ABSTRACT

Title of Dissertation:	FUNCTIONAL NEUROIMAGING OF THE SOCIAL REGULATION OF EMOTION IN SCHIZOPHRENIA
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Negative symptoms in schizophrenia are characterized by deficits in normative experiences and expression of emotion. Social anhedonia (diminished pleasure from social experiences) is one negative symptom that may impact patients' motivation to engage in meaningful social relationships. Past research has begun to examine the mechanisms that underlie social anhedonia, but it is unclear how this lack of social interest may impact the typically positive effects of social buffering and social baseline theory whereby social support attenuates stress. The present pilot study examines how social affiliation through hand holding is related to subjective and neural threat processing, negative symptoms, and social functioning.

Twenty-one participants (14 controls; 7 schizophrenia) developed social affiliation with a member of the research staff who served as the supportive partner during the threat task. Participants displayed greater subjective benefit to holding the hand of their partner during times of stress relative to being alone or with an anonymous experimenter, as indicated by self-reported increased positive valence and decreased

arousal ratings. When examining the effects of group, hand holding, and their interaction on the neurological experience of threat during the fMRI task, the results were not significant. However, exploratory analyses identified preliminary data suggesting that controls experienced small relative increases in BOLD signal to threat when alone compared to being with the anonymous experimenter or their partner, whereas the schizophrenia group results indicated subtle relative decreases in BOLD signal to threat when alone compared to either of the hand holding conditions. Additionally, within the schizophrenia group, more positive valence in the partner condition was associated with less severe negative symptoms, better social functioning, and more social affiliation, whereas less arousal was correlated with more social affiliation.

Our pilot study offers initial insights about the difficulties of building and using social affiliation and support through hand holding with individuals with schizophrenia during times of stress. Further research is necessary to clarify which types of support may be more or less beneficial to individuals with schizophrenia who may experience social anhedonia or paranoia with others that may challenge the otherwise positive effects of social buffering and maintaining a social baseline.

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by

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DEDICATION

I dedicate this dissertation to my family near and far who have supported me throughout the process and throughout my life, including Susan, Kevin, and Adam McCarthy. I also dedicate my dissertation to the most inspiring cohort of colleagues, Jennifer Dahne, Victoria Smith, Sarah Thomas, and Sharon Thomas who have been my Maryland family. Finally, this dissertation is for my husband, Chris Brown, who has provided love, patience, and encouragement throughout my doctoral journey.

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Chapter 1: Introduction

Negative symptoms in schizophrenia are characterized by deficits in social drive, as reflected in the negative symptoms of social anhedonia and asociality (Horan, Kring, Gur, Reise, & Blanchard, 2011). These negative symptoms persist over time, do not respond to available pharmacological treatments and are related to substantial functional impairment (Kirkpatrick, Fenton, Carpenter, & Marder, 2006; Buchanan et al., 2010; Blanchard, Kring, Horan, & Gur, 2011). In order to develop improved treatments for these social affiliative deficits it is necessary to better understand the underlying factors that may give rise to social anhedonia and asociality in schizophrenia. The present study sought to examine how patterns of brain activity that have been implicated in studies of the social regulation of emotion differ between individuals with schizophrenia and healthy controls and may be related to the negative symptoms of social anhedonia and asociality in schizophrenia.

Schizophrenia: A Public Health Concern

Schizophrenia is a severe, persistent mental illness involving disturbances in perception, cognition and interpersonal functioning (Liddle, 2000). The lifetime morbid risk for schizophrenia is estimated to be about 0.7% (Bhugra, 2005; McGrath, Saha, Chant, & Welham, 2008). Additionally, individuals with schizophrenia have been identified as suffering from higher natural and unnatural mortality rates (Brown, Barraclough, & Inskip, 2000; Saha, Chant, & McGrath, 2007), greater difficulties maintaining employment (Marwaha & Johnson, 2004; Mueser, K., Salyers, & Mueser, P., 2001), and being less likely to establish meaningful social relationships (Vaughn & Leff, 1976) compared to healthy controls. Thus, having a diagnosis of schizophrenia produces a substantial burden on the patient, their family, and society. Understanding the underlying nature of its psychopathology, as well as the relationship between symptoms and functional impairment is imperative to remediating the personal and societal costs of schizophrenia.

Treatments have been developed to address the psychopathology of schizophrenia, and they include pharmacological medications, cognitive remediation training, and psychosocial treatments (Penn & Mueser, 1996). Pharmacological prescriptions often include typical, atypical, and dopamine partial agonist antipsychotics (Miyamoto, Duncan, Marx, & Lieberman, 2005). Medication options are widely utilized by patients, but researchers have also developed cognitive remediation strategies to target cognitive deficits that are characteristic of people with schizophrenia (Pilling et al., 2002). Additionally, psychosocial treatments may involve supported employment, cognitive behavioral therapy, family-based services, token economy, and skills training (Dixon et al., 2010). Unfortunately, despite these available treatment strategies, about two-thirds of individuals diagnosed with schizophrenia continue to experience persistent or fluctuating symptoms over time, as described in the *Diagnostic and Statistical Manual of Mental Disorders* (4^{th} ed.; DSM-IV; American Psychiatric Association, 1994), and meta-analyses have highlighted the limited utility of cognitive remediation training and psychosocial interventions like social skills training (Pilling et al., 2002). Despite available treatment strategies for positive symptoms (delusions and hallucinations), negative symptoms remain an unmet treatment need (Kirkpatrick et al., 2006), and this calls for a better understanding of the social and emotional components associated with negative symptoms, which may impact the potential for psychiatric rehabilitation.

Overview of Negative Symptoms and Social Impairments in Schizophrenia

Negative symptoms are well documented in schizophrenia and are characterized by persistent deficits in motivation and pleasure (e.g., anhedonia, asociality and avolition), as well as deficits in expression (e.g., alogia and blunted affect) (Kirkpatrick et al., 2006). Recent reports on negative symptom assessments like the Clinical Assessment Interview for Negative Symptoms (CAINS; Kring, Gur, Blanchard, Horan, & Reise, 2013; Blanchard et al., 2011; Horan et al., 2011) advocate for distinguishing between the two primary domains of negative symptoms: 1) Motivation and Pleasure and 2) Expression deficits, as they appear to be statistically distinct but related constructs. Motivation and Pleasure negative symptoms capture motivation, interest, and engagement in social, vocational, and recreational areas of life (anhedonia, asociality, avolition), whereas Expression negative symptoms represent deficits in speech and expression of emotion (alogia and blunted affect) (Kring et al., 2013).

Negative symptoms have an established relationship with deficits in social and occupational functioning (Bellack, Morrison, Mueser, & Wade, 1989; Bellack, Morrison, Wixted, & Mueser, 1990). Specifically, negative symptoms have been associated with difficulty fulfilling social roles (e.g., spouse, parent) (Bellack et al., 2007) and developing close relationships (Ho, Nopoulos, Flaum, Arndt, & Andreasen, 1998). Furthermore, individuals without schizophrenia but with elevated negative symptoms, like social anhedonia, in community samples exhibit less friendly and more odd behaviors that elicit negative responses from observers who report feeling less interested in interacting with those individuals in the future (Baker, 2012).

Social impairment more generally is also an important feature of individuals at risk for and experiencing the symptoms of schizophrenia. In longitudinal studies of people at risk for schizophrenia, the most common presenting symptoms included social isolation and/or withdrawal (Lencz, Smith, Auther, Correll, & Cornblatt, 2004), and social withdrawal has also been identified as a characteristic of children with a genetic vulnerability for schizophrenia (Hans, Marcus, Henson, & Auerbach, 1992). Furthermore, research into the prodromal period of schizophrenia has reported that social impairment manifests in individuals approximately 2 to 4 years prior to the first admission, and that the failure to fully develop social skills is associated with the early onset of schizophrenia, whereas deterioration of developed social skills is related to late onset of illness (Häfner, Nowotny, Löffler, an der Heiden, & Maurer, 1995; Häfner, Löffler, Maurer, & Hambrecht, 1999).

In addition to poor social functioning, social skills deficits have also been identified in schizophrenia samples relative to those with affective disorders and healthy controls (Mueser, Bellack, Douglas, & Wade, 1991; Yamashita, Mizuno, Nemoto, & Kashima, 2005; Zanello, Perrig, & Huguelet, 2006). Such social skills deficits and overall social functioning impairments in individuals with schizophrenia may be related to difficulties with forming close lifelong relationships with others. For instance, individuals with schizophrenia are also less likely to be married relative to other psychiatric disorders like bipolar disorder and depression (Mueser et al., 2010), which suggests they may be lacking the benefits of greater happiness and health experienced by individuals with the social support of a marital relationship (Wood, Rhodes, & Whelan, 1989). Interestingly, males with schizophrenia may have greater challenges with successful social interactions, given that they tend to perform worse in role play tasks assessing social skill (Bellack, Mueser, Wade, Sayers, & Morrison, 1992; Mueser et al., 1993) and have more psychiatric hospitalization and worse psychosocial functioning compared to women with schizophrenia (Canuso & Pandina, 2007; Haas & Garratt, 1998). Thus, the social consequences related to negative symptoms and schizophrenia more broadly demonstrate a vital target for research and treatment development, particularly for males with schizophrenia spectrum disorders. The importance of having an adequate social support network is well illustrated in what is known as the social baseline theory, which is a new perspective on the buffering hypothesis.

Social Baseline Theory and the Buffering Hypothesis

The social baseline theory (SBT; Beckes & Coan, 2011) is another view on the buffering hypothesis in that social support buffers the effect of stress (Cohen & Wills, 1985). Specifically, SBT proposes that humans are inherently social beings with a need to affiliate, and we are best able to meet the challenges of life stressors and threat with the help of others around us, which is considered an assumed and normative state (Beckes & Coan, 2011; Coan & Sbarra, 2015). However, in the absence of baseline social resources, individuals experience more intense stress. Proximity to these social resources provides us with the ability to adapt to many different contexts and environments, and availability of social resources could be considered a default or baseline assumption for humans (Beckes & Coan, 2011; Coan & Sbarra, 2015). From another perspective, the state of being alone when anticipating threat carries greater cost than being near and interacting with other people, because the resources provided by a group allows for greater distribution of responsibility and a lighter load for each individual within the group (Beckes & Coan, 2011; Cohen & Wills, 1985). This line of thinking draws from examples across species. For instance, the animal literature documents the occurrence of social risk distribution, in that predatory threat is perceived as less burdensome when in the presence of a larger species-specific group, decreasing vigilance processing and allowing for more efficient foraging (Roberts, 1996). In humans, social support generally refers to people in an individual's life that are able to offer emotional support, companionship, and instrumental aid as resources during stressful life events (Hyde, Gorka, Manuck, & Gariri, 2011). Support for SBT in humans is illustrated by threats appearing more distant when with members of an in-group (Cesario & Navarrete, 2014), opponents appearing more physically formidable when an individual is alone versus with others (Fessler & Holbrook, 2013), hills seeming less steep when standing next to a friend compared to standing alone (Schnall, Harber, Stefanucci, & Profitt, 2008), and examples that social support in many forms can buffer the negative health effects of stressful life events and histories of abuse and neglect (Carr & Umberson, 2013; Cohen & Wills, 1985; Sperry & Widom, 2013; Turner, 1981). Thus, this literature suggests that the availability of social resources requires less recruitment of personal energy to deal with stress and ultimately regulates emotional responses to stress.

In schizophrenia, it is well established that social dysfunction and isolation are more likely to occur than in the general population. Individuals with schizophrenia may also experience added stress in their lives related to issues inherent to having a serious mental illness, such as difficulties with self-care (Holmberg & Kane, 1999), unemployment (Marwaha & Johnson, 2004), and internalized stigma, which is associated with diminished self-esteem, feelings of low self-efficacy, and greater symptom severity (Drapalski et al., 2013). Furthermore, individuals with schizophrenia, display deficits in oxytocin levels (Berardis et al., 2013) that are involved in social affiliation (Bora, Yucel, & Allen, 2009; IsHak, Kahloon, & Fakhry, 2011; Kosfel, Heinrichs, Zak, Fischbacher, & Fehr, 2005; Young & Wang, 2004) and social buffering effects in the face of stress (Hostinar, Sullivan, & Gunnar, 2013). Specifically, people with schizophrenia who have decreased oxytocin levels report perceiving facial stimuli as more threatening and experience abnormal stress reactivity in the hypothalamic-pituitary-adrenal (HPA) axis (Goldman, Marlow-O'Connor, Torres, & Carter, 2008). Because individuals with schizophrenia have fewer and poorer social relationships in combination with compromised oxytocin levels, they may often have fewer environmental and biological resources to deal with stress and daily life demands.

Given evidence that social affiliation and social support can influence emotion regulation in adaptive ways (Coan, Schaefer, & Davidson, 2006), it would follow that individuals with schizophrenia may have greater difficulty responding to distressing situations relative to healthy individuals without a psychiatric disorder. However, an important question is whether given adequate social resources, like affiliative and supportive people in their lives, would individuals with schizophrenia be able to incorporate such social resources when responding to threat – in other words, would they benefit from these social resources in the same manner as healthy controls?

Though it is unclear what is driving the development and maintenance of negative symptoms like social anhedonia and, ultimately, social impairments in schizophrenia, research has begun to examine how individuals with schizophrenia experience cognitive deficits, limited hedonic capacity (experience of pleasure), and reward processing difficulties that may contribute to negative symptoms and deficits in social affiliation.

Cognitive Deficits

Cognitive deficits and negative symptoms are both well-established constructs that are associated with functional impairment and poor quality of life in schizophrenia (Lipkovich et al., 2009; Savilla, Kettler, & Galletly, 2008). Some studies have also reported that negative symptoms are predictive of certain domains of cognition, such as executive functioning and selective attention (Lewandowski, Cohen, Keshavan, & Öngür, 2011), are moderately correlated with cognition, (see Harvey, Koren, Reichenberg, & Bowie, 2006 for a review), and may partially mediate the relationship between cognition and community functioning (Ventura, Hellemann, Thames, Koellner, & Nuechterlein, 2009).

Though cognition and negative symptoms appear to share a relationship with functional outcomes and are related to each other, path analyses have revealed that they are separable clinical features in schizophrenia spectrum disorders (Harvey et al., 2006). Specifically, when modeling the relationship between negative symptoms, cognition, and functional capacity with respect to daily social functioning, negative symptoms are related to social functioning but are not significantly related to cognition nor functional capacity (Harvey et al., 2006). Additionally, longitudinal studies (e.g., Harvey et al., 1996; Hughes et al., 2003) that have examined the course of cognition and negative symptoms over time have indicated that while they are both relatively stable features of schizophrenia, changes that do occur in negative symptoms are unrelated to change in cognition, in that the former does not significantly predict the latter over time (Harvey et al., 2006). Furthermore, the nature of the reported relationship between negative symptoms and measures of cognition may be dependent on the type of negative symptom measure. For example, the Scale for Assessment of Negative Symptoms (SANS; Andreasen, 1983) includes items that reflect what is typically considered negative symptoms (e.g., anhedonia) but overlap with what is arguably a facet of cognition, such as attention. Moreover, new measures of negative symptoms, like the Clinical Assessment Interview for Negative Symptoms (CAINS; Blanchard et al., 2011; Horan et al., 2011; Kring et al., 2013), have corrected the overlap of negative symptoms and attention seen in prior negative symptom measures, and the developers of the CAINS have reported that the motivation and pleasure subscale, which incorporates social anhedonia and asociality, did not significantly correlate with cognition, demonstrating good discriminant validity between negative symptoms and cognition (Kring et al., 2013). Finally, negative symptoms and cognition are often regarded as being different constructs, but their association may indicate that they have a shared underlying etiology (e.g., white matter abnormalities) (Harvey et al., 2006). Research on cognitive deficits has provided important insight about negative symptoms, and their relationship has provided useful elements of the framework for understanding how negative symptoms and social affiliation deficits manifest in schizophrenia. This area of study is complemented by research examining how individuals with schizophrenia process and engage in the experience of pleasure over time.

