AN INVESTIGATION OF THE EFFECTS OF OXYTOCIN ON SOCIAL COGNITION AND SOCIAL FUNCTIONING IN SCHIZOPHRENIA

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Abstract

CLARE MARKS GIBSON: An investigation of the effects of oxytocin on social cognition and social functioning in schizophrenia
(Under the direction of David L. Penn)

Social functioning is a core feature of schizophrenia, and it is related to outcome and disease onset. Social cognitive processes underlie social functioning and as such have been a treatment target in schizophrenia; however, psychosocial treatments targeting social cognition are often not available in clinics and there are no current psychopharmacological agents that improve social cognition or social functioning in schizophrenia. Consequently, there has been great interest in oxytocin (OT) as a potential treatment for social cognition in schizophrenia, and as an additive to current psychological approaches. OT stimulates prosocial behavior and antipsychotic-like effects in animals and humans, and there is preliminary evidence supporting OT's role in social cognition in humans. Therefore, the current study explored whether OT can improve social cognition and social functioning in schizophrenia using a six-week, double-blind design. Twenty individuals with schizophrenia were randomized to receive either intranasal OT or a saline placebo solution and completed a battery of social cognitive measures, as well as measures of social functioning, community functioning, neurocognition and psychiatric symptoms. Results showed improvements on self-reported cognitive empathy, deception detection, and global social skills in the OT condition as compared to the PL condition. In addition, post-hoc analyses demonstrated improved identification of intense facial emotions and a reduction in negative symptoms for the OT condition. These preliminary findings indicate OT may help improve certain components of social cognition in schizophrenia. Implications for the treatment of social functioning in schizophrenia and early intervention are discussed.

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AIHQ=Ambiguous Attributions and Hostility Questionnaire

BACS=Brief Assessment of Cognition in Schizophrenia

BSI-A=Brief Severity Index, anxiety items

ER-40=Emotion Recognition-40

IRI=Interpersonal Reactivity Index

LSAS= Liebowitz Social Anxiety Scale

OT=Oxytocin

PANSS=Positive and Negative Symptom Scale

RBANS=Repeatable Battery for the Assessment of Neuropsychological Status

SLOF-P/I=Specific Levels of Functioning Patient and Informant Version

ToM=Theory of Mind

CHAPTER I

Introduction

This study investigated the effects of oxytocin on social cognition in schizophrenia, as well as on community and social functioning. One of schizophrenia's hallmark features is social impairment (Bellack, Morrison, Wixted, & Mueser, 1990), which is related to critical disease-related factors, such as relapse (Sullivan, Marder, Liberman, Donahoe, & Mintz, 1990). Social cognition, our ability to perceive and interpret others' intentions (Fiske & Taylor, 2008), underlies social functioning. Indeed, individuals with schizophrenia show impaired social cognition (Penn, Sanna, & Roberts, 2008) and these impairments are associated with poor social functioning in schizophrenia (Couture, Penn, & Roberts, 2006). Thus, researchers have explored avenues to remediate social cognition. Since pharmacological agents have not appeared to be beneficial in improving social cognition (Harvey, Patterson, Potter, Zhong, & Brecher, 2006), psychotherapeutic approaches have been developed and show promise (Horan, Kern, Green & Penn, 2008). In light of the importance of social functioning in schizophrenia and a paucity of current treatments, there is a need to explore other potential therapeutic approaches, such as oxytocin.

Oxytocin (OT) is a neuropeptide that has been referred to as the "great facilitator of life" (Lee, Macbeth, Pagani, & Young, 2009) because of its role in human social behavior. OT has recently been applied to psychological disorders where social functioning is impaired, such as schizophrenia (Macdonald & Macdonald, 2010); however, there a limited

number of published studies evaluating the effects of exogenous OT on social cognition (Averbeck, Bobin, Evans, Shergill, 2012; Goldman, Gomes, Carter & Lee, 2011; Pedersen et al., 2011) and only one randomized control trial to evaluate daily OT dosing (Pedersen et al., 2011). Additionally, no study has evaluated the effects of OT on social and community functioning. This current study examined OT's role in improving social cognition, social functioning, and community functioning to elucidate the therapeutic potential of OT for schizophrenia.

