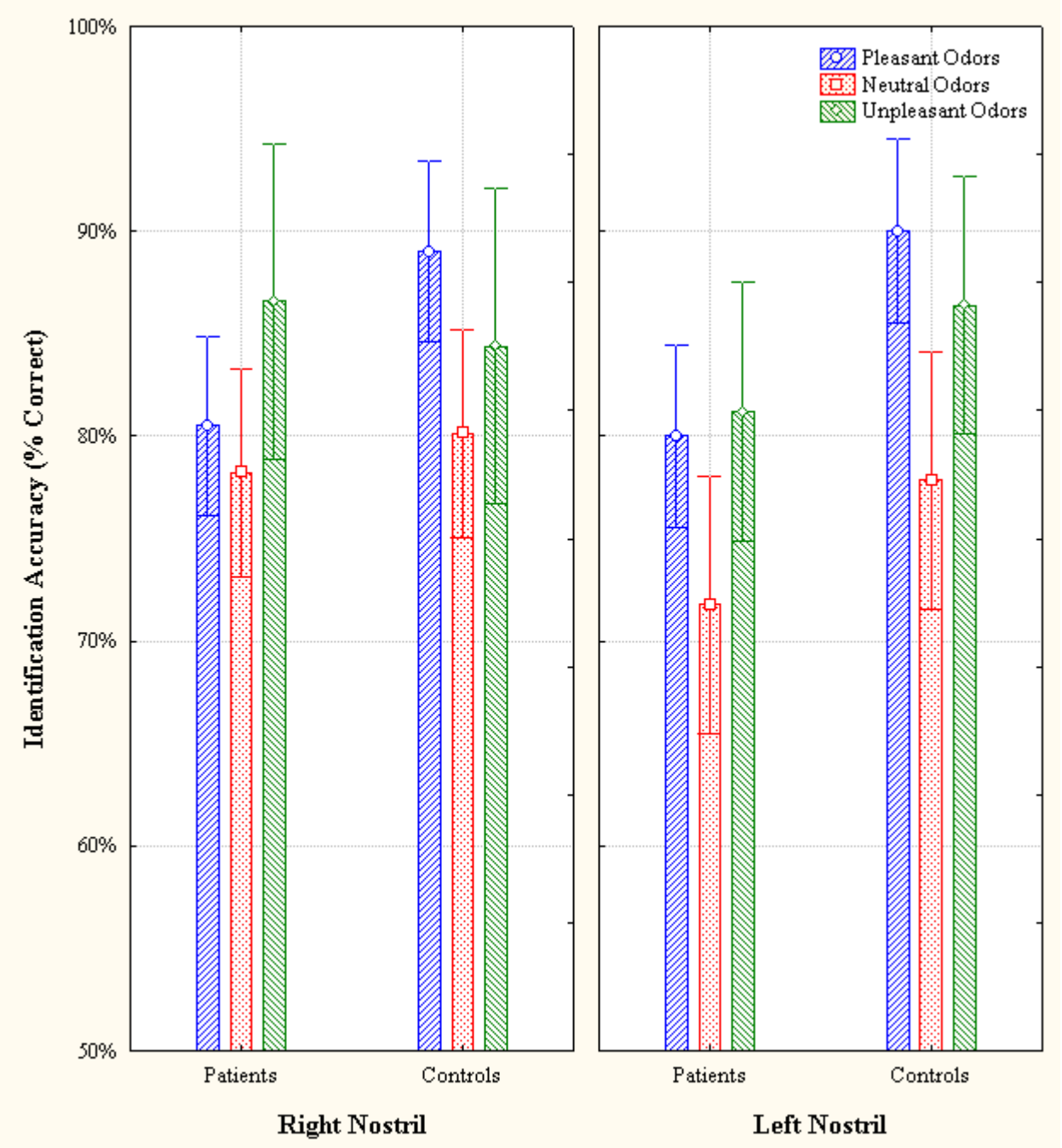

Figure 5: Mean Unirhinal Odor Identification Scores and SEs by Odor Valence Types