Hedonic Capacity

Many individuals with schizophrenia report having negative symptoms that involve deficits in the experience of pleasure and engagement in social interactions (e.g., Herbener & Harrow, 2002; Barch, 2005); however, negative symptoms like social anhedonia do not appear to reflect a simple a deficit of hedonic capacity. Support for this

this view comes from research findings stating that individuals with schizophrenia experience self-reported positive emotion in the moment similarly to controls, as assessed in emotionally evocative laboratory paradigms, as well as experience sampling studies (e.g., Cohen & Minor, 2010; Kring & Moran, 2008; Burbridge & Barch, 2007; Gard, D., Kring, Gard, M., Horan, & Green, 2007; Herbener, Harris, Keshavan, & Sweeney, 2007; Horan, Green, Kring, & Nuechterlein, 2006). In contrast, schizophrenia samples seem to experience more negative emotions in the moment relative to controls (Strauss & Gold, 2012). Interestingly, one of the most recent experience sampling studies found that individuals with schizophrenia and controls reported similar emotional experiences even in social situations, and people with increased negative symptoms exhibited comparable ability to experience positive affect relative to controls (Oorschot et al., 2013). However, individuals with schizophrenia did display a greater desire to isolate while in the company of other people, and this was especially true for individuals with more severe negative symptoms (Oorschot et al., 2013). This study suggests that hedonic capacity in the moment is largely intact and may be dissociable from the desire and motivation to be in social situations, which appears to characterize individuals with social anhedonia.

Research has indicated that disrupted anticipatory pleasure or "wanting" pleasurable rewards may offer an explanation for social anhedonia and social affiliation deficits in schizophrenia (e.g., Berenbaum & Oltmann, 1992; Cohen, Najolia, Brown, & Minor, 2011; Gard, D., Kring, Gard, M., Horan, & Green, 2007; Loas, Monestes, Yon, Thomas, & Gard, 2010), though these results have not been entirely consistent (Strauss, Wilbur, Warren, August, & Gold, 2011; Gold, 2011). Additional studies have identified difficulties in maintaining emotional experiences (Gard et al., 2011; Ursu et al., 2011), suggesting that negative symptoms like social anhedonia may have less to do with in the moment hedonic deficits, but rather involve emotion regulation and disruptions remembering positive experiences and later anticipating pleasurable rewards.

Reward Processing

Impairments in reward processing are also common findings in schizophrenia research that could explain mechanisms underlying social anhedonia (e.g., Gold, Waltz, Prentice, Morris, & Heerey, 2008; Pizzagalli, 2010). Thus far, there is evidence that individuals with schizophrenia have difficulty maintaining mental representations of reward value (Gold et al., 2008; Gold et al., 2012) and altered neural activity in during the anticipation of reward (Juckel et al., 2006; Dowd & Barch, 2012), which could impact the ability to anticipate social affiliation as being rewarding. Additionally, it appears that individuals with schizophrenia display abnormal probabilistic (Waltz & Gold, 2007) and reinforcement learning that is especially problematic for individuals with more severe negative symptoms (Polgár et al., 2008). In other words, individuals with schizophrenia may have trouble making decisions that would generate more rewarding experiences, and such decision-making may be related to impaired cost-benefit assessments. In monetary reward tasks, individuals with schizophrenia have shown a tendency to choose to exert less effort than controls, and within schizophrenia groups, less effort has been associated with worse negative symptoms (Gold et al., 2013; Green, Horan, Barch, & Gold, 2015). Interestingly, this pattern of decreased effortful decision-making has also been identified in other studies and does not appear to be due to differences in valuing monetary rewards between individuals with schizophrenia and controls (Fervaha et al., 2013). It is possible that diminished effortful decision-making is instead related to limited personal resources to meet effortful demands or differences in the value of monetary versus other types of rewards (e.g., social), which may alter the appraisal of effort and gain involved in reward tasks.

These findings have laid the groundwork for future studies to focus on increasing understanding of rewarding experiences that may be more closely related to social anhedonia, as many of the above studies assess responses to monetary reward rather than social affiliation, which is a core area of impairment in schizophrenia spectrum disorders (Meehl, 1962). Studies investigating both monetary and social rewards have indicated some overlap in relative increases in the BOLD signal regardless of reward type (e.g., Izuma, Saito, & Sadato, 2008). However, studies of people with autism have indicated that there are relative decreases in the BOLD signal in areas of the brain associated with reward (dorsal striatum) in response to social but not monetary reward (Delmonte et al., 2012). Furthermore, men seem to display less responsiveness in the mesolimbic circuit when anticipating social rewards than to monetary rewards compared to women (Spreckelmeyer et al., 2009), highlighting that differential reward processing occurs depending on the type of reward stimuli and sample demographics. Thus, it is imperative that research on reward processing in schizophrenia incorporate greater social stimuli and increasingly more ecologically valid experimental paradigms to move toward a comprehensive understanding of social anhedonia.

Social Regulation of Emotion

Recent research findings on the social regulation of emotion and neural circuits involved in affiliative relationships provide guidance on how to study the social deficits that appear to be at the core of negative symptoms in schizophrenia. Coan (2008) reviewed how social bonding and attachment involve brain circuitry related to dopaminergic projections originating in the ventral tegmental area (VTA) and extending to the ventral palladium, nucleus accumbens, and prefrontal cortex. Such bonding and soothing interactions appear to lesson the impact of stressful life events and provide health benefits (Berscheid, 2003). Furthermore, social relationships have been tied to physiological regulation of stress including the attenuation of autonomic responding and reduction of stress hormones from the HPA axis (DeVries, Glasper, & Detillion, 2003). This work has led to Coan's development of a novel fMRI hand holding paradigm for studying the in vivo social regulation of emotion. His hand holding task has been used to demonstrate that physical contact with an affiliative partner during threat of shock is associated with relative reductions in the BOLD signal of neural circuits associated with threat in romantic couples (Coan et al., 2006), as well as platonic friends (Coan, Beckes, & Allen, 2013). Additionally, an adaptation of the task has been used to examine how socially proximal caregivers standing near their anxious children who viewed threatening words in the scanner relative reductions in the BOLD signal of the hypothalamus, ventromedial, and ventrolateral prefrontal cortex (Conner et al., 2012). In other words, using a physical form of social support can attenuate recruitment of mental resources during physical threat. This can be interpreted as a down regulation of threat reactivity in the brain and a return to social baseline, according to the social baseline theory.

Coan's research indicates that neural systems associated with social behavior overlap with those supporting emotion and emotion regulation (Coan et al., 2006; 2008; Beckes, Coan, Hasselmo, 2012). For instance, the original study using romantic partners reported main effects of hand holding on reduced threat reactivity in the ventral anterior cingulate cortex (vACC), right dorsolateral prefrontal cortex (DLPFC), left caudate, superior colliculus, posterior cingulate, left supramarginal gyrus, and right post central gyrus (Coan et al., 2006). In a follow-up study, they reported that hand holding with an opposite-gendered friend resulted in significant decreases in brain activity during threat anticipation in similar but fewer brain regions, including the dorsal anterior cingulate cortex (dACC), left superior frontal gyrus, left supplementary motor cortex, and left putamen (Coan et al., 2013; Maresh, Beckes, & Coan, 2013). Interestingly, the degree of social regulation of neural circuits related to threat has been tied to better relationship quality and closeness between the subject of interest and their hand holding partner (Coan et al., 2006) and maternal support (Coan et al., 2013), particularly in areas like the anterior insula, which is one of the areas of the brain identified as responding to the anticipation of pain (Ploughaus et al., 1999) and emotional stimuli (Wylie & Tregallas, 2010). In addition, other researchers have found that the anterior insula and ACC are active during threat and pain cues (Decety, 2011), the vACC is implicated in modulating physiological arousal (Allman, Hakeem, Erwin, Nimchinsky, & Hof, 2001), and the dACC (Eisenberger et al., 2011) and anterior insula are areas associated with threat and pain that exhibit reductions of blood oxygenated level dependent (BOLD) activity when viewing pictures of people who provided participants with social support.

Though many of the above studies that illustrate the idea of the social regulation of emotion focus on receiving social support during threat or experience of physical pain, which may not appear to have an immediate relationship with social anhedonia, the literature on belongingness and social rejection indicates that there is a close relationship between social and physical pain (DeWall, Deckman, Pond, & Bonser, 2011). This relationship between social and physical pain suggests that the extent to which social factors regulate emotional reactivity to non-social threat could serve as a proxy for social attenuation of responses to social threat and stress more generally. Processing physical pain often involves the dACC and anterior insula (e.g., Rainville, Duncan, Price, Carrier, & Bushnell, 1997), and Eisenberger (2012) provides a review of how there are common brain regions associated with experiencing social and physical pain, implicating regions such as the dACC and anterior insula. Further evidence linking social and physical pain processes is the fact that socially painful experiences can be buffered by pharmacological strategies like Tylenol, which resulted in less reactivity in the dACC and anterior insula regions during a social exclusion task, as described by DeWall and colleagues (2011) and demonstrated in DeWall et al. (2010). Thus, studying the social regulation of emotion during threat of physical pain would be useful in understanding how such processes are related to negative symptoms in schizophrenia.

The Current Study

The results of this collection of research have been useful in identifying cognitive, hedonic, and reward processing abnormalities and possible neurobiological mechanisms that may explain negative symptoms like social anhedonia in schizophrenia. Unfortunately, we do not yet know how people with schizophrenia may or may not be benefitting from, not simply experiencing pleasure from or disinterest in, social support from people in the moment, particularly in moments of stress when social support is likely to be offered by others. Furthermore, it remains unclear how receiving social support and responding to social affiliation in schizophrenia may be related to negative symptoms like social anhedonia, how it is related to neurobiological processes, and whether responses to social support manifest in distinct patterns relative to people without a schizophrenia diagnosis. To our knowledge, no studies have examined the neurobiological benefits of social affiliation behaviors with individuals with schizophrenia. Examining how the recruitment of social resources during threat responding may or may not be intact in schizophrenia would help answer questions about the mechanisms involved in poor social functioning in individuals with schizophrenia and negative symptoms and would have implications for treatment engagement and maintenance.

Based on Coan's innovative research on the neural circuits related to the social regulation of emotion, we sought to apply his hand holding fMRI approach to the study of negative symptoms in schizophrenia and learn how the experience of social support during threat may be related to social functioning. One challenge of studying the social regulation of emotion in schizophrenia is that these individuals often lack the available healthy relationships that have been used in Coan's fMRI studies (e.g., spouses). Though many individuals with schizophrenia may have family members in their lives, the increased likelihood of the negative effects of expressed emotion (Kavanagh, 1992; Kymalainen & Weisman de Mamani, 2008) deterred us from seeking family members as partners in the hand holding task. Thus, we extended the work our lab has previously conducted on utilizing simulated social encounters (role plays) and video-based affiliative paradigms (Llerena, Park, Couture, & Blanchard, 2012) to develop interactive social methods to engage patients with confederates to build affiliative relationships in the laboratory. Participants and their confederate research partner completed three tasks to enhance social affiliation: a Conversation Task, an Implicit Fingertip Synchrony Task

(Yun, Watanabe, & Shimojo, 2012), and a Team Building Task. As a manipulation check and to assess change in social affiliation, participants completed ratings before and after the Social Affiliation Enhancement Tasks that measure interconnectedness with their research partner (Inclusion of the Other in the Self Scale; IOS; Aron, A., Aron, E., Smollan, 1992), willingness to interact them (Willingness to Interact Questionnaire; WILL; Coyne, 1976), mood (items from the Positive and Negative Affect Schedule; PANAS; Watson, Clark, & Tellegen, 1988), and a measure of overall reactions to the research partner (Reactions to Partner Questionnaire; PRP; Llerena et al., 2012). After completing this battery of tasks, we believed that participants would be able to experience social support and affiliation from their research partner as they might with a new friend or at least to a greater extent than they would experience with an anonymous experimenter.

Consistent with the Research Domain Criteria (RDoC) multiple-levels of analyses approach, the current study also aimed to examine how negative symptoms are associated with the subjective and neurobiological experience associated with social support during the attenuation of threat reactivity in a schizophrenia sample relative to healthy controls. While we examined one psychiatric diagnostic group relative to controls, schizophrenia is a heterogeneous illness and not all individuals with this diagnosis have negative symptoms. Investigating negative symptoms in a dimensional manner within a sample comprised of individuals with schizophrenia, as we did in the current study, allowed us to take a first step toward a transdiagnostic approach. We measured negative symptoms with the Clinical Assessment Interview for Negative Symptoms (CAINS; Blanchard et al., 2011; Horan et al., 2011; Kring et al., 2013) and the Social Anhedonia Scale – Brief

(SAS-B; Reise, Horan, & Blanchard, 2011). Additionally, because negative symptoms are so closely tied to deficits in functioning, we assessed the relationship between the social regulation of emotion during the hand holding task and measures of functioning.

The present study allowed us to explore whether individuals with schizophrenia have a fundamental deficit in experiencing the benefit of social support of down-regulating perceived threat. Alternatively, if patients displayed normative physiological responses to social affiliation in the context of threat, the results would also be informative in that patients would have the ability to benefit subjectively and or biologically from social support, but that impairments in social functioning may instead be due to limitations of social skills or their ability or opportunity to interact with other people. Results of this study would facilitate researchers to more closely target the needs of individuals with schizophrenia in developing and/or enhancing treatments for negative symptoms.

Aims and Hypotheses

Aim 1: Examine the effect of diagnostic status on subjective and biological responses to varying levels of social support during threat.

It was hypothesized that participants would experience more social regulation of emotion, as defined by more positive valence and less arousal, as well as attenuation of brain reactivity associated with threat vs. safe trial responding, when holding the hand of an anonymous experimenter and the greatest attenuation of threat when holding the hand of a socially affiliative research partner relative to holding no hand. Specifically, we expected that individuals with schizophrenia would have less attenuated reactivity in areas of the brain associated with threat (e.g., anterior insula, dACC) compared to healthy controls (i.e., healthy controls would show greater social regulation of emotion).

Aim 2: Within individuals with schizophrenia, examine the association between negative symptoms (i.e., social anhedonia, deficits in motivation and pleasure) and subjective and biological responses to threat when experiencing social support.

More severe negative symptoms were hypothesized to be associated with less social regulation of emotion during threat vs. safe trials (less threat attenuation) when holding the hand of a socially affiliative research partner.

Aim 3: As an exploratory aim, within individuals with schizophrenia, assess the association between social affiliation with the research partner and social functioning and subjective and biological responses to threat when experiencing social support.

Exploratory analyses were conducted to evaluate the possible association between impaired social regulation of emotion (failure to attenuate neural responses to threat social support from an affiliative partner) and less social affiliation and social functioning.