The introduction will provide the reader with the most relevant background concerning social functioning, social cognition, and oxytocin as they relate to schizophrenia. The introduction begins with a review of social functioning and its relationship to such variables as prognosis and quality of life. Then, a discussion of the processes that underlie social functioning namely, social cognition will be explored. Specifically, the social cognitive domains of emotion perception and theory of mind will be highlighted since current OT research indicates it has a beneficial impact on these areas. Other areas of social cognition, such as empathy, social judgment and attributional style will also be reviewed because OT may theoretically have a beneficial impact on these domains. This will lead to a broad review of oxytocin, followed by a more focused discussion of oxytocin's role in social cognition in healthy controls, and preliminary evidence of its role in psychological disorders, including schizophrenia. The introduction will end with the present study's aims and hypotheses.

Social Functioning in Schizophrenia

Social functioning deficits are a core feature of schizophrenia (Mueser & Bellack, 1998) and independent from other features of the illness such as negative and positive symptoms

(Bellack et al., 2004). Social functioning is a broad term that refers to a variety of socially related behaviors such as interpersonal skills, work and school functioning, and independent living skills (Couture et al., 2006). Specifically, individuals with schizophrenia have shown worse interpersonal skills (Pinkham & Penn, 2006; Sitzer, Twamley, Patterson, & Jeste, 2008) and display fewer prosocial behaviors (Brune, Abdel-Hamid, Sonntag, Lehmkamper, & Langdon, 2009) compared to non-clinical controls. In addition, poor social support (e.g., lack of contact with family and few friends) is related to prognosis and functioning, such as self-care and employment (Erickson, Beiser, Iacono, Fleming, & Lin, 1989; Evert, Harvey, Trauer, & Herrman, 2003).

Social functioning deficits do not appear to be a function of disease onset or chronicity; rather they are evident throughout the course of the illness. Addington et al. (2007) found social functioning deficits throughout the course of the illness including those in the prodrome (i.e., individuals displaying attenuated positive symptoms), and in first and multi-episode psychosis. Social functioning was also associated with quality of life in each of these groups. Supporting the evidence that social deficits are not necessarily a function of disease onset is that attenuated deficits in social behavior are observed in first-degree relatives (Dworkin, Lewis, Cornblatt, & Erlenmeyer-Kimling, 1994; Gibson, Penn, Prinstein, Perkins, & Belger, 2010; Tarbox & Pogue-Geile, 2008). Thus, evidence suggests social functioning could be considered a marker of disease vulnerability and not necessarily a byproduct of disease related variables, such as the effects of stigma, medication or institutionalization.

Researchers have developed a variety of methods to evaluate social functioning in schizophrenia. There are three main approaches to this area of research. First, self-report measures have been developed (e.g., social functioning scale [SFS];Birchwood, Smith,

Cochrane, Wetton, & Copestake, 1990), where participants rate their social functioning. Second, informant reports are widely used where a family member or mental health professional rates the affected family member's social behavior (e.g., The Specific Levels of Functioning Scale [SLOF]; Schneider & Struening, 1983). Both the self-report and informant reports capture overall community functioning, such as daily activities, daily skills, and work skills (Mausbach et al., 2010). Third, performance-based measures, such as role-plays are used to assess social skills, and are thought to capture functional capacity (Mausbach et al., 2010). Role-plays typically involve participants engaging in a videotaped conversation with a confederate and the participants' social skills are later evaluated and rated (Mueser & Bellack, 1998; Patterson, Goldman, McKibbin, Hughs, & Jeste, 2001). Objective measures such as role-plays are a valuable tool for measuring social behavior in light of research suggesting individuals with schizophrenia lack insight into their social skill deficits (Mueser & Bellack, 1998) and more generally have poor metacognitive abilities (Kircher, Koch, Stottmeister, & Durst, 2007). Performance-based tools are also associated with community functioning assessments. Mausbach et al. (2010), for example, assessed individuals with schizophrenia and bipolar disorder with a role-play measure and a community functioning assessment, the SLOF. Better role-play performance was related to both greater residential independence and informant ratings on the SLOF. Therefore, performance-based measures are a valid assessment of real-world functioning and alleviate the potential confound of poor insight and bias found in self-reports.