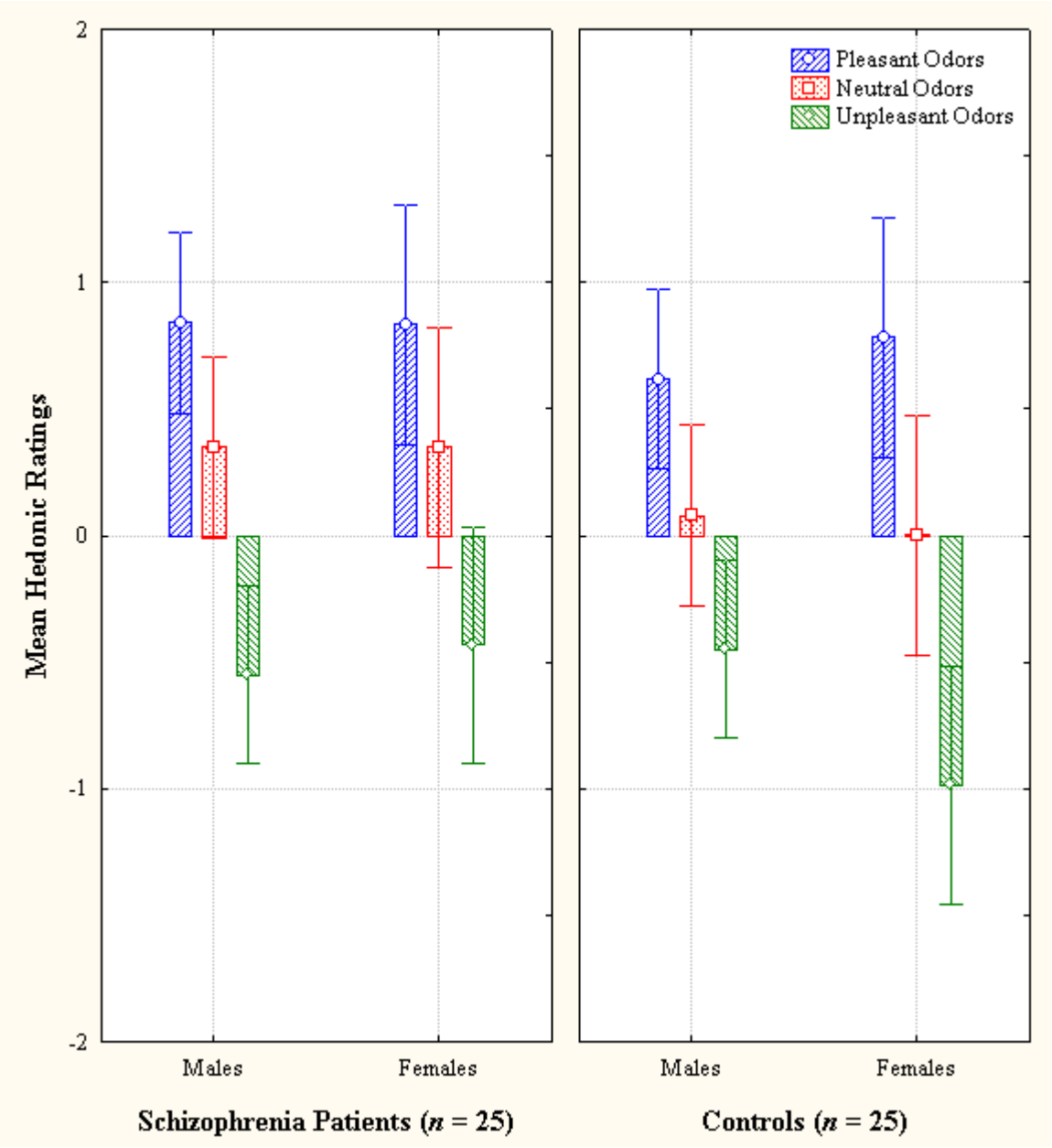

Figure 6: Mean Hedonic Ratings and SEs for Pleasant, Neutral, and Unpleasant Odors