Chapter 2: Methodology

Participants

Participants (N=23: 7 meeting criteria for schizophrenia or schizoaffective disorder and 16 healthy control participants) for this study were recruited from the Baltimore, MD metro area. Of note, two control participants were excluded from the neuroimaging analyses due to an equipment error and a preprocessing alignment issue. For study inclusion, participants were 1) male, 2) between the ages of 18-65, 3) diagnosed with a schizophrenia spectrum disorder, 4) right handed, 5) literate and fluent in English, 6) of normal hearing, and 7) if on medications, having had a stable regimen for at least 2 weeks. Potential participants were excluded if they 1) had magnetic resonance imaging contraindications (e.g., MR unsafe metal in the body), 2) claustrophobia, 3) history of neurological conditions, 4) exceeded the weight limitations of the scanner; 5) back problems that would prevent the participant from lying on their back for up to 1.5 hours; and 6) history of substance abuse or dependence within the past 6 months. Additional exclusion criteria for controls included 1) having a known psychological condition, including depression, post traumatic stress disorder (PTSD), clinical anxiety, and ADHD, 2) family history of psychosis in a first- or second-degree relative and 3) taking psychoactive drugs, including Zoloft, Ritalin, etc. Recruitment followed and extended upon strategies that have been used in prior studies of schizophrenia conducted at the University of Maryland School of Medicine which have been effective in recruiting participants with and without psychotic symptoms from the medical center and the community. Recruitment methods included both medical record review and referrals from hospital and community clinicians.

Of note, we followed the recruitment strategy of Coan's studies by including a single gender in the current study to more closely replicate prior experimental results using the hand holding paradigm (e.g., Coan et al., 2006). By focusing on a single gender this reduced within-group variability by establishing consistency with the sex of the research confederate who acted as the affiliative partner. In considering which sex to recruit for this study we ultimately considered the logistics of recruitment and the representation of gender within known outpatient samples of schizophrenia and in our available clinical samples. In large multi-site studies (e.g., Clinical Antipsychotic Trials of Intervention Effectiveness, CATIE; McEvoy et al., 2005), males typically characterize over 65% of the sample (74% of the 1,458 participants in the CATIE study were male). Similarly, in our recent large multi-site outpatient study of negative symptom assessment in 281 individuals with schizophrenia (Horan et al., 2011), 66.5% of the sample was male. Focusing on our recruiting clinics in Baltimore (e.g., Couture, Blanchard, & Bennett, 2011), a similar pattern of 63% male is obtained.

Thus, in considering the conceptual, methodological and logistical issues faced by the current study we selected to exclusively recruit males to interact with female research staff. To better understand potential impacts of opposite gender participants and research staff during the social affiliation enhancement tasks, we also utilized a continuous measure of participant heterosexuality from the Sell Assessment of Sexual Orientation (Sell, 1996) that was included to assess whether there were group differences in terms of heterosexuality ratings. If a significant difference had been identified, we would have used heterosexuality as a covariate in our analyses. Ultimately it is our goal to build on this preliminary study to develop a larger study to assess the social regulation of emotion in both men and women with schizophrenia and related disorders. However, the results of the present study are only generalizable to men and to social affiliation processes with individuals of the opposite sex.

Of note, we had originally proposed recruiting 60 participants (HC = 30, SZ = 30). However, logistical difficulties proved to be a formidable challenge to achieving the desired sample size though we did run a total of 55 participants through parts or all of the study procedures over the course of piloting to develop the task. Specifically, transporting participants from their recruitment sites in Baltimore and working with individuals with severe mental illness, many of whom have cognitive impairments that impact the ability to keep and complete scheduled appointments, created unique challenges. However, we believed that pursuing this study was important and necessary as an initial step to better understand the subjective and biological nature of how individuals with schizophrenia experience social affiliation during times of stress and how this experience is related to negative symptoms and social functioning. Furthermore, much of the research cited in the introduction featured majority Caucasian samples, so the inclusion of our majority African American sample may serve as an important contribution with respect to racial diversity despite our use of a single gender sample. Thus, for the purpose of this dissertation project and given unforeseen IRB delays, task complications, and restarting recruitment, the sample size is far smaller than had been originally proposed. A larger sample is required to make definitive claims about our hypotheses.

Symptom, Functioning, and Sexual Orientation Materials

Trained graduate students, master's level research assistants, or clinical psychologists administered measures to establish diagnostic criteria and characterize the sample in terms of symptoms, cognition, and functioning. Demographic data were collected including age, race, education, medication, and smoking (average number of cigarettes smoked daily).

Structured Clinical Interview for DSM-IV Axis I Disorders, Patient Edition (SCID-I/P; First, Spitzer, Gibbon, & Williams, 1996). We assessed the diagnostic status of participants using the SCID-I/P, a semi-structured interview, to establish diagnostic inclusion and exclusion data and rule out a history of substance abuse or dependence within the past month. The SCID-I/P is a well-established measure that uses a series of questions and the ability to probe for further responses to assess whether individuals meet criteria for a psychiatric diagnosis, as determined by endorsement of a cluster of symptoms that are derived from the DSM-IV.

Clinical Assessment Interview for Negative Symptoms (CAINS; Blanchard et al., 2011; Horan et al., 2011; Kring et al., 2013). The CAINS is a 13-item measure of negative symptoms that includes two subscales: Expression (EXP; 4 items) and Motivation and Pleasure (MAP; 9 items). The CAINS has been validated for use in schizophrenia spectrum disorders and has adequate test-retest reliability, good inter-rater agreement, and good convergent validity with other negative symptom measures (Kring et al., 2013). The MAP subscale includes items of social amotivation and social anhedonia items, whereas the EXP subscale assesses the expression of emotion (e.g., alogia, blunted affect). The MAP subscale was included as one of the two negative symptom variables in the present study.

The Social Anhedonia Scale – Brief (SAS-B; Reise et al., 2011) is a 17-item true/false self-report questionnaire that assesses trait levels of diminished pleasure experienced from social interactions with high scores indicating worse anhedonia. This measure was adapted from the RSAS (Eckblad, Chapman, Chapman, & Mishlove, 1982), because results of bi-factor item response theory modeling yielded a better statistical fit to the SAS-B than the fit of either one-dimensional or bi-factor models to the RSAS (Reise et al., 2011). The RSAS is a 40-item true/false self-report questionnaire that assesses trait levels of diminished pleasure experienced from social interactions. Sample items include, "If given the choice, I would much rather be with others than be alone," (keyed false) and "Making new friends isn't worth the energy it takes," (keyed true) (Eckblad et al., 1982). Although other measures like the Pleasure Scale (Fawcett, Clark, Scheftner, & Gibbons, 1983) and the Snaith-Hamilton Pleasure Scale (Snaith et al., 1995) also measure anhedonia, the RSAS has been one of the most widely used and established measures to specifically assess social anhedonia. The RSAS has documented good internal consistency (Blanchard, Mueser, & Bellack, 1998; Mishlove & Chapman, 1985), as well as high test-retest reliability (Blanchard et al., 1998; Blanchard, Horan, & Brown, 2001). The current study used the SAS-B as one of the two measures of negative symptoms.

Brief Psychiatric Rating Scale (BPRS; Overall & Gorham, 1962). The BPRS is a 24-item interview measure designed to assess current clinical symptomatology as experienced over the previous week and was used to assess positive symptom severity. Items are scored from 1 (not present) to 7 (extremely severe), and are interpreted through four subscale scores: Positive Symptoms, Agitation/Mania, Negative Symptoms, and

Depression/Anxiety). For the purposes of characterizing the study sample, the Positive Symptoms subscale served as a measure of psychotic or positive symptom severity. The BPRS is considered one of the most frequently used psychiatric scales (Kay, 1990), has a long history of use with schizophrenia samples (e.g. Shafer, 2005), and has good psychometric properties (e.g., Morlan & Tan, 1998).

Calgary Depression Scale for Schizophrenia (CDSS; Addington, D., Addington, J., Maticka-Tyndale, & Joyce, 1992). The CDSS is a 9-item semi-structured interview designed to assess depressive symptoms in people diagnosed schizophrenia. Items are rated from 0 (absent) to 3 (severe), and items are summed to create a total score of depressive symptoms. The CDSS has become the standard scale for assessing depression with individuals with schizophrenia as a result of its sound reliability and validity with this population (Müller et al., 2005). The CDSS was included to further characterize the symptom profile of the study sample.

Brief Cognitive Assessment Tool for Schizophrenia (B-CATS; Hurford, Marder, Keefe, Reise, & Bilder, 2011). The B-CATS includes 3 tests of cognitive functioning: (1) Trail Making Test B; (2) Category Fluency, and (3) Digit Symbol Test. Administration of the B-CATS requires approximately 10-11 minutes, and was selected as an alternative to comprehensive cognitive batteries that are often greater than 90 minutes in duration in order to reduce participant burden. The B-CATS has good convergent validity in that it correlates .86 with more comprehensive cognitive batteries that have been used in schizophrenia samples; correlations between the B-CATS and the comprehensive batteries without the B-CATS tests range from .73 to .82 (Hurford et al., 2011).

Role Functioning Scale (RFS; Goodman, Sewell, Cooley, & Leavitt, 1993; McPheeters, 1984). The RFS is a 4-item clinical interview that assesses functioning in four main areas: Working Productivity; Independent Living/Self Care; Family Network Relationships; and Extended Social Network Relationships. Structured questions elicit information in each of these domains on a 7-point Likert scale so that higher Global Role Functioning Index scores indicate better functioning and range from 4-28. The measure has been found to provide reliable and valid assessments of patient role functioning (Goodman et al., 1993). The Family Network Relationships (immediate social network) and the Extended Social Network Relationships were included as the two areas of interest for functioning in the present study.

Sell Assessment of Sexual Orientation (Sell, 1996). The Sell Assessment of Sexual Orientation is a 12-item measure that assesses Sexual Attractions, Sexual Contact, and Sexual Identity. This measure features assessment of heterosexuality and homosexuality on separate items rather than grouping them together on one scale. For the purposes of this study, we used the heterosexuality item to assess heterosexuality continuously on a 7-point scale from "Not at all heterosexual" to "Extremely heterosexual."

Social Affiliation Measures

Inclusion of the Other in the Self Scale (IOS; Aron et al., 1992). The IOS is one of the measures of social affiliation change, and it assesses the closeness of the relationship between the participants and the opposite-sex confederate as reported by the participant. Participants completed this before and after the social affiliation enhancement tasks. The IOS scale is a series of seven overlapping pairs of circles (Venn diagrams) on a continuum with circles being completely separate at one end and circles virtually overlapping at the other end; the pairs of circles in between the extremes become gradually more overlapped. Aron and colleagues (1992) reported that the scale has good test-retest reliability and convergent validity with other measures of relationship interconnectedness.

Willingness to Interact Questionnaire (WILL; Coyne, 1976). This was completed before and after the social affiliation enhancement tasks to assess change in social affiliation between the participants and confederate. Participants rate how willing they would be to have further interaction with their confederate research partner on a 5-point scale ranging from 1 (definitely willing) to 5 (definitely unwilling). Sample items include "How willing would you be to go to a movie with your partner?" and "How willing would you be to invite your partner to a social event?" The WILL questionnaire was reverse scored so that higher scores represent more willingness to interact with the research partner. The WILL has also demonstrated good internal consistency ($\alpha = .85$) (Joiner & Metalsky, 1995) and good validity (Coyne, 1976).

Positive Reactions to Partner Questionnaire (PRP; Llerena et al., 2012). The PRP is a 9-item self-report measure that is completed before and after the social affiliation enhancement tasks to assess social affiliation. Participants are asked to rate how strongly they agree or disagree with a series of statements about the social interaction with the confederate research partner (e.g., "I liked talking to my partner") on a 5-point scale ranging from 1 (completely agree) to 5 (completely disagree). The PRP was reverse scored so that higher scores represent more positive reactions to the research partner. The PRP has adequate interrater reliabtility ($\alpha = .77$) (Llerena et al., 2012).

Positive and Negative Affect Scale (PANAS; Watson et al., 1988). The PANAS was completed before and after the social affiliation enhancement tasks to assess changes in current mood. The PANAS is a 20-item self-report scale, and for the current study, an additional 4 items (sociable, lonely, rejected, friendly) was included to tap into social emotions. Participants rate their experience of 24 emotions (such as interested, upset, enthusiastic, nervous) on a 5-point scale ranging from 1 (very slightly or not at all) to 5 (extremely). Scores were summed to form a Positive Affect Score and a Negative Affect Score so that higher scores represent higher levels of positive and negative affect, respectively. This modified version of the PANAS has demonstrated good internal consistency (α = 0.89 Positive Affect; α = 0.71 Negative Affect) (Llerena et al., 2012).

Social Affiliation Enhancement Tasks

Three tasks were included to evoke social affiliation between participants and a member of the research staff and to facilitate a social relationship from which social support can be drawn during the fMRI Hand Holding Task. Tasks were video recorded and reviewed to provide regular feedback to the confederates with respect to accurate use of task scripts.

Conversation Task. The participant and confederate completed a 3.5-minute conversation that was developed for the current study, and the goal of the task was to get to know the other person. The interaction begins with the confederate introducing and speaking about herself guided by a script, then the participant is asked to speak about himself. The confederate interacted with positive affect, positive body language, and self-disclosure to promote social affiliation with the participant. This task incorporates principles that contribute to the development of trust and cooperation (Declerck, Boone, & Emonds, 2013).

Implicit Fingertip Synchrony Task (Yun et al., 2012). The Implicit Finger Tip Synchrony Task was designed to increase affiliation through implicit body movement synchronization. The task consisted of coordinated movements wherein the participant tracked and mirrored the hand movements of the confederate. Yun and colleagues (2012) have shown that this task increases implicit interpersonal synchrony and is associated with feeling more comfortable with one's partner (i.e., decreasing social anxiety).

Team Building Task. The Team Building Task was used to increase affiliation, and it was adapted from a competitive task used in a child study to increase the level of acquaintance between individuals (South, Oltmanns, & Turkheimer, 2005) that draws on principles of competition increasing in-group identification and cooperation (Brewer, 1979; Buttelmann & Böhm, 2014). The participant and confederate were told that they were a team and they were instructed to choose a team name and design and build a creative structure using blocks in 10 minutes. The team was told that they would be competing against another team and that their structures would be judged by the researchers on creativity, originality, and craftsmanship. After completing the block construction, digital photographs were taken of the structure, and performance feedback was given to the team. The research participant's team always "won," and the research staff partner was given two snacks to share with the participant. The confederate always offered both snacks to the participant to develop further rapport, trust, and social affiliation.

fMRI Experimental Paradigm

The Hand Holding Task (Coan et al., 2006) uses threat of mild shock to evoke stress in the study of social affiliation. The task was modified for the present study, and the final version involved six counterbalanced runs (three hand holding conditions x two runs per condition) of threat and safety cues. In a fixed random order within each block, 15 threat and 15 safety cues were presented to participants for a total of 30 trials of cues. Threat cues were represented by a red “X” on a black background, reflecting a 50% chance of receiving a mild electrical stimulation on the ankle (participants were told that they had “a chance of shock” to heighten the uncertainty and perceived threat of shock). On the other hand, safety cues were indicated by a blue “O” against a black background, which represented no chance of electrical stimulation. We administered mild electrical stimulations with an isolated physiological stimulator (Model E-13-22, Colbourne Instruments) with a 500ms duration at a mA level individually determined by each participant to control for differential pain thresholds. Participants in the scanner experienced an average of 7.5 mild electrical stimulations in each of the six blocks of trials. Trials began with a threat or safety cue lasting 1 second, and they were subsequently followed by the anticipation or delay period, which varied between 4 and 10 seconds, during which participants were instructed to focus on a fixation cross. Any electrical stimulation delivered occurred in the last 500ms of the anticipation period. The end of the trial was indicated with a small white circle, and subsequently participants were instructed to rest until the start of the next trial. A four to ten second blank screen inter-trial interval (ITI) occurred between each trial.

Self-Assessment Manikin (SAM) scales (Bradley & Lang, 1994). As part of the Hand Holding Task, participants made ratings for valence and arousal on the SAM scales at the end of each of the six blocks of trials. Participants in the scanner provided a verbal rating on a 5-point visual rating scale to provide one rating of valence ("How unpleasant or pleasant do you feel right now?") and one rating for arousal ("How calm or agitated do you feel right now?") upon completion of each handholding condition that corresponds to the six trials blocks. This provided information about the subjective experience of hand holding condition in addition to the biological experience during the functional runs.