The aforementioned measures are not unique to schizophrenia research, but are used to evaluate social functioning in other disorders (e.g., Mausbach et al., 2010). While social functioning deficits are observed in a variety of psychiatric disorders (e.g., Autism; Baron-

Cohen & Wheelwright, 2003; e.g., Depression; Erickson et al., 1989; e.g., Bipolar Disorder; Mausbach, et al., 2010), these social difficulties are more compromised and have shown to play a critical role in outcome in schizophrenia. Mausbach et al. (2010) found individuals with schizophrenia had worse functional and community functioning scores compared to individuals with bipolar disorder. Additionally, research evaluating social functioning and schizophrenia has highlighted the importance of this area as valuable in elucidating disease trajectory and as a treatment target. The role of social functioning as a target for early intervention is highlighted by the findings that social functioning is a robust a predictor of disease outcome (Addington et al., 2007; Niendam, Jalbrzikowski, & Bearden, 2009) and a predictor of disease onset (Cannon et al., 2008). Additionally, social functioning, such as availability of acquaintances has been a predictor of outcome in those with chronic schizophrenia (Evert et al., 2003; Erickson et al., 1989) and better social functioning is related to increased therapeutic alliance (Couture et al., 2006). Thus, social functioning is an essential area to target in schizophrenia as it is both related to outcome and relapse.

The relationship between social functioning and outcome has prompted researchers to evaluate treatments targeting social functioning. Since antipsychotics do not appear to improve social functioning (Bellack et al., 2004; Heinssen, Liberman, & Kopelowicz, 2000), a variety of psychological treatments aimed at improving social functioning have been developed and are efficacious at improving social functioning in schizophrenia (Granholm et al., 2005; Kurtz & Mueser, 2008; Roberts & Penn, 2009). Kurtz and Mueser's (2008) meta-analysis of social skills interventions in schizophrenia demonstrated moderate to large effect sizes for performance-based measures (e.g., role plays of social interactions), daily living skills and community functioning. Thus, interventions targeted at social skills demonstrate

social functioning is amenable to improvement; however, while social skills interventions for schizophrenia often include elements to facilitate generalization of skills (Kopelowicz, Liberman, & Zarate, 2006; Kurtz & Mueser, 2008), social interactions may be too nuanced and complex to fully address in social skills training. That is, social skills interventions for schizophrenia tend to focus more of specific skills (e.g., eye contact) but not on the underlying processes that might enhance skill generalization across a variety of social situations.

Social Cognition

One area that has received recent attention as a possible mechanism underlying social deficits in schizophrenia is social cognition. Social cognition refers to our ability to understand others intentions, beliefs, and emotions (Fiske & Taylor, 2008) and has been studied extensively in humans, as well as primates (Silk, 2007). The Social Brain hypothesis is consistent with an evolutionary basis of social cognition, where it is hypothesized that our brains have evolved to navigate complex social interactions and larger brain size is associated with increased social networks in primates (Dunbar, 2009).

Indeed, social cognition is related to social functioning in schizophrenia in that intact social cognition (e.g., the ability to understand what another person is thinking) facilitates social relationships and is related to social functioning (Addington, Saeedi, & Addington, 2006; Baslet, Termini, & Herbener, 2009; Bora, Eryavuz, Kayahan, Sungu, & Veznedaroglu, 2006; Pinkham & Penn, 2006; Zhu, et al., 2007). For reviews see Couture et al. (2006) and Fett et al. (2010). Furthermore, Pinkham and Penn (2006) found social cognition to be the strongest predictor of social functioning in schizophrenia. Similar to social functioning, current antipsychotics do not appear to improve social cognition (Penn et al., 2009). Overall,

these findings suggest that social cognitive processes underlie social functioning and are critical to the ability to effectively interact in the social world.

Although there is no definitive empirical consensus regarding the domains that constitute social cognition, a few domains have been theoretically proposed. Specifically, the major domains of social cognition in schizophrenia include emotion processing, theory of mind, social perception, and attributional style (Green, Olivier, Crawley, Penn, & Silverstein, 2005; Green et al., 2008; Penn et al., 2008). Emotion processing refers to the ability to identify and understand emotions in oneself and others (Green et al., 2008). Emotion processing is utilized in behaviors such as emotion recognition and empathy. Theory of Mind (ToM) is the ability to infer another person's mental or affective state and is critical to effective social functioning (Roncone et al., 2002). Social perception involves the integration of social information to inform judgments made about one's social world; for example the degree to which one may find another trustworthy. Attributions refer to the causal inferences one makes about a situation or event (Bentall, Kaney, & Dewey, 1991; Green, et al., 2008; Kinderman, Kaney, Morley, & Bentall, 1992). As Green et al. (2008) point out, social cognitive abilities are not mutually exclusive, per se, but rather there is a great deal of overlap; for instance, theory of mind may include an affective perspective-taking component—such that it becomes an integration of emotion recognition and theory of mind. Each of the components of social cognition will be discussed in more detail later in the introduction.