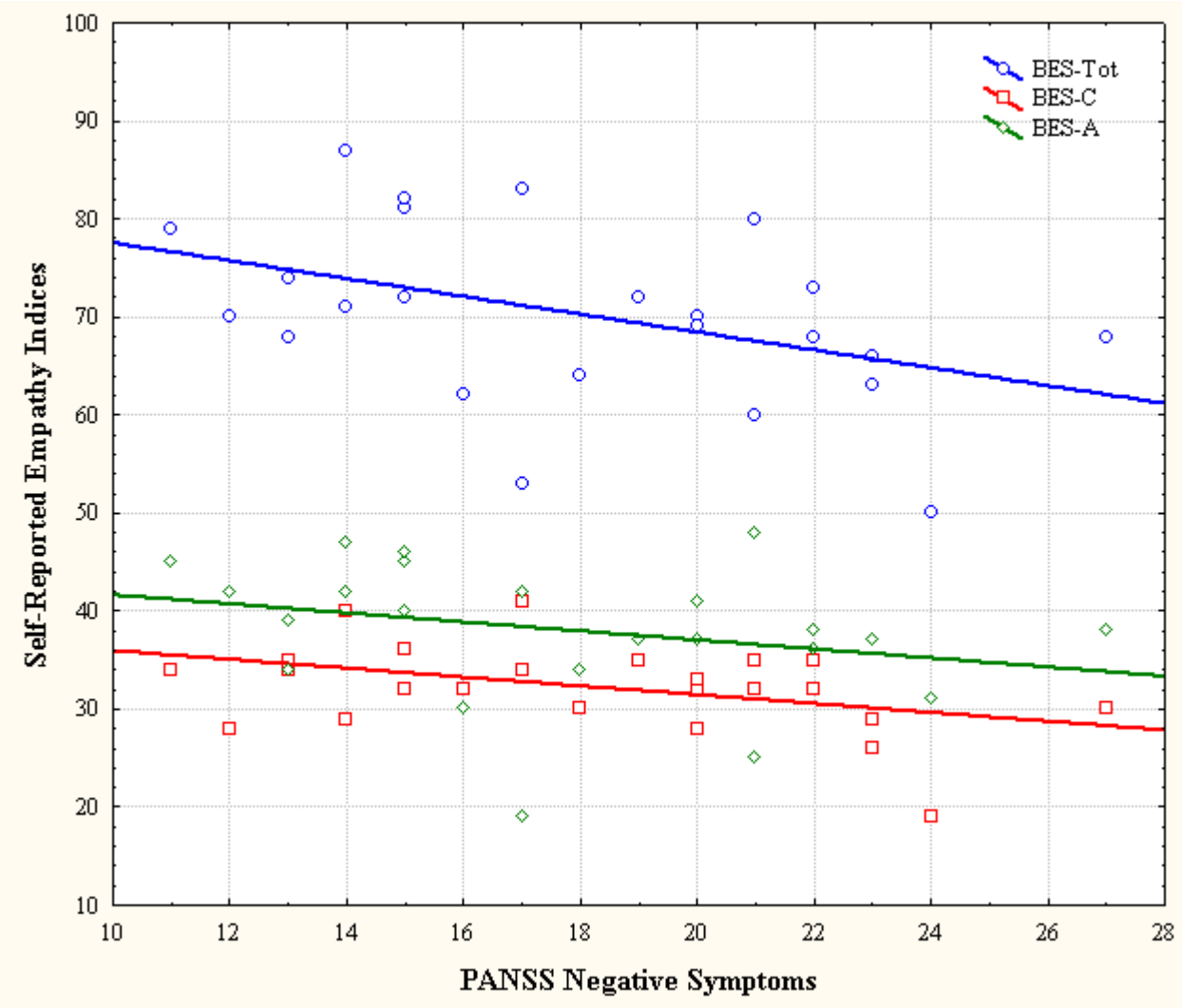

Figure 7: Distribution of Self-Reported Empathy Indices by Negative Symptoms Scores