Procedure

The study was conducted at the University of Maryland School of Medicine and the Maryland Neuroimaging Center (MNC) at the University of Maryland College Park over the course of two visits. Prior to study visits, participants were screened for exclusion criteria by chart review, referring clinician, and/or phone. The **First Visit** involved completing the informed consent process, interviews and questionnaires to assess demographic information, sexual orientation, diagnosis, symptom severity, cognitive ability, and social functioning. We used existing protocols to establish competency to provide informed consent in all screened participants. The **Second Visit** at the MNC occurred approximately 1 week or less from the first, and it involved an MRI safety evaluation, a series of 3 social affiliation enhancement tasks, questionnaires on social affiliation and mood, and the experimental brain-imaging paradigm. Participants were provided with transportation to the MNC or reimbursement for gas mileage if they choose to drive themselves to the second visit. After participants arrived at the, MNC, they viewed a picture of their female confederate research partner and asked to complete the first series of social affiliation measures. Then, they completed the three tasks to enhance social affiliation with their research partner (Conversation Task, Implicit Finger Tip Synchrony Task, and the Team Building Task), and then they made the second series of social affiliation ratings to assess change in affiliation.

Subsequently, participants were prepared for the scanning portion of the study. They reviewed a description of the scanning procedures and Hand Holding Task with research staff, and participants had an opportunity to listen to sounds of the scanner so that they know what to expect from the experience. Then, two Ag-AgCl mild electrical stimulation electrodes were attached to the participants' right or left ankle (counterbalanced across participants), a respiration belt was attached around the chest, and skin conductance and a pulse monitor were attached to the fingers of the non-dominant hand (psychophysiological data were collected for potential use in pre-processing and additional manipulation checks, but they were not included in the scope of analyses for the present study). Given mixed findings of an abnormal pain tolerance in individuals with schizophrenia (de la Fuente-Sandoval, Favila, Gómez-Martín, Pellicer, & Graff-Guerrero, 2010; de la Fuente-Sandoval, Favila, Gómez-Martín, León-Ortiz, & Graff-Guerrero, 2012; Dworkin, 1994; Jochum et al., 2006), participants entered the scanner and completed an individualized calibration of shock to select a level that was "highly unpleasant but not painful," as has been used in prior studies using electric shock (e.g., Choi, Padmala, & Pessoa, 2012). Additionally, participants were given the opportunity to increase their level of shock between runs to address habituation effects and to maintain the experience of shock as "highly unpleasant but not painful." Participants subsequently completed a high-resolution anatomical scan before beginning the experiment. Then, participants completed the experimental paradigm (Hand Holding Task) with six blocks, two for each of three conditions: alone, holding the hand of an anonymous female experimenter (unseen by the participant prior to the study), and holding the hand of an affiliative research partner. To minimize any halo effect of hand holding with an anonymous experimenter, both the research partner and anonymous experimenter were clearly identified to the participant upon entering the scanner room through visual instructions and verbal communication from the research staff. The order of three handholding blocks was counterbalanced across participants. Participants' right hands were used for all handholding. At the end of each scan run, participants made verbal ratings of their subjective experience of valence and arousal. At the end of the study, participants were debriefed and receive $50.00 (and an additional $35.00, if they provided their own transportation) for their study compensation.

Imaging Acquisition and Analysis

Neuroimaging data were collected with a Siemens 3 Tesla MAGNETOM Trio high-speed scanning device at the University of Maryland College Park's Maryland Neuroimaging Center to collect functional magnetic and structural images, with a 12-channel head coil, which was selected to allow for more head room for participants that required the use of magnetic resonance safe goggles to view the experimental presentation. Before collecting the functional images, a T1-weighted magnetization-prepared rapid gradient-echo (MPRAGE; Mugler & Brookeman, 1990) anatomical scan was collected with 176 ascending sagittal slices (0.45mm slice gap), 1900ms TR, 2.58ms TE, 9° flip angle, 230mm FOV, 0.9x0.9x0.9mm voxels to aid in localization of functional reactivity during data processing. During each experimental block, we collected 156 functional images (volumes) with the following parameters: 44 interleaved oblique axial echo-planar slices (0% slice gap) with volumes comprising the whole brain, 2500ms repetition time (TR), 25ms echo time (TE), 90° flip angle, 192mm field of view (FOV), 64 x 64 matrix, and 3x3x3mm voxels.

Pre-processing of the imaging data was conducted using Analysis of Functional Neural Images (AFNI) software (Cox, 1996; http://afni.nimh.nih.gov/afni) with afni_proc.py. Slice timing correction was conducted with Fourier interpolation to align all slices to the first slice, six-parameter rigid-body motion correction with Fourier interpolation, and spatial normalization of anatomical volumes and then functional data to standard space (TT_N27 Talairach template) using a 12-parameter affine transformation. Spatial smoothing was conducted using a Gaussian filer with a full-width at half maximum of 6mm, twice the voxel size (Poldrack, Mumford, Nichols, 2011), and each voxel's time series was scaled to a mean of 100. Final voxel resolution of the data was 54x64x50 at a 3mm isometric voxel size. All trials were included in analyses, including those in which participants received shocks. To address gross motion artifacts, we excluded participants with more than 3mm of head motion within runs. The first three TRs of data were removed to account for signal saturation. The expected neural response was convolved with a canonical hemodynamic response to model the BOLD signal at each voxel as in the original study (Coan et al., 2006), and the motion parameters were entered as covariates. Threat and safe trials were each modeled as combined onset cue, delay phase, and end cue (starting at the onset of the threat or safe cue with a duration lasting to the end of the 1s end cue) rather than solely the delay "anticipation period." This approach to modeling the data was selected due to high correlations between the three components of the trials (r's > .5), which would have challenged our ability to interpret potential effects of interest as being restricted to the anticipation period. Additionally, for the purposes of this study we had a greater interest in contrasts between trial types to assess differences in general threat processing due to group or hand holding rather than between specific components within a trial as examined in other studies in which transient and sustained responses to threat have been found to vary over time (McMenamin et al., 2014; Somerville et al., 2013). Shocks occurred in the last 500ms of the delay phase between onset and end cues, and they were modeled with shock onset defined as 500ms before the end cue with a corresponding duration of 500ms across all trials. A TT_N27 gray matter mask was used to restrict results to gray matter.

Prior to the analyses of interest, we assessed the neural response to shock and the threat response as indicated by the contrast between relative increases in the BOLD signal to threat vs. safety cues (threat – safety = response) across groups and trials and within the baseline alone hand holding condition. For the main analyses, we examined effects of group and hand holding condition in three *a priori* ROIs: dACC, left and right anterior insula using average parameter estimates from 6mm radius spheres based on peak coordinates from a meta-analysis on threat processing in instructed fear studies (Mechias, Etkin, & Kalisch, 2010). The coordinates were converted to Talaraich space (Talairach & Tournoux) using the mni2tal transformation, and spheres were created with 3dundump and resampled to the functional data resolution with 3dresample: dACC (x=0, y=-16, z=36), left anterior insula (x=31, y=-20, z=9), and right anterior insula (x=-34, y=-21, z=3). A second a priori ROI approach was used by employing anatomical masks based on the Harvard-Oxford Cortical and Subcortical atlases: dACC and left and right insula that were resampled with 3dresample to match the grid of the functional data. A third approach involved using voxel-wise t-tests to explore whole brain analyses for completeness to better understand the extent of hand holding effects across the brain beyond the ROIs, as the Hand Holding Task had not yet been studied in a schizophrenia sample. We expected to identify effects in areas of the brain related to threat processing, including the dACC, anterior insula, right dorsolateral prefrontal cortex (right DLPFC), caudate-nucleus accumbens (NAcc), putamen, right postcentral gyrus, superior colliculus, posterior cingulate, and left supramarginal gyrus, as these regions were previously identified as having a hand holding effect in the original study (Coan et al., 2006).

All imaging analyses were conducted using an uncorrected voxel-wise threshold of p=.001, p=.05 cluster extent threshold corrected for family wise error rate (FWER) unless otherwise noted (Woo et al., 2014). Significant clusters in analyses with no cluster extent were defined as having a minimum of 2 contiguous voxels using the first-nearest neighbor clustering method. Cluster extents were determined by Monte Carlo simulations with 3dClustSim using the autocorrelation function (ACF) option based on the 3dFWHMx estimates of smoothing for each participant averaged across the whole sample and across participants within each of the two groups for whole brain analyses. Small volume correction using this method was conducted for each anatomically defined ROI. However, when assessing the effects of group and hand holding, average parameter estimates were extracted from the spherical ROIs using 3dmaskave to analyze in SPSS as done in recent studies using the Hand Holding Task (Beckes et al., 2012), and we used a significance threshold of p = .05, uncorrected. Regions of peak voxels in significant clusters were identified according to the Talairach Daemon (Lancaster et al., 2000).

Data Analysis

We conducted analyses in several stages. First, we assessed group differences in demographics, cognitive and social functioning, and symptom severity. Next, we performed manipulation checks for the entire sample on 1) changes in the self-reported social affiliation ratings that participants made before and after the Social Affiliation Enhancement Tasks, 2) response to shock, and 3) response to threat. Subsequently, for **Aim 1 Valence and Arousal** we assessed effects of group, hand holding, and group x hand holding for the self-reported valence and arousal ratings. For **Aim 1: Imaging Data**, we performed pre-processing of the neuroimaging data to correct for artifacts, noise, and movement, as described above. Following pre-processing, level 1 analyses were conducted to create parameter estimates of threat vs. safe contrasts for each participant. Level 2 analyses assessed effects of group, hand holding, and group x hand holding on neural responses to threat. For **Aim 2: Correlations with Negative Symptoms**, we examined the association between negative symptoms (motivation and pleasure; social anhedonia) and the attenuation of subjective (self-reported valence and arousal) and neural responses to threat. Finally, for **Aim 3: Exploratory Correlations with Social Affiliation and Functioning**, we assessed the relationship between measures of social affiliation and functioning and the attenuation of subjective (self-reported valence and arousal) and neural responses to threat. These analyses are described below. Behavioral data were analyzed with SPSS 21.0, and neuroimaging data were analyzed with AFNI 16.0.00, R 3.2.2, and SPSS 21.0.

Aim 1: Valence and arousal. To address whether individuals with schizophrenia would experience (1) attenuated subjective valence and arousal when holding the hand of a stranger and even greater attenuation when holding the hand of the confederate compared to holding no hand and (2) less attenuated subjective reactivity to threat relative to healthy controls when holding another person's hand, we conducted a repeated measures ANOVA with group (control, schizophrenia) as the between subjects variable and hand holding condition (alone, anonymous experimenter, partner) as the within subjects variable for the self-report SAM ratings of valence and arousal. Post hoc analyses were conducted using paired t-tests.

Aim 1: Imaging data. For the fMRI data, similarly to the self-report data, we conducted a repeated measures ANOVA using 3dMVM to assess the effects of group, hand holding, and their interaction on the attenuation of neural reactivity to threat. The dependent variable was the difference in BOLD signal when processing threat trials relative to safe trials. We took three approaches to analyzing the effect of group and hand holding on threat processing. One approach employed three regionally specific spherical ROIs: dACC, left, and right anterior insula with coordinates selected from a meta-analysis of instructed fear studies (Mechias et al., 2010). The second approach used three larger *a priori* anatomically defined ROIs: dACC, left, and right insula. The third approach was more exploratory and used whole brain analysis to assess relative changes in the BOLD signal between threat and safe trials. In each approach, we conducted planned comparisons to test whether group differences appeared within each hand holding condition, whether differences appeared between the contrasting hand holding conditions (confederate vs. stranger vs. no hand) within groups, and whether those differences were significant across groups. Our data analysis plans followed similar analyses used in the original handholding study (Coan et al., 2006). However, instead of using statistically derived ROIs, we chose to use *a priori* ROIs based on coordinates from an independent meta-analysis in addition to conducting nonselective whole brain analyses to avoid potential circularity (Kriegeskorte, Simmons, Bellgowan, & Baker, 2009), since we did not conduct a localizer task.

Aim 2: Correlations with negative symptoms. To address our hypotheses that individuals with schizophrenia who have more severe negative symptoms would experience less social regulation of emotion under conditions of threat, we conducted Pearson's correlations between negative symptoms with respect to both social anhedonia (SAS-B) and the cluster of negative symptoms tapping into motivation and pleasure deficits (CAINS_MAP) and 1) the SAM valence and arousal ratings and 2) the average fMRI parameter estimates (between threat and safety cues) in the *a priori* ROI spheres during the partner condition. The ROI spheres were selected to extract average parameter estimates for correlations, as they are smaller than the anatomical ROIs, decreasing potential heterogeneity across voxels and increasing the likelihood that the average is a closer representation of any signal present within the ROI.

Aim 3: Exploratory Correlations with Social Affiliation and Functioning. To address our hypothesis that greater attenuation of subjective and neural responses during the partner condition would be positively associated with social affiliation with the confederate and functioning in the schizophrenia group, we conducted Pearson's correlations between the average fMRI parameter estimates (threat vs. safe cues) in each ROI sphere, social affiliation on the Inclusion of the Self in the Other (IOS), Positive Reactions to Partner (PRP), and Willingness to Interact (WIQ), as well as social functioning (immediate/extended social networks) on the Role Functioning Scale (RFS).

Chapter 3: Results

Sample Characteristics

Demographic, clinical interview, and self-report ratings are described in Table 1. Independent t-tests and chi-square analyses yielded no significant differences in age, race, heterosexuality, social functioning, or selected shock level between groups (p's > .05). Of note, our sample was primarily African American with the exception of one Caucasian participant in the schizophrenia group. Independent t-tests indicated that individuals in with schizophrenia experienced more unemployment; given that Levene's test for equality of variances was found to be violated ($F(1, 21) = 39.06$, $p < .001$), a t statistic without the assumption of homogeneity of variance was computed ($t(15) = 2.61$, $p = .020$). The schizophrenia group also reported greater use of financial disability services than controls; given that Levene's test for equality of variances was found to be violated ($F(1, 21) = 4.97$, $p = .037$), a t statistic without the assumption of homogeneity of variance was computed ($t(15) = -10.25$, $p < .001$). Results from independent t-tests found that the schizophrenia group reported significantly fewer years of education ($t(21) = -2.16$, $p = .043$) and less cognitive ability on the Trail Making B subtest of the B-CATS than the control group ($t(20) = -4.06$, $p = .001$; one control participant was missing data for this measure). Group differences on the Digit Symbol and Category Fluency B-CATS subtests were not significant (p's > .05). With respect to symptom severity, the schizophrenia group displayed significantly greater social anhedonia on the SAS-B relative to controls; given that Levene's test for equality of variances was found to be violated ($F(1, 21) = 8.02$, $p = .01$), a t statistic without the assumption of homogeneity of variance was computed ($t(6.71) = -2.84$, $p = .026$). The schizophrenia group also displayed significantly more expressive negative symptoms on the CAINS_EXP and elevated motivation and pleasure negative symptoms on the CAINS_MAP that approached significance compared to controls. Levene's test for equality of variances was violated for each of these tests (CAINS_EXP $F(1, 21) = 25.23$, $p < .001$; CAINS_MAP $F(1, 21) = 13.30$, $p = .002$), so *t* statistics are reported with equal variances not assumed (CAINS_EXP $t(6) = -4.26$, $p = .005$; CAINS_MAP $t(6.55) = -2.34$, $p = .055$). Depression scores on the CDSS were also significantly higher in the schizophrenia group compared to controls, as were scores for positive symptom severity on the BPRS that approached significance. Levene's test for equality of variances was violated for each of these tests (CDSS $F(1, 21) = 28.52$, $p < .001$; BPRS $F(1, 21) = 12.44$, $p = .002$), so t statistics were conducted with equal variances not assumed (CDSS $t(6.02) = -2.50$, $p = .046$; BPRS $t(6.02) = -2.33$, $p = .059$).