The importance of social cognition in improving social functioning is highlighted by the evidence suggesting social cognition accounts for a greater proportion of variance in social functioning compared to neurocognition (Couture, Penn, et al., 2006; Fett et al., 2010; Penn,

Corrigan, Bentall, Racenstein, & Newman, 1997). In a recent meta-analysis, Fett et al. (2010) found that social cognition explained more variance in community functioning compared to neurocognition. Specifically, social cognition explained 16 percent and neurocognition six percent of the variation in functional outcome. The functional outcome variables in their meta-analysis included community functioning (e.g. work and social functioning), social problem solving (e.g., ability to generate solutions to daily social occurrences) and social skills (as measured by role plays). When Fett et al. controlled for potential moderators such as gender, age, illness chronicity, and inpatient status, there was no effect on the relationship between social cognition and functional outcome, although these moderators slightly mitigated the relationship between neurocognition and functional outcome. Fett et al. recommend that more research should evaluate the relationship between social cognition, neurocognition and social skills and social problem solving, since a majority of the studies found in their review focused predominately on community functioning.

In the next section, I will review the specific components of social cognition as measured in schizophrenia research. Specific attention will be paid to areas of social cognition that are most integral to research on oxytocin and social cognition in schizophrenia, namely emotion perception and theory of mind, as they have received the greatest amount of attention in the literature. Furthermore, there is preliminary evidence oxytocin can improve functioning in these areas. Other domains of social cognition that have not received the same amount of attention will be discussed, namely empathy, social perception (e.g., trustworthiness), and attributional style. These domains will be explored since they are theoretically related to oxytocin, and there is preliminary research demonstrating oxytocin can improve these areas of social cognition.

Emotion Recognition

Emotion recognition is well studied in schizophrenia, specifically facial emotion recognition. (For reviews see Chan, Li, Cheung, & Gong, 2010; Kohler, Walker, Martin, Healey, & Moberg, 2009; Marwick & Hall, 2008; Morris, Weickert, & Loughland, 2009). Meta-analyses and narrative reviews indicate individuals with schizophrenia have worse facial emotion perception in schizophrenia compared to healthy controls. Other areas of emotion perception, such as vocal emotion recognition are also impaired (for a meta-analysis see Hoekert, Kahn, Pijnenborg, & Aleman, 2007). Chan et al.'s (2010) meta-analysis found large effect sizes for emotion perception in schizophrenia, which were higher than control tasks such as overall face and age recognition deficits. Additionally, facial emotion recognition deficits appears to be specific to emotionally laden stimuli; for instance (Schneider et al., 2006) found individuals with schizophrenia performed worse on a facial emotion recognition task compared to more difficult non-emotional tasks (e.g., age discrimination). Thus, facial emotion perception does not appear to be a generalized cognitive deficit, but is specific to emotion recognition.

The facial emotion recognition measures are similar across studies. Participants are shown facial stimuli and asked to guess the emotion displayed. One of the first and most widely used measures of facial emotion recognition is the Facial Emotion Identification Task (FEIT; Kerr & Neale, 1993); however the FEIT is limited in ethnicity (i.e., the stimuli are all Caucasian faces), which could be problematic because of evidence of a same-race emotion bias seen in emotion perception in schizophrenia (Pinkham et al., 2008). More recent emotion recognition measures, such as the Penn Emotion Recognition 40 (ER-40) display a variety of ethnically diverse faces that express one of four basic emotions: happy, sad, angry,

fear, as well as neutral faces. The ER-40 has showed high-levels of test-retest reliability in schizophrenia samples and does not show ceiling effects (Carter, Barch, Gur, Pinkham, & Ochsner, 2009), which is often a cited problem in tests of emotion recognition (Kohler & Martin, 2006) measures.

Emotion perception is critical to effective social interactions and overall social functioning. Poor affect recognition is related to worse social functioning in schizophrenia (Addington et al., 2006; Couture, Penn, et al., 2006; Pan, Chen, Chen, & Liu, 2009) and worse interpersonal skills (Pinkham & Penn, 2006). Meyer and Kurtz (2009) found affect perception was a stronger predictor of social skills than neurocognition. Interestingly, emotion perception deficits are not limited to individuals with chronic schizophrenia, but are also seen in individuals experiencing their first-episode (FE) of psychosis (Addington et al., 2006; Edwards, Pattison, Jackson, & Wales, 2001; Pinkham et al., 2005), individuals in the prodrome (Addington, Penn, Woods, Addington, & Perkins, 2008; Addington et al., 2006), and is similarly related to social functioning deficits at these early stages of illness (Addington, et al., 2006). There is also evidence of emotion perception deficits in the unaffected first-degree relatives (Li, Chan, Zhao, Hong, & Gong, 2010).