Table 1 Demographic and Clinical Characteristics

	Patient Group (n = 25)			Control Group (n = 25)		
Characteristic	Mean	SD	% (N)	Mean	SD	% (N)
Age (years)	39.6	11.9		39.6	11.1	
Sex (Males)			64 (16)			64 (16)
Sex (Females)			36 (9)			36 (9)
Years of Education[a]	12.2	1.8		14.2	1.9	
Mother's Education (years)	12.8	3.5		13.3	3.0	
Father's Education (years)	12.1	4.7		12.4	3.3	
Smoking characteristics						
Smoking Status[b]						
Current Smoking			64 (16)			16 (4)
Past Smoking			16 (4)			32 (8)
Never Smoked			20 (5)			52 (13)
Pack-years[c]	19.3	31.6		1.2	4.0	
Illness Duration (years)	16.2	11.3		-	-	
Age of Onset (years)	24.2	11.0		-	-	
PANSS Total Score*	37.1	6.9		-	-	
PANSS Composite Score	2.3	6.8		-	-	
PANSS - Positive	20.4	5.2		-	-	
PANSS - Negative	18.1	4.2		-	-	

[a] Significant group difference ($p < .001$)
[b] Significant group difference ($p = .01$)
[c] Significant group difference ($p = .01$)
* PANSS = Positive and Negative Symptom Scale

Table 2 Scores of Total Empathy and Empathy Subtypes in Patients and Controls

	Schizophrenia (*n* = 25)				Controls (*n* = 25)			
	Males		Females		Males		Females	
BES Variables	Mean	SD	Mean	SD	Mean	SD	Mean	SD
BES-Tot	71.0	7.7	68.7	11.2	65.6	6.0	78.4	6.0
BES-A	38.8	6.4	36.3	7.4	31.8	5.3	41.1	4.2
BES-C	32.3	3.7	32.3	6.0	33.8	3.4	37.3	2.7
BES-A % Score	72.7	8.1	66.1	13.4	75.0	7.5	74.8	7.6
BES-C % Score	70.5	11.7	71.9	13.3	57.8	9.6	83.0	6.1

BES = Basic Empathy Scale, BES-Tot = BES-Total Score; BES-C = BES-Cognitive Empathy; BES-A = BES – Affective Empathy.

Table 3 Olfactory Identification and Odor Ratings

Variable	Schizophrenia (n = 25)				Controls (n = 25)			
	Left Nostril		Right Nostril		Left Nostril		Right Nostril	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Odor Identification Items[a]								
Pleasant % Correct	80.0	12.0	80.5	11.5	90.0	10.2	89.0	10.4
Neutral % Correct	71.8	18.8	78.2	12.5	77.9	11.5	80.1	12.8
Unpleasant % Correct	81.2	18.9	86.6	20.9	86.4	11.5	84.4	17.2
Total Raw Scores	15.4	1.8	16.2	1.7	17.0	1.6	17.0	1.3
Intensity Ratings (IR)[b]								
IR – Pleasant Odors	3.7	1.1	3.8	1.0	3.4	0.8	3.4	0.8
IR – Neutral Odors	3.6	0.8	3.5	0.9	3.3	0.8	3.0	0.7
IR – Unpleasant Odors	3.6	0.8	3.6	1.0	3.3	0.8	3.1	0.7
IR – Total	3.6	0.9	3.6	0.9	3.2	0.7	3.2	0.7
Valence Ratings (VR)[c]								
VR – Pleasant	3.9	0.8	3.8	0.8	3.7	0.6	3.7	0.6
VR – Neutral	3.3	0.8	3.4	0.9	3.1	0.7	3.0	0.7
VR – Unpleasant	2.5	0.9	2.5	0.8	2.3	0.7	2.4	0.8
VR – Total	3.7	0.7	3.4	0.8	3.2	0.5	3.2	0.6

[a] Scores are derived from the University of Pennsylvania Smell Identification Test.

[b] Scores represent mean ratings on a 5-point unipolar Self-Assessment Manikin Rating scale (1 = no intensity, 5 = extreme intensity).

[c] Scores represent mean ratings on a 5-point bipolar Self-Assessment Manikin Rating scale (1 = extremely unpleasant, 3 = neutral, 5 = extremely pleasant).