Table 1. Demographic, Clinical Interview, and Self-Report Measures

	HC	SZ
	N(%)	N(%)
Male	16 (100%)	7 (100%)
Race		
African American	16 (100%)	6 (85.7%)
Caucasian	0 (0%)	1 (14.3%)
Employment*	5 (31.3%)	0 (0%)
Financial Disability Services*	2 (12.5%)	7 (100%)
	M (SD)	M (SD)
Age	44 (12.63)	48.43 (10.72)
Education*	12.94 (2.46)	10.71 (1.70)
Heterosexuality	5.6 (2.44)	6.29 (1.89)
B-CATS		
Digit Symbol	7.44 (1.97)	5.43 (2.76)
Category Fluency	41.38 (9.29)	33.14 (11.39)
Trail Making B (seconds)*	70.07 (30.20)	155 (69.45)

CAINS_MAP*	4.75 (4.04)	16.14 (12.62)
CAINS_EXP*	0.00 (0.00)	5.71 (3.55)
SAS-B*	2.31 (1.78)	7.71 (4.89)
CDSS*	.19 (.40)	7.29 (7.50)
BPRS Positive*	8.31 (.60)	16.71 (9.53)
RFS		
Immediate Social Network	6.88 (.50)	4.57 (2.82)
Extended Social Network	6.75 (.77)	5.00 (2.16)
IOS		
Pre	2.44 (2.28)	3.86 (2.12)
Post	5.25 (1.69)	5.14 (1.95)
PRP		
Pre	31.25 (4.20)	30.71 (5.65)
Post	34.25 (3.00)	33.43 (5.00)
WIQ		
Pre	22.38 (5.30)	22.29 (5.50)
Post	26.25 (3.57)	25.29 (4.61)
PANAS Positive		
Pre	40.06 (6.81)	31.00 (12.37)
Post	42.31 (7.76)	36.43 (10.13)
PANAS Negative		
Pre	11.69 (3.32)	13.86 (2.41)
Post	10.56 (1.26)	13.43 (3.31)
SAM Valence		
Alone	6.75 (2.14)	6.43 (1.62)
Anonymous Experimenter	6.88 (1.93)	6.29 (2.14)
Partner	7.69 (1.54)	6.71 (2.14)
SAM Arousal		
Alone	4.19 (2.04)	4.71 (2.14)
Anonymous Experimenter	4.06 (1.73)	5.00 (2.38)
Partner	3.63 (1.89)	4.57 (2.51)
Initial Shock Level	2.2 (1.0)	2.14 (1.11)
Final Shock Level	2.69 (2.04)	2.57 (1.28)

*Significant t-tests at $p < .05$

HC = healthy controls; SZ = schizophrenia/schizoaffective; B-CATS = Brief Cognitive Assessment Tool for Schizophrenia; CAINS_MAP = Clinical Assessment Interview for Negative Symptoms – Motivation and Pleasure; CAINS_EXP = Clinical Assessment Interview for Negative Symptoms – Expression; SAS-B = Social Anhedonia Scale – Brief; CDSS = Calgary Depression Scale for Schizophrenia; BPRS = Brief Psychiatric Rating Scale; RFS = Role Functioning Scale; IOS = Inclusion of the Other in the Self; PRP = Positive Reactions to Partner Questionnaire; WIQ = Willingness to Interact Questionnaire; PANAS = Positive and Negative Affect Scale; SAM = Self-Assessment Manikin (Valence: higher scores reflect more positive valence; Arousal: higher scores reflect greater agitation)

Effects of the Social Affiliation Enhancement Tasks

A key aspect of this study was the goal of establishing affiliative feelings toward an experimental confederate so that this relationship could then be used in the Hand Holding fMRI task. Analyses were conducted to determine if subjective affiliative feelings toward the interaction partner indeed increased as a result of the Social Affiliation Enhancement Tasks. A repeated measures ANOVA was conducted to assess differences across time points (pre vs. post), between group (control vs. schizophrenia), and the group x time interaction for each social affiliation measure rated before and after the Social Affiliation Enhancement Tasks that preceded the fMRI Hand Holding Task. A significant main effect of time was found for the Inclusion of the Other in the Self scale ($F(1, 21) = 24.58$, $p < .001$), the Positive Reactions to Partner questionnaire ($F(1, 21) = 13.83$, $p = .001$), the Willingness to Interact Questionnaire ($F(1, 21) = 34.10$, $p < .001$), and positive affect on the PANAS ($F(1, 21) = 12.54$, $p = .002$). However, the effects of group and group x time were not significant for the IOS, PRP, or WIQ, and there were no significant main effects or interactions for negative affect on the PANAS (p's $> .05$). These results reflect significant increases in social affiliation, and they are consistent with the intent of creating a social bond with the experimental confederate/affiliative hand holding partner.

Effect of Shock

To ensure that participants were experiencing shock during the task, we examined the main effect of shock across the entire sample (collapsing across groups and conditions) with one-sample t-tests that compared relative changes in BOLD signal to baseline. We also examined the group x shock interaction with independent t-tests, which we followed with post hoc analyses using one-sample t-tests within each group for significant interactions. Effects of shock were examined with 1) ROI spheres: bilateral anterior insula and dACC, 2) larger anatomical ROIs: bilateral insula and dACC, and 3) whole brain voxel-wise analyses (Table 2). All following imaging analyses in this section were conducted using an uncorrected voxel-wise threshold of p=.001, p=.05 cluster extent corrected for family wise error rate (FWER), with small volume correction for anatomically defined ROIs, unless otherwise noted. ROI spheres were analyzed with a threshold of $p = .05$, uncorrected.

Regions of interest – spheres. There was a significant main effect of shock in the left anterior insula ($t(20) = 2.48$, $p = .022$), the dACC ($t(20) = 3.25$, $p = .004$), and the main effect of group approached significance in the right anterior insula ($t(20) = 2.00$, $p = .059$). However, the group x shock effect was not significant any of the ROI spheres (p's > .05). In the ROI spheres, these results suggest that both groups were similarly sensitive to shock.

Regions of interest – anatomical. Across all participants for the anatomical ROIs, one-sample t-tests indicated that there was a significant main effect of shock in the right insula (t(20) = 3.91), left insula (t(20) = 4.71), and dACC (t(20) = 4.32) (Table 2). In the right insula, independent t-tests indicated a significant group x shock effect in that controls experienced a significant elevated BOLD signal to shock compared to the schizophrenia group ($t(19) = 4.07$). The group x shock effect was not evident in the left insula or dACC (p's > .001, uncorrected). Subsequent post hoc analyses were conducted to assess the extent of shock experienced in each group for the right insula. There was a significant relative increase in BOLD signal to shock relative to baseline in the right insula for the control group, ($t(13) = 4.86$), but the effect of shock was not significant in the schizophrenia group ($p > .001$, uncorrected). On balance, the null results of group x shock effect suggest that both groups displayed similar sensitivity to shock in the majority of ROIs.

Whole brain analyses. Expanding our focus to a whole brain analysis across all participants, significant relative increases in BOLD signal to shock were apparent in the right inferior parietal lobule ($t(20) = 5.74$), left inferior parietal lobule ($t(20) = 5.29$), and left insula ($t(20) = 5.91$) (Table 2). We also found significant relative decreases in the left fusiform gyrus ($t(20) = -4.00$) and right middle occipital gyrus ($t(20) = -4.04$). In controls, whole brain analyses indicated relative increases in BOLD signal in the right inferior frontal gyrus ($t(13) = 4.40$), right inferior parietal lobule ($t(13) = 6.27$), left inferior parietal lobule ($t(13) = 5.16$), and the left insula ($t(13) = 5.48$). On the other hand in the schizophrenia group, there were significant relative decreases in BOLD signal to shock in the right superior temporal gyrus ($t(6) = -6.54$), left middle temporal gyrus ($t(6) = -10.45$ and -6.02), right fusiform gyrus ($t(6) = -6.02$), and right lingual gyrus ($t(6) = -7.73$, p's $< .001$, uncorrected). Independent t-tests assessing between groups differences indicated that controls experienced a significant relative increase in BOLD signal to shock compared to the schizophrenia group in the left middle temporal gyrus ($t(19) = 3.93$), right cerebellar tonsil ($t(19) = 4.07$), right inferior frontal gyrus ($t(19) = 4.07$), right culmen and dentate ($t(19) = 4.07$), right superior temporal gyrus ($t(19) = 4.07$), and left insula ($t(19) = 4.07$, p's $< .001$, uncorrected).

Table 2. Effect of Shock: ROI and Whole Brain Analyses

Peak Location	k	mm³	Peak Voxel Coordinates x	y	z	t-statistic
All Participants						
ROI dACC	16	432	1.5	-4.5	41.5	4.32
ROI R insula	10	270	-40.5	-1.5	-6.5	3.91
ROI L insula	9	243	37.5	-1.5	3.5	4.71
R inferior parietal lobule	260	7020	-64.5	28.5	32.5	5.74
L inferior parietal lobule	169	4563	61.5	25.5	23.5	5.29
L fusiform gyrus	62	1674	25.5	61.5	-9.5	-4.0
L insula	51	1377	37.5	4.5	-0.5	5.91
R middle occipital gyrus	45	1215	-28.5	88.5	17.5	-4.04
Healthy Controls						
ROI R insula	90	2430	-49.5	-16.5	-3.5	4.86
R inferior frontal gyrus	227	6129	-49.5	-16.5	-0.5	4.4
R inferior parietal lobule	212	5724	-64.5	28.5	32.5	6.27
L inferior parietal lobule	129	3483	61.5	25.5	23.5	5.16
L insula	119	3213	43.5	-10.5	2.5	4.58
Schizophrenia						
R superior temporal gyrus	6	162	-34.5	-22.5	-24.5	-6.54
L middle temporal gyrus	4	108	49.5	28.5	-9.5	-10.45
L middle temporal gyrus	3	81	58.5	31.5	-9.5	-6.02
R fusiform gyrus	2	54	-40.5	52.5	-9.5	-6.02
R lingual gyrus	2	54	-25.5	79.5	-6.5	-7.73
HC vs. SZ						
ROI R insula	5	135	-25.5	-13.5	-18.5	4.07
L middle temporal gyrus	7	189	58.5	28.5	-9.5	3.93
R cerebellar tonsil	5	135	-31.5	55.5	-33.5	4.18
R inferior frontal gyrus	5	135	-25.5	-13.5	-18.5	4.07
R inferior frontal gyrus	5	135	-49.5	-19.5	-3.5	4.64
R culmen and R dentate	3	81	-19.5	58.5	-21.5	3.96
R superior temporal gyrus	3	81	-40.5	31.5	17.5	4.02
L insula	2	54	43.5	-7.5	2.5	4.44

p = .05 cluster corrected at voxel-wise uncorrected threshold p = .001
Talairach coordinates are presented in RAI order; k = voxels

Effect of Threat

To assess whether the Hand Holding Task elicited relative increases or decreases in the BOLD signal in response to threat that could potentially be attenuated by social support, we examined the effects of threat vs. safe trials with 1) ROI spheres: bilateral anterior insula and dACC, 2) larger anatomical ROIs: bilateral insula and dACC, and 3) whole brain voxel-wise analyses (Table 3). All analyses in this section were conducted using an uncorrected voxel-wise threshold of p=.001, p=.05 cluster extent corrected for family wise error rate (FWER), with small volume correction for anatomically defined ROIs, unless otherwise noted. ROI spheres were analyzed with a threshold of $p = .05$, uncorrected.

Regions of interest – spheres. There was a significant main effect of threat in the right anterior insula ($t(20) = 3.80$, $p = .001$), left anterior insula ($t(20) = 2.92$, $p = .009$), and the dACC ($t(20) = 3.76$, $p = .001$). However, the group x threat effect was not significant any of the ROI spheres (p's > .05) across hand holding conditions or within the baseline alone condition, which suggests that both groups were similarly sensitive to detecting and processing threat.

Regions of interest – anatomical. Collapsing across groups and hand holding conditions, paired t-tests indicated that there was a significant main effect of threat vs. safe trials in the right insula ($t(20) = 4.81$), the left insula ($t(20) = 4.72$), and the dACC ($t(20) = 4.24$). Between groups, we did not detect significant group x threat effects in any ROI ($t(19) < 3.88$, $p > .001$, uncorrected) across hand holding conditions or within the baseline alone condition. These results also suggest similar sensitivity to threat between groups.

Whole brain analyses. Across all participants, whole brain analyses of the threat-safe effect across groups and hand holding conditions indicated significant relative increases in BOLD activation in the right inferior occipital gyrus ($t(20) = -4.15$), left middle occipital gyrus ($t(20) = -4.56$), right medial frontal gyrus ($t(20) = -4.24$), left fusiform gyrus ($t(20) = -4.57$), right inferior frontal gyrus ($t(20) = -4.33$), and the right middle frontal gyrus ($t(20) = -4.42$). Significant relative decreases in the BOLD signal were also identified in the right cuneus ($t(20) = -4.55$) and left lingual gyrus ($t(20) = -3.85$).

For controls across hand holding conditions, whole brain analyses also indicated significant relative increases in BOLD signal in the right cingulate gyrus ($t(13) = 4.98$) and right inferior occipital gyrus ($t(13) = 4.38$) with a decrease in relative BOLD signal in the left posterior cingulate ($t(13) = -4.29$). Specifically, in the alone condition, controls exhibited a significant relative increase in BOLD signal in the left inferior occipital gyrus ($t(13) = 4.67$) and a relative decrease in the left posterior cingulate ($t(13) = -6.74$). In the schizophrenia group, whole brain analyses identified a small significant relative increase in BOLD signal to threat in the left middle occipital gyrus ($t(6) = 8.26$, $p < .001$, uncorrected). Additionally, in the alone condition, the schizophrenia group displayed a relative increase in BOLD signal in the right claustrum ($t(6) = 6.43$) and a relative decrease in the right superior frontal gyrus ($t(6) = -6.47$, $p < .001$, uncorrected). Between group independent t-tests suggested that the schizophrenia group experienced significantly greater relative increases to BOLD signal to threat compared to controls in the left inferior temporal gyrus, right inferior frontal gyrus ($t(=19) = -5.05$) and right inferior frontal gyrus ($t(19) = -3.95$, $p < .001$, uncorrected). In the alone condition, individuals with schizophrenia also displayed a significant elevation in BOLD signal to threat in the left posterior cingulate compared to controls ($t(19) = -3.91$).