In addition, negative emotions such as fear and anger appear to be more difficult to identify (Marwick & Hall, 2008; Morris et al., 2009) and could be related to anxiety when looking at faces in schizophrenia (Morris et al., 2009). Additionally, individuals high in negative symptoms have displayed worse emotion perception (Chan, et al., 2010; Strauss, Jetha, Ross, Duke, & Allen, 2010). There are even neurological correlates with emotion misidentification; for example, Gur et al. (2007) found greater amygdalar activation was associated with incorrect identification of angry and fearful faces in individuals with

schizophrenia compared to a healthy control sample, where increased amygdalar activation was related to improved fear identification. In addition, increased amygdalar response to fearful facial stimuli was associated with flat affect.

Aside from disrupted limbic activation, poor emotion recognition is linked to decreased efficiency in scan paths such that individuals with schizophrenia do not attend to critical facial features such as the eye and mouth region (Combs et al., 2008; Morris et al., 2009). Similar restricted scanning of emotion-laden faces is observed in first-degree relatives (Loughland, Williams, & Harris, 2004). Furthermore, interventions targeted at training individuals with schizophrenia to focus attention to critical facial features (i.e., the center region of the face) have shown to be efficacious (Combs, Chapman, Waguspack, Basso, & Penn, 2010).

Theory of Mind

Theory of Mind (ToM) is the ability to infer another person's mental state and is important for effective social functioning (Roncone et al., 2002). Reviews indicate individuals with schizophrenia have poor ToM (e.g., Bora, Yucel, & Pantelis, 2009; Sprong, Schothorst, Vos, Hox, & van Engeland, 2007) and ToM deficits are observed throughout the course of the illness (Bora et al., 2009). Frith (2004) argues that there is heterogeneity in ToM deficits in schizophrenia, such that those with negative symptoms may have a true ToM deficit, and those with predominately positive symptoms have a ToM, but they "over-mentalize." That is, Frith argues that individuals high in positive symptoms (e.g., paranoia) have a theory of mind and an ability to hypothesize about another's intentions, but they make erroneous conclusions (e.g., paranoid thinking such as the other person is thinking about a

plan to harm them). Frith notes this difficulty with mentalizing naturally leads to social discomfort and social withdrawal.

The construct of ToM has been divided into social perceptual and social cognitive components (Sabbagh, 2004), as well as affective and cognitive components (Shamay-Tsoory, Shur, Barcai-Goodman, et al., 2007). The cognitive components of ToM are thought to depend on underlying cognitive processes, which require mentalizing about other's *beliefs* and *intentions*. Social perceptual ToM relies on more automatic perceptual abilities, and involves mentalizing about the *emotional* states of others. The affective component of ToM similarly requires mentalizing about emotional states (i.e., affective perspective-taking) versus beliefs (Shamay-Tsooray et al., 2007). There is neurological research supporting these distinctions between ToM components; for example different areas of the brain are evoked when performing social perceptual versus cognitive ToM tasks (Shamay-Tsoory, Aharon-Peretz, & Levkovitz, 2007). Additionally, individuals with schizophrenia have shown worse performance on the affective component of ToM as compared to the cognitive component (Shamay-Tsoory, Shur, Barcai-Goodman, et al., 2007). Thus, it is prudent to consider and evaluate ToM as a multidimensional rather than a unitary construct.

There are well-established ToM measures, which are routinely applied to schizophrenia samples. The cognitive ToM measures generally tap into the ability to successfully complete picture sequencing tasks and answer questions about the beliefs of the characters in the stories. These tasks evaluate higher orders of ToM (e.g., second order theory of mind, where a participant is asked to imagine what another person is thinking about someone else). One frequently used picture-sequencing measure, The Brune Task (Brune, 2003), involves arranging a series of cards into a logical sequence and then answering

questions about the characters' mental states. Individuals with schizophrenia have shown worse performance on cognitive ToM measures (Brune, 2005) compared to healthy controls. Although there is clearly a cognitive load to such tasks, differences between schizophrenia and healthy controls remain on ToM tasks even after controlling for cognitive variables, such as executive functioning (Brune, 2005).