Table 4 Unirhinal Olfactory Identification Analyses

	SS	df	MS	F	p
Group	28.36	1	28.36	9.20	0.004
Sex	0.68	1	0.68	0.22	0.64
Group x Sex	0.28	1	0.28	0.09	0.77
Error	141.84	46	3.08		
Total	171.16	49			
	SS	**df**	**MS**	**F**	**p**
Nostril	2.75	1	2.75	1.25	0.27
Nostril x Group	3.58	1	3.58	1.63	0.21
Nostril x Sex	0.35	1	0.35	0.16	0.69
Nostril x Group x Sex	0.06	1	0.06	0.03	0.87
Error	100.87	46	2.19		
Total	107.61	50			

SS = Sum of Squares; df = degrees of freedom, MS = Mean Sum of Squares

Table 5 Unirhinal Olfactory Valence Identification Accuracy by Group and Sex

	Patients (n = 25)	Controls (n = 25)			
Identification Accuracy	Rank Sum	Rank Sum	Mann-Whitney U	Z	p
Right Nostril					
Pleasant % Correct	517.5	757.5	192.5	-2.46	0.02
Neutral % Correct	603.5	671.5	278.5	-0.67	0.51
Unpleasant % Correct	676.0	599.0	274.0	0.83	0.46
Left Nostril					
Pleasant % Correct	488.5	786.5	163.5	-3.08	0.003
Neutral % Correct	564.5	710.5	239.5	-1.44	0.16
Unpleasant % Correct	613.5	661.5	288.5	-0.49	0.64
	Males (n = 32)	Females (n = 18)			
Identification Accuracy	Rank Sum	Rank Sum	Mann-Whitney U	Z	p
Right Nostril					
Pleasant % Correct	829.0	446.0	275.0	0.28	0.80
Neutral % Correct	754.0	521.0	226.0	-1.27	0.22
Unpleasant % Correct	858.5	416.5	245.5	0.95	0.39
Left Nostril					
Pleasant % Correct	722.5	552.5	194.5	-2.01	0.06
Neutral % Correct	893.5	381.5	210.5	1.59	0.12
Unpleasant % Correct	762.5	512.5	234.5	-1.14	0.28

Table 6 Unirhinal Olfactory Hedonic Ratings by Odor Valence

	SS	df	MS	F	p	H-F ε
Group	3.43	1	3.43	1.47	0.23	-
Sex	0.21	1	0.21	0.09	0.76	-
Group x Sex	0.60	1	0.60	0.26	0.62	-
Error	107.652	46	2.34			
Total	111.89	49				
	SS	**df**	**MS**	**F**	**p**	**H-F ε**
Nostril	0.04	1	0.04	0.11	0.74	-
Nostril x Group	0.01	1	0.01	0.02	0.89	-
Nostril x Sex	0.15	1	0.15	0.40	0.53	-
Nostril x Group x Sex	0.37	1	0.37	0.95	0.33	-
Error	17.69	46	0.38			
Total	18.26	50				
	SS	**df**	**MS**	**F**	**p**	**H-F ε**
Valence	87.73	1.7*	43.86	138.43	< 0.001*	0.85
Valence x Group	0.34	1.7*	0.17	0.54	0.56*	0.85
Valence x Sex	0.98	1.7*	0.49	1.55	0.22*	0.85
Valence x Group x Sex	2.087	1.7*	1.04	3.29	0.05*	0.85
Error	29.15	78.5*	0.32			
Total	120.89	82.5*				
	SS	**df**	**MS**	**F**	**p**	**H-F ε**
Nostril x Valence	0.33	2*	0.16	1.19	0.31*	1.00
Nostril x Valence x Group	0.48	2*	0.24	1.73	0.18*	1.00
Nostril x Valence x Sex	1.18	2*	0.59	4.28	0.08*	1.00
Nostril x Valence x Group x Sex	0.40	2*	0.20	1.46	0.24*	1.00
Error	12.64	92*	0.14			
Total	15.03	100*				

*Assumption of sphericity was violated for valence according to the Mauchly's test, $\chi^2(2) = 15.11$, $p < .001$. Therefore, degrees of freedom and p-values were adjusted using Huynh-Feldt (H-F) estimates of sphericity as all ε values were greater than 0.75; SS = Sum of Squares; df = degrees of freedom, MS = Mean Sum of Squares