Table 3. Threat-Safe Contrasts: ROI and Whole Brain Analyses

			Peak Voxel Coordinates			
Peak Location	k	mm^3	x	y	z	t-statistic
All Participants						
ROI dACC	53	1431	-1.5	-7.5	47.5	4.24
ROI R insula	20	540	-46.5	-19.5	-0.5	4.81
ROI L insula	8	216	28.5	-25.5	2.5	4.72
R inferior occipital gyrus	262	7074	-31.5	91.5	-6.5	4.15
L middle occipital gyrus	81	2187	49.5	70.5	-6.5	4.56
R medial frontal gyrus	71	1917	-1.5	-7.5	47.5	4.24
L fusiform gyrus	62	1674	19.5	94.5	-12.5	4.57
R cuneus	61	1647	-1.5	79.5	29.5	-4.55
L lingual gyrus	57	1539	10.5	52.5	5.5	-3.85
R inferior frontal gyrus	49	1323	-49.5	-16.5	-0.5	4.33
R middle frontal gyrus	49	1323	-49.5	-7.5	38.5	4.42
Healthy Controls						
R cingulate gyrus	147	3969	-1.5	-16.5	38.5	4.98
R inferior occipital gyrus	111	2997	-28.5	91.5	-6.5	4.38
L posterior cingulate	52	1404	7.5	55.5	5.5	-4.29
Healthy Controls - Alone						
L posterior cingulate	61	1647	7.5	55.5	8.5	-6.74
L inferior occipital gyrus	48	1296	37.5	82.5	-12.5	4.67
Schizophrenia						
L middle occipital gyrus[a]	3	81	43.5	73.5	-9.5	8.26
Schizophrenia – Alone						
R claustrum	2	54	-28.5	-7.5	5.5	6.43
R superior frontal gyrus	2	54	-13.5	-16.5	56.5	-6.47
HC vs. SZ						
L inferior temporal gyrus	2	54	37.5	10.5	-36.5	-5.05
R inferior frontal gyrus	2	54	-13.5	-31.5	-18.5	-3.95

R inferior frontal gyrus	2	54	-22.5	-16.5	-15.5	-3.95
HC vs. SZ – Alone						
L posterior cingulate	2	54	4.5	49.5	11.5	-3.91

p = .05 cluster corrected at voxel-wise uncorrected threshold p = .001
[a]p = .001, uncorrected
Talaraich coordinates are presented in RAI order; k = voxels

Aim 1: Self-Reported Valence and Arousal Ratings within the fMRI Task

Ratings of valence and arousal were summed across the two runs for each of the three hand holding conditions. Repeated measures ANOVAs were conducted to assess effects of group (control, schizophrenia), hand holding condition (alone, anonymous experimenter, partner), and the group x hand holding interaction. For valence and arousal, there were no significant effects of group (F(1, 21) = 0.75 valence, 0.90 arousal, p's > .05), hand holding (F(2, 42) = 1.50 valence, 1.09 arousal, p's > .05), or the group x hand holding interaction (Mauchly's test of sphericity was violated $\chi^2(2) = 10.45$, p = .005, so the F statistic was computed using the Greenhouse-Geisser correction F(1.42, 29.85) = 0.32; F(2, 42) = 0.30 arousal, p's > .05).

Exploratory results from combined sample: pilot plus final participants. Given the low power of our small sample size that had complete fMRI data, we also conducted an exploratory analysis of valence and arousal ratings for all participants who completed SAM ratings for the project across two different versions of the Hand Holding Task (N = 51; 32 HC and 19 SZ). The first version of the fMRI task involved a lower chance of and also fewer shocks (approximately 17% instead of 50%), so valence and arousal data would be subject to potentially less robust effects due to inclusion of ratings completed during a less threatening task. However, the increased sample size offers an opportunity to explore potential effects of group, hand holding and the interaction of group x hand holding on the subjective ratings of valence and arousal. Of note, one control group rating for valence and arousal in the anonymous experimenter condition was missing, and one schizophrenia group rating was missing for the valence and arousal for the alone condition.

Valence. A repeated measures ANOVA with the expanded sample identified a significant main effect of hand holding on valence (Mauchly's test of sphericity was found to be significant, violating the assumption of sphericity, $\chi^2(2) = 6.54$, $p = .038$, so the F statistic was computed using the Greenhouse-Geisser correction $F(1.77, 83.01) = 4.24$, $p = .022$). However, the main effect of group and the interaction effect of group x hand holding were not significant (p's > .05). To clarify the source of the hand holding effect on valence, we conducted several post hoc analyses. Post hoc paired t-tests indicated that the participants experienced significantly more positive valence with their affiliative partner (M = 7.29, SD = 2.08) than the being alone (M = 6.68, SD = 2.24) ($t(49) = 2.35$, $p = .023$) or holding the hand of the anonymous experimenter (M = 6.74, SD = 2.13) ($t(49) = 2.68$, $p = .010$). The difference in valence between the anonymous experimenter and alone condition was not found to be significant ($p > .05$).

Arousal. A repeated measures ANOVA found a significant main effect of hand holding on arousal ($F(2, 94) = 4.48$, $p = .014$). However, the main effect of group and the interaction effect of group x hand holding were not significant (p's > .05). To clarify the source of the hand holding effect on arousal, we conducted several post hoc analyses. Post hoc paired t-tests showed a significant decrease in arousal (increased sense of calm) when holding the hand of the affiliative partner (M = 3.51, SD = 2.00) compared to being alone (M = 4.16, SD = 2.11) ($t(49) = -2.34$, $p = .023$) or with the anonymous experimenter (M = 4.12, SD = 2.00) ($t(49) = -2.78$, $p = .008$). Again, the difference in arousal between the anonymous experimenter and alone condition was not found to be significant ($p > .05$).

The above exploratory results from the combined sample of pilot and study participants (N = 51; 32 HC and 19 SZ) demonstrated significant effects of holding the hand of an affiliative partner in the fMRI protocol. Specifically, across groups participants reported more positive valenced affect and less arousal when holding the hand of the affiliative partner compared to when alone or holding the hand of an anonymous stranger. These findings are consistent with the expectation that the affiliative partner would reduce subjective distress compared to the other hand holding conditions. However, it is important to note that the analyses of these self-report data in the smaller sample that had complete fMRI data (N = 21; 14 HC and 7 SZ) were not significant for condition or group.

Aim 1: Imaging Data

All analyses in this section were conducted using an uncorrected voxel-wise threshold of p=.001, p=.05 cluster extent corrected for family wise error rate (FWER), with small volume correction for anatomically defined ROIs, unless otherwise noted. ROI spheres were analyzed with a threshold of $p = .05$, uncorrected.

Omnibus effects of group and hand holding. To assess the effects of group, hand holding, and the group x hand holding interaction on BOLD threat processing in each group, we conducted mixed effects ANOVA using the threat-safe contrasts with 3dMVM in AFNI (Chen, Adleman, Saad, Leibenluft, & Cox, 2014) and a repeated measures ANOVA in SPSS for the ROI spheres (Table 4).

Regions of interest – spheres. Using the targeted ROI spheres (dACC, bilateral anterior insula), we did not observe a significant main effect of group (dACC ($F(1, 19) = .64$), right anterior insula ($F(1, 19) = .01$), left anterior insula ($F(1, 19) = .22$), hand holding (dACC ($F(1, 19) = 2.31$), right anterior insula ($F(1, 19) = .01$), left anterior insula ($F(1, 19) = 1.55$), or the group x hand holding interaction (dACC ($F(1, 19) = 2.31$), right anterior insula ($F(1, 19) = .01$), left anterior insula ($F(1, 19) = 1.55$), p's > .05).

Regions of interest – anatomical. For the larger ROIs (dACC, bilateral insula), the group x hand interaction yielded null results ($F(2,38) < 8.33$), as did the main effects of group ($F(1,19) < 15.08$) and hand ($F(2,38) < 8.33$). As an exploratory analysis, we examined the results with a more lenient threshold of $p < .001$, no extent correction, but the ROI analyses remained non-significant ($F(2,38) < 8.33$, $p > .001$, uncorrected).

Whole brain analyses. The whole-brain analyses indicated no significant main effect of group or hand holding (group $F(1,19) < 15.08$ and hand $F(2,38) < 8.33$) or the group x hand interaction ($F(2,38) < 8.33$). In the exploratory whole brain analysis with a lower threshold of p = .001, no extent correction, we found a small significant main effect of group in the left inferior temporal gyrus ($F(1,19) = 25.75$) and right inferior frontal gyrus ($F(1,19) = 19.70$). The main effect of hand holding condition was also significant in the left cerebellar tonsil ($F(2,38) = 11.81$), right superior temporal gyrus ($F(2,38) = 10.75$), right inferior parietal lobule ($F(2,38) = 8.93$), and right cerebral tonsil ($F(2,38) = 9.33$). However, the group x hand interaction remained non-significant ($F(2,38) < 8.33$).

Table 4. Omnibus Effects of Group and Hand Holding: Whole Brain Analyses

			Peak Voxel Coordinates			
Peak Location	k	mm^3	x	y	z	F-statistic
Group						
L inferior temporal gyrus	2	54	37.5	10.5	-36.5	25.75
R inferior frontal gyrus	2	54	-19.5	-16.5	-15.5	19.70
Hand Holding						
L cerebellar tonsil	8	216	28.5	34.5	-42.5	11.81
R superior temporal gyrus	3	81	-49.5	-19.5	-24.5	10.75
R inferior parietal lobule	3	81	-43.5	40.5	47.5	8.93
R cerebellar tonsil	2	54	-31.5	34.5	-36.5	9.33
Group x Hand Holding						
-	-	-	-	-	-	-

p = .001, no extent correction
*Anatomical ROIs
Talaraich coordinates are presented in RAI order; k = voxels

Planned comparisons. Given the preliminary nature of this pilot study as well as specific hypotheses about the directionality of expected effects, we conducted planned comparisons to better understand the data through exploratory analyses despite the null omnibus tests of group, hand holding, and group x hand holding effects (Table 5).

Regions of interest – spheres. In taking a more targeted approach to examining potential effects of group, handholding, or their interaction, average threat vs. safe contrast parameter estimates were extracted and analyzed in SPSS. However, no significant effects where seen in the ROI spheres (dACC or bilateral anterior insula) with a threshold of $p = .05$, uncorrected, as described below.

Independent t-tests were conducted to examine group differences in hand holding effects. However, the analyses did not find a significant effect of threat between groups for the alone condition (dACC ($t(19) = 1.07$), right anterior insula ($t(19) = .08$), left anterior insula ($t(19) = -.19$), p's > .05), the anonymous experimenter condition (dACC

($t(19) = .12$), right anterior insula ($t(19) = -.02$), left anterior insula ($t(19) = -1.03$), p's > .05), or the partner condition (dACC ($t(19) = 1.13$), right anterior insula ($t(19) = .03$), left anterior insula ($t(19) = -.11$), p's > .05).

Effects of hand holding within groups were examined with paired t-tests. Within controls, we not find a significant effect of hand holding for the alone vs. partner contrast (dACC ($t(13) = -.64$), right anterior insula ($t(13) = -.30$), or left anterior insula ($t(13) = -2.08$), p's > .05). Additionally, we did not observe a significant difference in the alone vs. anonymous contrast (dACC ($t(13) = 1.06$), right anterior insula ($t(13) = .82$), or left anterior insula ($t(13) = -.47$), p's > .05) or the anonymous vs. partner contrast (dACC ($t(13) = -1.46$), right anterior insula ($t(13) = -.83$), or left anterior insula ($t(13) = -1.90$), p's > .05).

Within the schizophrenia group, we found a similar null effect of hand holding for individuals with schizophrenia for the alone vs. partner contrast (dACC ($t(6) = .08$), right anterior insula ($t(6) = -.04$), or left anterior insula ($t(6) = .08$), p's > .05). We also did not observe a significant difference in the alone vs. anonymous contrast (dACC ($t(6) = -1.04$), right anterior insula ($t(6) = -.08$), or left anterior insula ($t(6) = -1.00$), p's > .05) or the anonymous vs. partner contrast (dACC ($t(6) = 1.45$), right anterior insula ($t(6) = .05$), or left anterior insula ($t(6) = 1.07$), p's > .05).

The group x hand holding interaction was examined with independent t-tests that did not identify a significant effect of hand holding between groups for the alone vs. partner (dACC ($t(19) = -.45$), right anterior insula ($t(19) = -.14$), left anterior insula ($t(19) = -.99$), p's > .05), alone vs. anonymous (dACC ($t(19) = .23$), right anterior insula ($t(19) = -.24$), left anterior insula ($t(19) = -.75$), p's > .05), and anonymous vs. partner contrasts (dACC ($t(19) = -.1.08$), right anterior insula ($t(19) = .82$), left anterior insula ($t(19) = -.87$), p's > .05).

Regions of interest – anatomical. Given the narrow focus of the ROI spheres, we also examined the potential effects in the larger anatomically defined ROIs. Significant effects were not found in the anatomically defined dACC or bilateral insula ROIs. We subsequently explored these analyses with a more lenient threshold of $p < .001$, uncorrected below.

Between groups, we did not identify significant effects for any of the hand holding conditions for the dACC or bilateral insula ROIs (t(19) < 3.88). Within groups, controls displayed no significant effects of hand holding in the dACC or bilateral insula ROIs ($t(13) < 4.22$). Similarly, null effects of hand holding were observed in the schizophrenia group ($t(6) < 5.96$). Additionally, independent t-tests displayed no significant effects of group on any of the hand holding contrasts in the dACC or bilateral insula (t(19) < 3.88).

Whole brain analyses. We observed null contrasts between groups, hand holding conditions, and the group x hand holding interaction in the whole brain analyses. However, we explored these analyses with a more lenient threshold of $p < .001$, uncorrected, and the results are detailed below.

There were significant effects of group that indicated greater relative increases in BOLD signal in the schizophrenia group than in the control group. When alone, the effect was observed in the left posterior cingulate ($t(19) = -3.91$). When holding the hand of the anonymous experimenter, the effect was observed in the right ventral cerebellum ($t(19) = -4.57$). However, when participants were with their affiliative partner, the effect was observed in the left precentral gyrus ($t(19) = -4.30$), right middle temporal gyrus ($t(19) = -4.04$), right middle frontal gyrus ($t(19) = -4.62$), and right posterior cingulate ($t(19) = -4.7$).

Next, effects of hand holding within groups were examined. Controls demonstrated significant relative increases in BOLD signal in response to threat in the alone vs. partner condition in the left cerebellar tonsil ($t(13) = 5.72$), right fusiform gyrus ($t(13) = 4.62$), right thalamus ($t(13) = 4.46$), and left precuneus ($t(13) = 4.37$), whereas there was significant relative decrease in signal to threat in the left inferior frontal gyrus ($t(13) = -4.2$). The alone vs. anonymous experimenter contrast produced a significant relative increase in BOLD signal to threat in the left cingulate gyrus ($t(13) = 4.24$), and the anonymous experimenter vs. partner contrast yielded a significant relative increase in BOLD signal to threat in the right inferior temporal gyrus ($t(13) = 4.59$). The results indicate that across the majority of significant brain regions, more affiliative hand holding decreased relative activation to threat vs. safe trials.

The schizophrenia group showed a significant relative decrease in BOLD signal to threat vs. safe trials when alone vs. partner contrast in the left cuneus ($t(6) = -6.01$), right lentiform nucleus ($t(6) = -5.97$; 1mm away from the amygdala), left middle occipital gyrus ($t(6) = -7.83$), and right middle frontal gyrus ($t(6) = -6.27$). Similarly, we also identified a significant relative decrease in BOLD signal to threat vs. safe trials for participants in the schizophrenia group in the alone vs. anonymous experimenter contrast in the left postcentral gyrus ($t(6) = -7.53$). However, there was no significant difference in relative BOLD signal for the anonymous experimenter vs. partner contrast when responding to threat vs. safe trials ($t(6) < 5.96$, $p > .001$, uncorrected).

For the group x hand holding effect, there was a subtle relative increase in BOLD signal in the control vs. schizophrenia group for the alone-partner contrast ($t(19) = 3.96$) in the left tuber, the alone vs. anonymous contrast ($t(19) = 3.93$) in the left ventral cerebellum, and the anonymous vs. partner contrast in the right inferior temporal gyrus ($t(19) = 4.01$).