Social perceptual and affective ToM measures involve perceiving the affective states of others. Although social perceptual and affective ToM converges on emotion perception, research indicates these ToM components are independent of general emotion recognition (Kington, Jones, Watt, Hopkin, & Williams, 2000). One highly cited social perceptual and affective measure, The Reading the Mind in the Eyes Test or the Eyes Test (Baron-Cohen, Wheelwright, Hill, Raste, & Plumb, 2001) is often used in the schizophrenia literature (e.g., Bora, et al., 2006; Bora, Gokcen, & Veznedaroglu, 2008; de Achaval, et al., 2010; Shur, Shamay-Tsoory, & Levkovitz, 2008). Compared to healthy controls, individuals with schizophrenia perform worse on the Eyes Test (Bora et al., 2006; de Achaval et al., 2010; Irani et al., 2006; Kelemen et al., 2005; Kelemen, Keri, Must, Benedek, & Janka, 2004). ToM deficits on the Eyes Test are observed in first-episode psychosis (Kettle, O'Brien-Simpson, & Allen, 2008) and in unaffected first-degree relatives (Irani et al., 2006). Kelemen et al. (2005) tested ToM in remitted medicated and unmedicated participants and found no difference in performance between these groups. Thus, it seems ToM deficits are not a result of years of illness or medication, and could be considered a disease-related endophenotype.

Some studies have found a significant relationship between worse performance on ToM tasks and increased negative symptoms (Kelemen, et al., 2005). Shamay-Tsoory, Shur, Barcai-Goodman et al. (2007) found negative symptoms were more closely related to

performance on an affective ToM measure than a cognitive ToM measure. Interestingly, the Eyes Test and negative symptoms were found to be the most robust predictors of social functioning in Bora et al. (2006), although negative symptoms and the Eyes Test were not correlated with one another. Bora et al. suggest negative symptoms and ToM may have separate yet significant associations with social functioning. These findings are consistent with those who have found ToM is associated with social skills (Brune, 2005; Couture et al., 2006); and others who found ToM to be one of the social cognitive variables most related to functioning (Fett et al., 2010).

Empathy

Empathy is another area of social cognition that has received recent attention in schizophrenia research (Lee, Farrow, Spence, & Woodruff, 2004). Leiberg and Anders (2006, p. 419) define empathy as the "ability to accurately perceive and understand another person's emotions and react appropriately." Similar to ToM, empathy taps into the broader affective (i.e., an emotional experience) and cognitive (i.e., affective perspective taking) domains of emotional processing (Decety & Jackson, 2004). Empathy is related to social functioning in schizophrenia (Baslet et al., 2009) and less empathy is associated with negative symptoms (Bora et al., 2008; Shamay-Tsoory, Shur, Barcai-Goodman, et al., 2007).

The most widely used measure in the empathy and schizophrenia literature is the Interpersonal Reactivity Index (IRI; Davis, 1983). The IRI is a 28-item self-report measure, which uses a five-point likert scale tapping into the affective and cognitive dimensions of empathy. The IRI comprises four subscales: Empathic Concern (e.g., feelings of compassion and concern for others), Perspective Taking (e.g., taking the viewpoint of other people), Fantasy (e.g., a tendency to relate to characters in movies and books) and Personal Distress

(e.g., anxiety as a result of other people's distress).

Individuals with schizophrenia have demonstrated empathic difficulties, such as lower empathic concern on the IRI compared to healthy controls (Shamay-Tsoory, Shur, Harari, & Levkovitz, 2007), and lower self-reported affective perspective-taking ability as compared to healthy controls (Haker & Rossler, 2009; Montag, Heinz, Kunz, & Gallinat, 2007; Shamay-Tsoory, Aharon-Peretz, et al., 2007). The majority of the studies have found increased self-reported personal distress in response to other's emotional experiences (Derntl, et al., 2009; Haker & Rossler, 2009; Montag, et al., 2007). Thus, there is some evidence that individuals with schizophrenia appear able to self-reflect on their empathic deficits; however, Derntl et al. (2009) found that empathic deficits were more impaired when using behavioral tasks of empathy (i.e., they implemented a task where participants chose the emotion that a person would most likely feel in a variety of scenarios) as compared to the self-report measure. Derntl et al. (2009) argue that while self-report measures provide some information about empathy, using only self-report measures of empathy is limiting. This suggests that self-reported empathy in schizophrenia should be supplemented with other measurement strategies.