Table 7 Unirhinal Olfactory Intensity Ratings by Odor Valence

	SS	df	MS	F	p	H-F ε
Group	12.60	1	12.60	3.72	0.06	-
Sex	1.16	1	1.16	0.34	0.56	-
Group x Sex	0.68	1	0.69	0.20	0.66	-
Error	155.89	46	3.39			
Total	170.33	49				
	SS	**df**	**MS**	**F**	**p**	**H-F ε**
Nostril	0.04	1	0.04	0.35	0.56	-
Nostril x Group	0.01	1	0.01	0.04	0.84	-
Nostril x Sex	0.11	1	0.11	0.93	0.34	-
Nostril x Group x Sex	0.002	1	0.002	0.01	0.91	-
Error	5.57	46	0.12			
Total	5.73	50				
	SS	**df**	**MS**	**F**	**p**	**H-F ε**
Valence	4.69	1.9*	2.34	8.83	>0.001*	0.93
Valence x Group	1.05	1.9*	0.52	1.97	0.15*	0.93
Valence x Sex	0.12	1.9*	0.06	0.23	0.80*	0.93
Valence x Group x Sex	0.71	1.9*	0.36	1.34	0.27*	0.93
Error	24.42	85.1*	0.27			
Total	30.99	92.7*				
	SS	**df**	**MS**	**F**	**p**	**H-F ε**
Nostril x Valence	0.001	2*	0.001	0.02	0.98*	1.00
Nostril x Valence x Group	0.02	2*	0.01	0.29	0.75*	1.00
Nostril x Valence x Sex	0.13	2*	0.07	2.00	0.14*	1.00
Nostril x Valence x Group x Sex	0.01	2*	0.01	0.19	0.83*	1.00
Error	3.03	92*	0.03			
Total	3.19	100*				

*Assumption of sphericity was violated for valence according to Mauchly's test, $\chi^2(2) = 9.50$, $p < .01$. Therefore, degrees of freedom and p-values were adjusted using Huynh-Feldt (H-F) estimates of sphericity as all ε values were greater than 0.75.

Table 8 Correlations of Empathy and Odor Identification Performance Indices

	Total Raw Scores		Right Nostril			Left Nostril		
	UPSIT-R	UPSIT-L	%P	%N	%U	%P	%N	%U
BES-T	.10	-.06	.03	.17	-.03	-.07	-.09	.08
BES-C	.01	.24	.14	-.05	-.13	.18	.11	.18
BES-A	.12	-.24	-.05	.18	.05	-.20	-.18	-.01

Values are Pearson correlations across entire sample of schizophrenia patients (n = 25) and health controls (n = 25); significance is two-tailed; No statistically significant relationships; BES = Basic Empathy Scale, BES-T = BES – Total Score; BES-C = BES – Cognitive Empathy; BES-A = BES – Affective Empathy; UPSIT = University of Pennsylvania Smell Identification Test, UPSIT-R = UPSIT – Right Nostril Total; UPSIT-R = UPSIT – Left Nostril Total; %P = Percent Correct for Pleasant Odors, %N = Percent Correct for Neutral Odors, %U = Percent Correct for Unpleasant Odors.

Table 9 Correlations of Empathy Indices and Odor Ratings

	Hedonic Ratings						Intensity Ratings					
	Right Nostril			Left Nostril			Right Nostril			Left Nostril		
BES Indices	P	N	U	P	N	U	P	N	U	P	N	U
BES-T	.33*	.23	.08	.42*	.10	-.23	.10	.07	.08	.19	.11	.20
BES-C	.11	.07	.03	.16	.09	-.16	.02	-.04	.02	.12	.13	.04
BES-A	.35*	.25	.09	.44*	.08	-.19	.11	.12	.08	.18	.05	.23

Values are Pearson correlations across sample of schizophrenia patients (n = 25) and health controls (n = 25); significance is two-tailed; *p < .05, **p < .003 (Bonferroni-corrected alpha for 18 comparisons between ratings and empathy scores conducted separately for hedonic and intensity ratings); BES = Basic Empathy Scale, BES-T = BES – Total Score; BES-C = BES – Cognitive Empathy; BES-A = BES – Affective Empathy; P = Pleasant Odors, N = Neutral Odors, U = Unpleasant Odors