Table 5. Planned Comparisons: Effects of Group and Hand Holding: Whole Brain Analyses

			Peak Voxel Coordinates			
Peak Location	k	mm^3	x	y	z	t-statistic
Group – HC vs. SZ						
Alone						
L posterior cingulate	2	54	4.5	49.5	11.5	-3.91
Anonymous						
R ventral cerebellum	4	108	-16.5	34.5	-51.5	-4.57
Partner						
L precentral gyrus	4	54	16.5	28.5	62.5	-4.3
R middle temporal gyrus	2	54	-61.5	19.5	-3.5	-4.04
R middle frontal gyrus	2	54	-31.5	-46.5	2.5	-4.62
R posterior cingulate	2	54	-1.5	52.5	14.5	-4.7
Hand Holding – HC	k	mm^3	x	y	z	t-statistic
Alone vs. Partner						
L cerebellar tonsil	3	81	28.5	34.5	-42.5	5.72
R fusiform gyrus	3	81	-49.5	34.5	-24.5	4.62
R thalamus	3	81	-13.5	28.5	-0.5	4.46
L precuneus	2	54	7.5	58.5	56.5	4.37
L inferior frontal gyrus	2	54	43.5	-7.5	29.5	-4.20
Alone vs. Anonymous						
L cingulate gyrus	3	81	16.5	37.5	23.5	4.24
Anonymous vs. Partner						
R inferior temporal gyrus	12	324	-67.5	25.5	-18.5	4.59
Hand Holding – SZ	k	mm^3	x	y	z	t-statistic

Alone vs. Partner						
L cuneus	4	108	19.5	85.5	8.5	-6.01
R lentiform nucleus	2	54	-22.5	7.5	-6.5	-5.97
L middle occipital gyrus	2	54	16.5	94.5	17.5	-7.83
R middle frontal gryus	2	54	-22.5	-22.5	56.5	-6.27
Alone vs. Anonymous						
L postcentral gyrus	2	54	31.5	22.5	44.5	-7.53
Anonymous vs. Partner						
-	-		-	-	-	-

Group x Hand Holding	k	mm^3	x	y	z	t-statistic
Alone vs. Partner						
L tuber	3	81	25.5	79.5	-27.5	3.96
Alone vs. Anonymous						
L ventral cerebellum	4	108	10.5	34.5	-51.5	3.93
Anonymous vs. Partner						
R inferior temporal gyrus	2	54	-64.5	16.5	-15.5	4.01

p = .001, no extent correction
Talaraich coordinates are presented in RAI order; k = voxels; L = left, R = right

Aim 2: Exploratory Correlations with Negative Symptoms

We sought to explore the relationship between self-reported and biological responses to threat within the affiliative partner condition and negative symptoms within individuals with schizophrenia. Given our small final sample (N=7) we again utilized all pilot and final study participants (N=19) to increase power. In the schizophrenia group for the partner hand holding condition, Pearson's correlations were used to assess the relationship between negative symptoms and ratings of valence and arousal on the SAM, as well as average parameter estimates for the threat – safe contrast in the ROI spheres (Table 6).

Valence and arousal. More positive self-reported valence within the partner condition was correlated with less severe negative symptoms on the CAINS_MAP (r = -.64, p = .003). However, valence was not significantly related to social anhedonia on the SAS-B (p > .05). Additionally, arousal ratings were not found to be significantly associated with either negative symptom measure (p's > .05).

Imaging data. Similarly, the average parameter estimates for the threat – safe contrast for the spherical ROIs (dACC, bilateral anterior insula) were not significantly correlated with negative symptoms (p's > .05).

Finally, to explore more about the relationship between negative symptoms and the social affiliation ratings that may have impacted the experience of self-reported valence and arousal, as well as neural responses to threat, during the fMRI task, we examined correlations between negative symptoms and social affiliation ratings (Table 7). The affiliation ratings completed following the three Social Affiliation Enhancement Tasks were included in these correlations to best reflect the relationship between negative symptoms and the quality of the participants' relationship with their affiliative partner immediately prior to engaging in the fMRI Hand Holding Task. Individuals in the schizophrenia group exhibited significant negative correlations between motivation and pleasure negative symptoms on the CAINS_MAP and social closeness on the IOS (r = -.56, p = .013), positive reactions to the partner on the PRP (r = -.53, p = .020), and willingness to have future interaction with the partner on the WIQ (r = -.61, p = .005). Specifically, social anhedonia as measured by the SAS-B also displayed the same pattern of negative correlations with the IOS (r = -.53, p = .019), PRP (r = -.58, p = .009), and WIQ (r = -.61, p = .006). Though we did not observe a group effect on social affiliation ratings, these findings provide support for the notion that greater symptom severity measured dimensionally rather than categorically is related to less social affiliation.

Table 6. SZ Correlations: Valence, arousal, negative symptoms, social affiliation, and functioning

	SAM Valence	SAM Arousal	dACC	R Insula	L Insula
CAINS_MAP	**-.64****[a]	.05	-.26	-.17	-.11
SAS-B	-.42	.16	-.40	-.28	-.18
RFS Immediate	**.55***	-.34	.34	.10	.14
RFS Extended	**.50***	-.10	.46	.41	.38
IOS	.32	-.35	-.08	.16	.24
PRP	.31	**-.55***	.54	.75	.74
WIQ	**.53***	-.44	.72	**.76***	.73
Trail Making B	-	-	-.54	-.58	-.61
Smoking	-	-	.001	-.34	-.31

*$p < .05$; ** $p < .01$
[a]Correlation survived Bonferroni correction for multiple comparisons at $p = .01$
Correlations for the schizophrenia group between clinical measures and self-report valence/arousal SAM ratings from the expanded sample (N = 19). Correlations were also conducted for average parameter estimates for threat vs. safe trials in the partner hand holding condition for each of three regions of interest. Correlations for smoking (cigarettes per day) and cognitive functioning with the B-CATS trail making B subtest were conducted with parameter estimates from the alone baseline condition. SZ = schizophrenia/schizoaffective; SAM = Self-Assessment Manikin (Valence: higher scores reflect more positive valence; Arousal: higher scores reflect greater agitation); dACC = dorsal anterior cingulate; R = right; L = left; Insula = anterior insula; CAINS_MAP = Clinical Assessment Interview for Negative Symptoms – Motivation and Pleasure; SAS-B = Social Anhedonia Scale – Brief; RFS Immediate/Extended = Role Functioning Scale Immediate/Extended Social Network Relationships; IOS = Inclusion of the Other in the Self, PRP = Positive Reactions to Partner; WIQ = Willingness to Interact Questionnaire

Table 7. SZ Correlations: Negative symptoms and social affiliation

	IOS	PRP	WIQ
CAINS_MAP	**-.56***	**-.53***	**-.61****[a]
SAS-B	**-.53***	**-.58****[a]	**-.61****[a]

*$p < .05$; ** $p < .01$
[a]Correlation survived Bonferroni correction for multiple comparisons at $p = .01$
Correlations for the schizophrenia group between clinical measures and self-report social affiliation ratings from the expanded sample (N = 19) made after completing the Social Affiliation Enhancement Tasks
CAINS_MAP = Clinical Assessment Interview for Negative Symptoms – Motivation and Pleasure; SAS-B = Social Anhedonia Scale – Brief; IOS = Inclusion of the Other in the Self, PRP = Positive Reactions to Partner; WIQ = Willingness to Interact Questionnaire;

Aim 3: Exploratory Correlations with Social Affiliation and Functioning

We sought to explore the relationship between self-reported and biological responses to threat within the affiliative partner condition and both social affiliation and functioning within individuals with schizophrenia. Given our small final study sample (N=7) we again utilized all pilot and final study participants (N=19) to increase power. In the schizophrenia group for the partner hand holding condition, Pearson's correlations were used to assess the relationship between ratings of valence and arousal on the SAM, as well as average parameter estimates for the threat – safe contrast in the ROI spheres, and 1) social functioning and 2) social affiliation (rated after the affiliation enhancement tasks) (Table 6).

Valence and arousal. More positive self-reported valence correlated with better functioning for immediate ($r = .55$, $p = .014$) and extended social networks on the RFS ($r = .50$, $p = .029$), and more willingness to interact with their partner in the study on the WIQ ($r = .53$, $p = .020$). Valence was not significantly related to social closeness on the IOS or positive reactions to partner on the PRP (p's > .05). Unlike valence, the arousal ratings were only observed to have a statistically significant association with positive reactions to their partner (PRP) in that more positive reactions were related to less arousal and more calm ($r = -.55$, $p = .015$). All other correlations between subjective arousal ratings and functioning, or social affiliation were not significant (p's > .05).

Imaging data. Similarly, the average parameter estimates for the threat – safe contrast for the spherical ROIs (dACC, bilateral anterior insula) were not significantly correlated with social affiliation or functioning with the exception of an association between more willingness to interact with the partner and a relative increase in BOLD signal to threat vs. safe in the right anterior insula sphere (*r* = .76, *p* = .046).

Finally, as a quality assurance check to examine whether nicotine use or attentional capacity may have impacted neural threat processing in the alone condition (e.g., Mechias et al., 2010; Naqvi, Rudrauf, Damasio, & Bechara, 2007), we assessed correlations between average parameter estimates of the threat vs. safe contrast in the ROI spheres and average number of daily cigarette smoked and cognitive ability as measured by number of on the Trail Making Test B (the only test of cognition with a statistically significant difference across groups (Table 6). There were no significant correlations between the Trail Making Test B or average daily number of cigarettes and the variables of interest (*p*'s > .05), suggesting that these variables did not impact the neuroimaging data.

Chapter 4: Discussion

In this pilot study, we sought to examine how schizophrenia and the negative symptoms of this disorder are related to impaired social affiliation using a novel experimental paradigm. The specific aims of the project included 1) assessing whether individuals with schizophrenia would benefit subjectively or biologically from hand holding with an affiliative partner during times of stress and whether the extent of this effect would be less pronounced than in healthy controls; 2) examining whether negative symptom severity would be related to subjective and biological reactions to threat within the schizophrenia group during the partner hand holding condition; and 3) exploring the possible relationship between the quality of social affiliation with the research partner and social functioning with subjective and biological responses to threat within the schizophrenia group during the partner hand holding condition. Additionally, the project sought to develop social affiliation between participants and a research partner in the laboratory. By doing so, this bond allowed us to study the effects of hand holding during times of stress in a controlled setting with a population of people who may not have close family members or friends to serve as an affiliative hand holding partner.

We sought to establish a social affiliative bond between participants and an experimental confederate through three tasks (a conversation task, a fingertip synchrony task, and a team building task) prior to the scanning session. Across groups, participants demonstrated increases in social affiliation on all affiliation measures, involving interpersonal closeness (IOS), positive reactions to their partner (PRP), willingness for future interactions (WIQ), and positive affect (PANAS). Of note, the effects of group and the group x time interaction were not significant. The lack of a group effect on favorable social affiliation ratings is somewhat at odds with prior studies using the WIQ and PRP that reported decreased appraisal of socially affiliative video stimuli in sub-clinical individuals with social anhedonia relative to controls (Llerena et al., 2012). On the other hand, the potential to increase social engagement and trust for individuals with schizophrenia and social partners has been illustrated in examples of pharmacological interventions with atypical antipsychotics (Tse et al., 2016) and oxytocin, though the results are somewhat mixed (Bhat, Buckner, & Ara, 2016). Additionally, many reports on social support in schizophrenia cite the difficulty of patients developing or accessing support due to social skills deficits (e.g., Segrin & Swiatkowski, 2016), but our participants did not have to rely on their social skills to elicit positive social reinforcement from our affiliative research staff, which may have contributed to more positive appraisals of the research partners. Furthermore, an ecological momentary assessment study reported that individuals with schizophrenia did not significantly differ from controls on the extent to which they set goals motivated by social relatedness needs (Gard et al., 2014). The fact that individuals with schizophrenia in the present study demonstrated the ability to build social affiliation in the moment also highlights a contrast with the negative anticipation of social inclusion that individuals with schizophrenia may experience relative to healthy controls (Engel, Fritzsche, & Lincoln, 2016). Our findings suggest that it is possible to develop social affiliative relationships in a controlled research setting within a relatively short amount of time (approximately 30 minutes), which is a novel development that allowed for further study of how such affiliation functions in the context of research questions, such as how individuals with schizophrenia may experience the social support as a resource to help regulate emotion or buffer the effects of stress.

Regarding our primary hypotheses, we anticipated that the control and schizophrenia groups would both exhibit an effect of hand holding in response to threat vs. safe trials, similarly to Coan et al. (2006) with the expectation that this effect would be smaller in the schizophrenia group. Using the N = 21 study sample, analyses indicated a lack of the expected main effects or interactions of group or hand holding condition for the self-report valence and arousal ratings. These unexpected null results suggest a failure of the affiliative hand holding partner to have an impact on subjective responses within the fMRI protocol. However, in exploratory analyses with an expanded sample of participants who completed valence and arousal ratings across two versions of the Hand Holding Task during piloting revealed significant main effects of hand holding on self-reported valence and arousal. Specifically, participants reported feeling more pleasant (positive valence) and calm (lower arousal) with their affiliative partner compared to being with the anonymous experimenter or being alone. The results for valence are consistent with those reported by Coan et al. (2006), but they are inconsistent with hand holding studies that reported null findings for arousal (Coan et al., 2006) or valence and arousal (Maresh et al., 2013).

Our self-report data offer partial support for our hypothesis that holding the hand of an affiliative partner would result in attenuated subjective responses to stress to a greater degree than hand holding with an anonymous experimenter or being alone. This finding fits well with the social baseline and stress buffering theories of the benefits of social support, including social touch and proximity (Coan & Sbarra, 2015; Cohen & Will, 1985). Additionally, the fact that participants rated hand holding with their partner as more positive and calming than the other hand holding conditions in the context of threat aligns closely with prior findings that describe hand holding with an opposite sex partner during a shock task also increases relative BOLD signal activation in the ventral striatum, which is related to reward processing (Inagaki & Eisenberger, 2012). Of note, the null effect between the alone and anonymous experimenter conditions was also found in prior hand holding studies (Coan et al., 2006; Maresh et al., 2013). Given the trend of participants reporting similar ratings of valence and arousal between these two conditions, one interpretation is that people do not seem to believe that holding the hand of anyone is better than no one when completing the Hand Holding Task. Furthermore, our sample may have been even less likely to benefit from the support of an anonymous person, because individuals with schizophrenia have been identified as having a bias to perceive neutral or ambiguous social stimuli as more threatening than healthy controls (Underwood, Kumari, & Peters, 2016), as was seen in their elevated arousal ratings to the anonymous experimenter. However, we chose to still include the anonymous experimenter condition to control for physical touch, as this was the first investigation of the hand holding task with individuals with schizophrenia and we did not have a specific rationale to remove the condition. Though the hand holding effect on self-reported valence and arousal was observed across the sample, the hypothesized group differences for these effects were not supported. Due to our relatively small sample size, further research is necessary to conclude that there is no difference in perceived benefit of social touch via hand holding between healthy controls and individuals with schizophrenia.

The results from the neuroimaging data analyses failed to find robust support for a significant group, hand holding, or group x hand holding interaction effect on the attenuation of neural threat processing in the dACC and bilateral anterior or whole insula regions of interest. Additionally, the results were not significant for the anatomically defined or spherical ROIs for any of the subsequent exploratory analyses using a more lenient threshold or planned comparisons across hand holding conditions or groups.

In the whole brain analyses, we identified only some small effects of group in areas including the inferior frontal gyrus, which has been associated with threat (Gold, Morey, & McCarthy, 2015), as well as for hand holding in the superior temporal gyrus and inferior parietal lobule. In the whole brain comparisons of hand holding conditions within each group, we found only minimal evidence for the expected hand holding effect in areas associated with threat processing, such as the thalamus, inferior frontal gyrus, and fusiform gyrus in controls, but in the schizophrenia group suggestions of an opposite effect emerged in the occipital gyrus, middle frontal gyrus, and postcentral gyrus. However, the original study reported main effects of hand holding in the vACC, DLPFC, caudate, superior colliculus, supramarginal gyrus, posterior cingulate, and postcentral gyrus (Coan et al., 2006) with a subsequent study also noting hand holding effects in the dACC, supplementary motor cortex, putamen, and superior frontal gyrus (Coan et al., 2013). The lack of significant effects in the present study could have been due to several reasons, including potentially insufficient shock and threat inductions, a hand holding manipulation with a less socially salient partner than previous research with the Hand Holding Task, and the limits of the present data analysis strategy given such a small sample size.