Another way empathy has been studied is via imitative paradigms (i.e., where participants' ability to mimic another's behavior is assessed). These paradigms are based on research demonstrating that simulation of other's emotional states is a mechanism for feeling empathy and demonstrating concern to others (Decety & Jackson, 2004). Individuals with schizophrenia show significantly lower imitative abilities compared to healthy controls (Haker & Rossler, 2009; Park, Matthews, & Gibson, 2008). And, decreased contagion behavior has been related to decreased levels of self-reported empathy on the IRI (Haker &

Rossler, 2009).

Thus, there is evidence of empathic deficits in schizophrenia, and greater levels of distress in response to others' emotional states are experienced in this clinical population; however, there appears to be some indication that self-report measures of empathy are limiting when used in isolation and without other measurement approaches. Given empathy's role in forging relationships with others and the evidence for disrupted empathic processing in schizophrenia, this is a valuable area to assess further and perhaps target in treatment.

Social perception: Evaluation of trustworthiness

Social perception is another area of social cognition underling social functioning. Social perception involves using verbal and nonverbal information to make inferences or judgments about social information (Green et al., 2005). Social perception is a broad domain that includes a variety of social inferences one may make, including inferences about a person, situation, or social role based on the available social cues. As Green et al. (2005) explain, social perception converges on emotion perception, but the focus is slightly different; for example an emotion perception task may require one to indicate how someone feels, whereas a social perceptual measure may require one to infer what series of events would have lead a person to feel a particular way.

Individuals with schizophrenia have shown social perceptual abnormalities (Baas, van't Wout, Aleman, & Kahn, 2008; Couture, Penn, Addington, Woods, & Perkins, 2008; Penn, Ritchie, Francis, Combs, & Martin, 2002). Specifically, Penn et al. (2002) found that individuals with schizophrenia did not use contextual cues (e.g., the title of social scenes) in making social judgments (e.g., correctly sequencing the social scenes). Furthermore, failure to use contextual cues was related to impaired social behavior on the ward, such as social

competence and social interest in Penn et al. (2002). Indeed, poor social perception is related to a variety of functional outcomes, such as worse social problem solving (Couture et al., 2006) and social perception appears to mediate the relationship between neurocognition and functional outcome (Couture et al., 2006). This suggests that social perception is an integral component of everyday functioning.

There are a variety of social perceptual measures; however, for the purpose of the current study, I focused on one measure that is particularly pertinent to oxytocin research, namely the Trustworthiness Task (Adolphs et al., 1998). As will be discussed later, trustworthiness judgments are influenced by intranasal oxytocin (Kosfeld, Heinrichs, Zak, Fischbacher, & Fehr, 2005) and oxytocin levels seem to be related to trustworthiness in schizophrenia (Keri, Kiss, & Kelemen, 2009). Overall, trustworthiness tasks require individuals to assess the level of trustworthiness of a series of facial stimuli (i.e., the degree to which they either trust or distrust the face shown). The Trustworthiness Task (Adolphs et al., 1998) displays facial stimuli where participants rate trustworthiness on a scale from negative three (very untrustworthy) to positive three (very trustworthy). Making such trustworthiness judgments not only requires immediate perception of the stimuli, but also accessing past experiences with people or situations similar to the presented stimuli.

On trustworthiness measures, some have found a bias to rate untrustworthy faces (i.e., faces rated as untrustworthy by healthy controls) as trustworthy in schizophrenia (Bass et al., 2008; Couture et al., 2008). Additionally, this bias is not better accounted for by poor facial recognition (Bass et al., 2008). Although it is somewhat surprising that untrustworthy versus trustworthy faces are perceived differently than healthy controls in individuals with schizophrenia, some have noted this could be related to fact that positive affect is easier to

detect (Bass et al., 2008). Additionally, similar social judgment biases have been observed in first-degree relatives (Bass et al., 2008) and individuals in the schizophrenia prodrome (Couture et al., 2008). Such findings indicate that social perception is another area of social cognition that appears to be trait and not state-related.

It should be noted that some have also found a bias in rating the normed trustworthy versus untrustworthy faces (Pinkham, Hopfinger, Pelphrey, Piven, & Penn, 2008a; Pinkham, Hopfinger, Ruparel, & Penn, 2008b) particularly for subgroups of individuals with predominately paranoid symptoms. Pinkham et al. (2008a) and Pinkham et al. (2008b) found that individuals with predominately paranoid symptoms rated faces as more untrustworthy than participants with fewer positive symptoms and healthy controls. Additionally, Pinkham et al. (2008a) found reduced amygdalar activation in the paranoid schizophrenia sample when rating untrustworthy faces as compared to healthy controls and the non-paranoid schizophrenia sample, and reduced amygdalar activation was related to worse social functioning. These findings are consistent with studies assessing trustworthiness judgments in individuals with bilateral amygdala damage (Adolphs et al., 1998), where trustworthiness biases are also observed. Pinkham et al. (2008a) hypothesize that abnormal amygdalar activation may be related to impaired trustworthiness judgments in schizophrenia.