Table 10 Correlations of Odor Identification Accuracy and Odor Ratings

			Total Raw Scores		Right Nostril			Left Nostril		
			UPSIT-R	UPSIT-L	%P	%N	%U	%P	%N	%U
Hedonic Ratings	Right Nostril	P	.11	-.08	.15	.01	.04	-.19	-.02	.22
		N	.07	-.02	.06	.09	.02	-.24	.04	.21
		U	.15	-.06	.20	.11	-.08	-.21	.13	-.05
	Left Nostril	P	-.16	-.02	-.11	-.14	-.02	-.12	-.14	.33*
		N	-.07	.05	.06	-.15	.04	-.10	-.02	.23
		U	-.01	-.02	.17	-.10	-.11	-.12	.05	-.02
Intensity Ratings	Right Nostril	P	.16	.10	.07	.02	.24	-.01	-.05	.32*
		N	.10	.01	-.04	.09	.13	-.10	-.01	.19
		U	-.03	.18	-.11	-.12	.22	.09	-.01	.30*
	Left Nostril	P	.06	.25	.13	-.07	.06	.13	.16	.21
		N	-.03	.21	.01	-.03	-.03	-.03	.16	.32*
		U	-.17	.12	-.12	-.22	.06	.03	-.07	.37**

Values are Pearson correlations across entire sample of schizophrenia patients (n = 25) and health controls (n = 25); significance is two-tailed; * Statistically significant $p < .05$, ** Statistically significant $p < .01$; ***$p < .001$ (Bonferroni-corrected alpha for 48 comparisons between ratings and olfactory identification scores conducted separately for hedonic and intensity ratings), UPSIT = University of Pennsylvania Smell Identification Test, UPSIT-R = UPSIT – Right Nostril Total; UPSIT-R = UPSIT – Left Nostril Total; %P = Percent Correct for Pleasant Odors, %N = Percent Correct for Neutral Odors, %U = Percent Correct for Unpleasant Odors; P = Pleasant Odors, N = Neutral Odors, U = Unpleasant Odors

Table 11 Correlations of Empathy and Schizophrenia Symptoms

	Basic Empathy Scale		
	Total	Affective	Cognitive
PANSS-T	> .001	.12	-.18
PANSS-P	.17	.12	.15
PANSS-N	-.43*	-.30	-.42*

Values are Pearson correlations; significance is two-tailed; * Statistically significant $p < .05$, ** Statistically significant $p < .01$; PANSS = Positive and Negative Symptom Scale, PANSS-T = PANSS Total Score, PANSS-P = PANSS Positive Symptoms, PANSS-N = PANSS Negative Symptoms; UPSIT = University of Pennsylvania Smell Identification Test, UPSIT-R = UPSIT – Right Nostril Total; UPSIT-R = UPSIT – Left Nostril Total.

Table 12 Correlations of Olfactory Performance Indices and Schizophrenia Symptoms

	Odor Identification		Right Nostril			Left Nostril		
	UPSIT-R	UPSIT-L	%P	%N	%U	%P	%N	%U
PANSS-T	.35	-.16	.40*	.32	-.14	.21	-.25	-.18
PANSS-P	.54**	.05	.41*	.27	.21	.05	-.05	.11
PANSS-N	-.28	-.30	-.42*	-.07	.03	-.12	-.30	-.05

Values are Pearson correlations across sample of schizophrenia patients (n = 25); significance is two-tailed; * Statistically significant $p < .05$, ** Statistically significant $p < .01$; PANSS = Positive and Negative Symptom Scale, PANSS-T = PANSS Total Score, PANSS-P = PANSS Positive Symptoms, PANSS-N = PANSS Negative Symptoms; UPSIT = University of Pennsylvania Smell Identification Test, UPSIT-R = UPSIT – Right Nostril Total; UPSIT-R = UPSIT – Left Nostril Total.