When examining the effect of shock across the entire sample, we observed significant increases in BOLD signal in the dACC and bilateral anterior and whole insula

ROIs, which are involved in the experience of pain (Wager et al., 2013). When comparing the groups, the control and schizophrenia groups appeared to have statistically similar increases in BOLD signal to shock except in the right insula ROI. Specifically, the control group displayed an effect of shock in the right insula, we did not see significant this effect in the schizophrenia group. However, within individuals with schizophrenia, minor relative decreases in BOLD signal to shock in whole brain analyses were found in areas including the middle temporal gyrus, which is consistent with BOLD signal decrease to shock in past studies with individuals with schizophrenia (Kumari et al., 2009). While there were null group effects of shock in the majority of ROIs, given our limited statistical power we are unable to definitively state that there would be no group effects of shock if a larger sample were available. Additionally, it may have been the case that the intensity of shock was not sufficiently averse to elicit enough threat to be attenuated by social support.

One factor that could have impacted the lack of increased BOLD signal in the right insula ROI for the schizophrenia group is the individually calibrated level of shock used in the task. However, the groups did not select significantly different initial or final shock intensities that they deemed "highly unpleasant but not painful." Another possible explanation is that the schizophrenia group may have had higher thresholds for pain as suggested by prior studies (e.g., de la Fuente-Sandoval et al., 2012). Yet, when reviewing the frequency of initial and final individually calibrated shock levels for each group, 5 (35.7%) controls but only 2 (28.6%) individuals with schizophrenia reached the max shock level of 4mA, which may explain why certain individuals may not have experienced sufficient levels of shock to trigger relative changes in BOLD signal.

Alternatively, perhaps participants in the schizophrenia group were more conservative in selecting their subjectively "highly unpleasant but not painful" shock levels. Whether or not this is the case, the shock levels selected by participants in the study were noticeably weaker and longer (means = 2.14mA to 2.84mA for 500ms) than the shock used across all subjects in previous studies by the Coan group (4mA for 20ms) (Coan et al., 2006; Maresh et al., 2013). We may have seen greater relative changes in the BOLD signal in response to shock if we had used methods identical to the original studies, but then the experience of shock would have been subject to individual differences in pain thresholds (Diatchenko et al., 2005).

Reviewing the effects of threat vs. safe trials collapsing across groups tells a similar story in that participants overall experience effects of threat in the dACC and bilateral anterior and whole insula ROIs. However, there was no group x threat interaction effect in the ROIs. Whole brain analyses also displayed a main threat effect in several areas including the inferior and middle occipital gyrus, inferior frontal gyrus, middle frontal gyrus, and fusiform gyrus that have been associated with threat processing and shock expectancy (Carter, O'Doherty, Seymour, Koch, & Dolan, 2006; Choi, Padmala, Spechler, & Pessoa, 2014; Coan et al., 2006; Gold et al., 2013; Grupe, Oathes, Nitschke, 2013; Maresh et al., 2013).

Our findings of null group x threat interaction effects in the ROIs are somewhat consistent with the idea that individuals with schizophrenia may have intact processing of nonsocial threats, despite difficulty detecting social threats (Pinkham et al., 2014). The present results also raise the question as whether we would have observed a significant group effect of threat with a larger sample size, as prior research has failed to observe significant increases in relative BOLD signal during the anticipation of shock in individuals with schizophrenia (Linnman, Coombs, Goff, & Holt, 2013).

In addition to limitations of the shock and threat effect, another potential reason for the absence of a strong hand holding effect was that our study substantially differed from prior studies using the Hand Holding Task in terms of the nature of the relationship between participants and their affiliative hand holding partners. Other studies had used spouses, mothers, and close friends to serve as hold holders (Coan et al., 2006, 2013; Maresh et al., 2013), but our study used a relatively weaker social relationship with a research partner. Though the quality of this relationship was positive and created a socially affiliative bond, the short duration of the relationship and limited opportunity for interaction and trust to build compared to years of developing a relationship with family members or close friends may not have been quite enough to create a hand holding effect in the present study.

A prominent factor that also reduced the likelihood of finding a significant hand holding effect was our small sample size. Given a larger sample, it is possible that we could have identified hand holding effects in the neural responses to threat that were similar to the self-report valence and arousal ratings. Additionally, our data analytic strategy may have been improved with additional analyses by employing a fixed effects model, which would have increased our power but limited results to the present sample. We could have also modified our preprocessing stream to control for effects of respiration and heart rate or used a different form of spatial normalization (e.g., nonlinear). Given greater time and resources, examining physiological data would also have provided a more comprehensive understanding about whether there were possible effects of hand holding undetected by our neuroimaging methods. Furthermore, we could have used a different region of interest approach to examine only areas identified as having a hand holding effect from the original Hand Holding Task report (Coan et al., 2006), though using ROI coordinates from a single study in a different population with a different data processing stream may not have translated well for use in the present project.

In reviewing data with respect to our final two aims, correlations within the schizophrenia group in the partner hand holding condition offer evidence partially supporting our hypotheses that more positive self-reported valence and lower arousal ratings (SAM), as well as attenuated neural threat processing in the spherical ROIs (dACC, bilateral anterior insula), would be associated with fewer negative symptoms, better social functioning, and higher ratings of social affiliation with the affiliative partner. Specifically, reports of positive valence or feeling more pleasant were associated with fewer motivation and pleasure deficits (CAINS_MAP) but were not related to social anhedonia specifically (SAS-B). Positive valence was also positively correlated with social functioning in immediate and extended social networks (RFS), as well as with more willingness to interact with the partner (WIQ); no significant associations were found with perceived social closeness (IOS) or explicit positive reactions to the partner (PRP). The only significant correlation with arousal indicated that lower arousal (feeling more calm) was associated with more positive reactions to the partner.

To better clarify the lack of observed group difference in social affiliation, we also conducted correlations between negative symptoms and social affiliation ratings. It appeared that though the schizophrenia group overall demonstrated similar affiliation ratings to controls, more severe negative symptoms (motivation and pleasure, as well as social anhedonia in particular) were related to lower ratings of social affiliation. This pattern is consistent with the idea that individuals with schizophrenia may be able to experience positive affect in the moment but that in social situations elevated negative symptoms have been associated with increased urges to isolate (Oorschot et al., 2013).

Additionally, all correlations with parameter estimates of threat processing for the ROIs were null with the exception of a surprisingly positive relationship between threat processing in the right anterior insula and willingness to interact with the partner. It may be that the more participants were interested in further interaction with their partner, the higher the stakes became to potentially perform well during the hand holding task. A further speculation is that this association may have been impacted by a possible experience of social threat if the male participants felt anxious about appearing vulnerable while holding the hand of and being observed by their female partners with whom they had greater social affiliation ratings.

We also examined correlations with cognition and cigarette use for individuals with schizophrenia in the alone condition, as these variables could have impacted the neural effects of threat. For instance, difficulty with distractibility may reduce the effects of threat or emotional stimuli though non-conscious processing may still allow for emotional reactions (Mechais et al., 2010), and nicotine has been shown to impact insular activity (Naqvi et al., 2007). Given that there was a significant difference between the patient groups with respect to cognition on only the B-CATS Trail Making Test B (requiring visuospatial working memory and switching attention between different stimuli; Jedraski-Styla et al., 2014), we examined their correlations with threat processing. However, cognition on this measure and cigarette use (average number of cigarettes smokes daily) were not significantly correlated with average threat vs. safe parameter estimates in any ROIs.

Limitations. The current study has several limitations. Though we had intended to recruit a robust sample, due to recruitment and data collection challenges with individuals with a serious mental illness, our sample size was small. Given the present sample size, we were limited in statistical power and the potential to detect significant effects of group and hand holding. Additionally, all of the participants in the schizophrenia group were taking medication. However, since medications and doses are determined by symptom severity we would be unable to disentangle the dose effects of medication from symptom severity itself (Green et al., 2015). Furthermore, prior studies found no effect of medication on responses to shock tasks in schizophrenia (e.g., Linnman et al., 2013).

Another limitation is that all of our participants were middle aged, African-American males who were tasked with building affiliative relationships with young, Caucasian female research staff. Given our sample's demographic characteristics, care must be taken when generalizing these findings to female participants, particularly because there is evidence suggesting gender differences in pain (Linnman, Beucke, Jensen, Gollub, & Kong, 2012) and threat (Han, Gao, Humphreys, & Ge, 2008) processing. Additionally, it is possible that participants may have reacted differently to a research partner who was more closely matched to their age, race, or gender when completing the social affiliation tasks, as the therapeutic alliance literature suggests that the matching of demographic characteristics between clients and mental healthcare providers providing social and psychological support impacts the quality of their relationship and treatment engagement (Wintersteen et al., 2005). Thus, future research would benefit from examining building social affiliation with and receiving social support from people who are more closely demographically matched to the individual or group of interest. Additionally, research suggests that the extent to which social support buffers the psychological consequences of stress may vary over the lifetime (Ajrouch, Abdulrahim, and Antonucci, 2013). Though the current study presents cross-sectional pilot data, future research may benefit from longitudinal assessments of how the benefits of social support may change over time or vary across individuals with first-episode vs. chronic psychosis.

With respect to the perception of threat, another limitation of the study may be that responses to the study's threat cues or shock level (highly unpleasant but not painful) may not have been as distressing as the experience of threat and stress encountered in participants' daily lives. For instance, one's ability to self-soothe may contribute to a lack of differences in threat anticipation. Moreover, individual differences in pain threshold is a potential limitation, particularly for individuals who reported that the shock level was no longer highly unpleasant but not painful but were unable to increase their level of shock due to the hardware limitations of shock available beyond 4mA. These potential ceiling effects in eliciting stress could be masking larger effects of our findings, and one would expect greater neurobiological responses to threat of shock as shock intensity increases (Drabant et al., 2011). We also did not assess pain sensitivity using quantitative sensory testing (Rolke et al., 2006), so we are unable to state whether the groups experienced differences in pain sensitivity that could have impacted the perceived stress and, ultimately, the perceived benefit of social support during the fMRI paradigm.

Another potential issue is that given the passive nature of the hand holding task, and the propensity for clients with schizophrenia to experience higher rates of impaired attention and sleep quality, it is possible that differences in performance could be due to variation in how well participants paid attention to the task. If attention during the task was compromised by distraction or disengagement from the task, potentially due internal stimuli related to psychosis (e.g., auditory hallucinations), this might have impacted the extent to which participants processed or anticipated the threat (Brooks, Nurmikko, Brimson, Singh, & Roberts, 2002). If it were the case that participants did not find the task threatening enough, then there would be limited need for and ability to assess the benefits of social support. Future iterations of this research would potentially benefit from including an activity to encourage focus on the stimuli (e.g., pressing a button each time participants see a threat or safety cue or counting how many shocks they received during each run). However, this could prove counterproductive if the task itself distracts from the typical threat anticipation process, which could dilute the experience of threat. It may also be useful to incorporate eye tracking to quantitatively assess the extent to which participants' visual gaze is focused on the cues and targets of interest during the task.

Another concern is that there may be variability with respect to one's level of comfort with physical touch or invasion of personal space. For instance, individuals with schizophrenia have been cited as having a larger boundary for personal space than healthy controls (de la Asuncion, Docx, Sabbe, Morrens, & Bruijn, 2015; Deus & Jokić-Begić, 2006; Holt et al., 2015; Park et al., 2009) particularly with elevated paranoia

(Schoretsanitis, Kutynia, Stegmayer, Strik, & Walther, 2016). Our study did not include measures of personal space preferences, but they may have also impacted the extent to which individuals found a physical form of social support comforting in times of stress. Another consideration is that participants in the present sample may comprise a self-selecting group who were more open to physical contact with strangers and are willing to engage in a shock task. Given this openness to intimate interactions with strangers and a threatening task, one may speculate that participants may have entered the study with higher baseline social affiliation, lower perception of threat, or greater perceived ability to cope with threat than the general population. Finally, we did not assess differences of participants' attitudes toward touch, which can have a variety of interpretations depending on the situation, the individual, and past experiences (Wilhelm, Kochar, Roth, & Gross 2001). It is possible that touch may have been perceived as supportive or threatening depending on the appraisal of the intention or purpose of the touch. Some participants indicated during the study overview that holding someone's hand was supposed to make you "feel better" or "comfort" them. However, other participants may have perceived this ambiguous situation differently or in a more threatening manner.

Conclusions. This study provides some of the first data investigating how to actively build social affiliation in the laboratory in individuals with schizophrenia. Our study demonstrated that it is possible to quickly establish a relationship with a new person in the span of approximately 30 minutes. This relationship was subjectively beneficial to participants under times of stress relative to being with a stranger or being alone. Additionally, the positive valence with the partner was associated with fewer negative symptoms, better social functioning, and higher social affiliation with the partner. However, the hand holding effect was not observed in our imaging data. The results show proof of concept of measuring the effects of social support during times of threat in individuals with schizophrenia, and we now need to further refine experimental methods to enhance the experience of threat and examine effects in a larger sample.

Our results demonstrating the ability to build social affiliation in individuals with schizophrenia provides support for implementing psychosocial interventions with the aim of increasing access to, frequency of, and the ability to engage in social interactions. Additionally, these findings suggest the importance of building rapport between mental health providers and social supports of clients, particularly those with negative symptoms, who may not perceive benefits from such relationships though they may have a positive quality. Such rapport is may be especially important early in the course of illness, as diminished social support often appears prior to the first episode of psychosis in schizophrenia (Gayer-Anderson & Morgan, 2013), and it is associated with greater duration of untreated psychosis and negative symptom severity (Thorup et al., 2006). It will be important to continue to understand what factors may attenuate threat processing, as elevated stress sensitivity and threat anticipation has been associated with more intense psychotic experiences in individuals with first episode psychosis relative to healthy controls (Reininghaus et al., 2016).

Future directions of this research might include assessing what factors would facilitate the ability to efficiently build and maintain social affiliation over time (e.g., duration of interventions, matching demographic features), as well as what mechanisms may increase the benefits of experiencing social support (e.g., amount and type of support, enhancing the ability to calculate the costs/benefits of support, increasing attention to enhance engagement in social interactions, challenging beliefs about the acceptability of seeking or receiving help, neurochemical agents). Specifically, understanding how individuals with schizophrenia may benefit from social support from therapists compared to friends or family, as well as the availability of such individuals is worth exploring to build a comprehensive picture of how social resources are identified and valued. Combining self-report measures with ecological momentary assessment and ambulatory psychophysiological variables in studies of how social support buffers the effect of stress on a daily basis may help to address this issue.

Future research may also benefit from examining clinical control groups (e.g., depression) to understand how others who may share similar experiences of anhedonia to individuals with schizophrenia experience social support similarly or differently during times of stress. Within these groups, it would also be useful to better understand how the benefits of social support are perceived and experienced at different stages of illness (e.g., first-episode psychosis vs. chronic). Additionally, it would be informative to better understand the patterns of subjective and biological benefits of social support across cultures of individuals with schizophrenia is important, as researchers have identified cultural differences in how individuals experience implicit social support (knowledge of a social support network) compared to explicit social support (instrumental help, direct emotional support) (Taylor, Welch, Kim, & Sherman, 2007). Such cultural differences may also impact the likelihood of help seeking from family, friends, and treatment resources (Taylor et al., 2004). In sum, the present pilot study is only the beginning of a line of work that seeks to explore how people with and without schizophrenia build and benefit from social support.

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