Table 13 Correlations of Olfactory Ratings and Schizophrenia Symptoms

			PANSS-T	PANSS-N	PANSS-P
Hedonic Ratings	Right Nostril	P	-.08	-.12	.07
		N	-.22	-.04	-.04
		U	-.09	-.33	-.09
	Left Nostril	P	.03	-.003	.13
		N	-.13	.08	.06
		U	.06	.02	.13
Intensity Ratings	Right Nostril	P	.23	.02	.28
		N	.24	.01	.33
		U	.26	.07	.37
	Left Nostril	P	.41*	-.29	.17
		N	.27	-.20	.31
		U	.15	-.10	.20

Values are Pearson correlations across sample of schizophrenia patients (n = 25); significance is two-tailed; *Statistically significant $p < .05$, **$p < .003$ (Bonferroni-corrected alpha for 18 comparisons between schizophrenia symptoms and ratings, conducted separately for hedonic and intensity ratings), PANSS = Positive and Negative Symptom Scale, PANSS-T = PANSS Total Score, PANSS-P = PANSS Positive Symptoms, PANSS-N = PANSS Negative Symptoms; P = Pleasant Odors, N = Neutral Odors, U = Unpleasant Odors

APPENDIX: IRB APPROVAL LETTER

University of Central Florida Institutional Review Board
Office of Research & Commercialization
12201 Research Parkway, Suite 501
Orlando, Florida 32826-3246
Telephone: 407-823-2901, 407-882-2901 or 407-882-2276
www.research.ucf.edu/compliance/irb.html

Notice of Expedited Initial Review and Approval

From **:** **UCF Institutional Review Board**
FWA00000351, Exp. 5/07/10, IRB00001138

To : **Jeffrey S. Bedwell** and **Kiminobu Sugaya**

Date : **February 14, 2008**

IRB Number: **SBE-08-05420**

Study Title: **Neurocognitive Functioning in Schizophrenia**

Dear Researcher:

Your research protocol noted above was approved by **expedited** review by the UCF IRB Chair on 2/14/2008. **The expiration date is 2/13/2009.** Your study was determined to be minimal risk for human subjects and expeditable per federal regulations, 45 CFR 46.110. The categories for which this study qualifies as expeditable research are as follows:

2. Collection of blood samples by finger stick, heel stick, ear stick, or venipuncture as follows: ***(a)*** Subjects are ***healthy, nonpregnant adults*** who weigh at least 110 pounds; amounts drawn may not exceed 550 ml over 8 weeks; and collection may not occur more frequently than 2 times per week. ***or (b)*** Subjects are ***other adults and children***, considering the age, weight, and health of the subjects the collection procedure; the amount of blood to be collected; and the frequency with which it will be collected. For these subjects, the amount collected may not exceed the lesser of 50 ml or 3 ml per kg over 8 weeks, and collection may not occur more frequently than 2 times per week.

7. Research on individual or group characteristics or behavior (including, but not limited to, research on perception, cognition, motivation, identity, language, communication, cultural beliefs or practices, and social behavior) or research employing survey, interview, oral history, focus group, program evaluation, human factors evaluation, or quality assurance methodologies.

The IRB has approved a **consent procedure which requires participants to sign consent forms.** Use of the approved, stamped consent document(s) is required. Only approved investigators (or other approved key study personnel) may solicit consent for research participation. Subjects or their representatives must receive a copy of the consent form(s).

All data, which may include signed consent form documents, must be retained in a locked file cabinet for a minimum of three years (six if HIPAA applies) past the completion of this research. Any links to the identification of participants should be maintained on a password-protected computer if electronic information is used. Additional requirements may be imposed by your funding agency, your department, or other entities. Access to data is limited to authorized individuals listed as key study personnel.

To continue this research beyond the expiration date, a Continuing Review Form must be submitted 2 – 4 weeks prior to the expiration date. Advise the IRB if you receive a subpoena for the release of this information, or if a breach of confidentiality occurs. Also report any unanticipated problems or serious adverse events (within 5 working days). Do not make changes to the protocol methodology or consent form before obtaining IRB approval. Changes can be submitted for IRB review using the Addendum/Modification Request Form. An Addendum/Modification Request Form **cannot** be used to extend the approval period of a study. All forms may be completed and submitted online at http://iris.research.ucf.edu .

Failure to provide a continuing review report could lead to study suspension, a loss of funding and/or publication possibilities, or reporting of noncompliance to sponsors or funding agencies. The IRB maintains the authority under 45 CFR 46.110(e) to observe or have a third party observe the consent process and the research.

On behalf of Tracy Dietz, Ph.D., UCF IRB Chair, this letter is signed by:

Signature applied by Joanne Muratori on 02/14/2008 04:59:45 PM EST

IRB Coordinator

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