Related research has found poor social perception in individuals high in persecutory delusions (Haut & Macdonald, 2010). Haut and MacDonald (2010) did not find differences in trustworthiness ratings when comparing a schizophrenia and healthy control sample, but patients higher in persecutory delusions were less likely to use social information, such as attractiveness in assessing trustworthiness compared to healthy controls and patients lower in

persecutory delusions. This is consistent with Penn et al. (2002) who also found individuals with schizophrenia did not use contextual cues in forming social judgments.

Attributional Style

Lastly, attributional style was investigated in the current study. Attributional style refers to the reasons one makes for the causes of a situation, and is widely studied in a variety of psychological disorders (e.g., Depression; Alloy, Peterson, Abramson, & Seligman, 1984; Joiner, 2001). Studies have shown that healthy controls tend to demonstrate what is referred to as a self-serving bias. That is, causal attributions tend to be "self-serving" in that negative life events are attributed to external factors (e.g., "I failed the exam because he is not a good teacher"), while positive life events are attributed to internal factors (e.g. "I passed the exam because I am proficient in this subject matter") (Campbell & Sedikides, 1999).

Attributional style has been of great interest to schizophrenia researchers because of its association with symptoms, such as paranoia (An et al., 2010; Bentall, Corcoran, Howard, Blackwood, & Kinderman, 2001; Martin & Penn, 2002). Individuals with increased paranoia are more likely to demonstrate an exaggeration of the self-serving bias (Bentall et al., 2001). Furthermore, when external attributions are broken down into personal (e.g., an *individual* purposefully caused an event) and situational (e.g., a situation was caused accidentally) factors, individuals with schizophrenia show a tendency towards external-personal attributions (i.e., "personalizing bias"; Kinderman & Bentall, 1997), which may function to preserve one's self-image (Bentall et al., 2001). A reliance on external attributions is related to persecutory delusions as it reinforces beliefs that others are causing one harm and cannot be trusted (Bentall et al., 2001; Kinderman & Bentall, 1997). Indeed Aakre, Seghers, St-Hilaire, & Docherty (2009) found paranoid patients were more likely to use external-personal

attributions in explaining negative events compared to patients who did not currently have paranoid delusions. Lastly, as has been noted earlier, social cognitive domains are not mutually exclusive but have a degree of overlap. Bentall and Kinderman (1998) have argued that poor ToM interferes with the ability for individuals with schizophrenia to make situational attributions. This assertion is supported by empirical data; for example, Randall, Corcoran, Day, & Bentall (2003) found that ToM was a predictor of making more external attributions in schizophrenia. Therefore it seems that improving ToM could also have an effect on attributional style in schizophrenia.

There are a variety of measures of attributional style in schizophrenia (e.g., the Ambiguous Intentions Hostility Questionnaire, Combs et al. 2007; the Internal Personal and Situational Attributions Questionnaire; Kinderman & Bentall, 1996; the Attributional Style Questionnaire, Peterson et al., 1982). These measures present participants with hypothetical scenarios where they have to discern the causes of the events. On the Attributional Style Questionnaire (ASQ; Peterson et al., 1982) and the Internal Personal and Situational Attributions Questionnaire (IPSAQ; Kinderman & Bentall, 1996), participants rate whether the event was caused by them or another person in the scenario (external-internal dimension). The IPSAQ further evaluates whether the cause is perceived as external-personal or external-situational. Studies have shown discrepancies between the ratings of participants and independent raters (e.g., individuals with schizophrenia have indicated their causes of negatives events are related to internal factors, while independent raters score them as external attributions; Martin & Penn, 2002; Randall et al., 2003). In addition to such discrepancies, there have been issues concerning the reliability and validity of these instruments (Bentall, et al., 2001).

A recent measure, the Ambiguous Intentions Hostility Questionnaire (AIHQ; Combs et al. 2007) has sound psychometric properties and is a promising new measure of attributional style in schizophrenia. Similar to other attributional measures, participants indicate the causes of a variety of situations that have occurred to them. They also indicate what they would do about the situations. The situations, however, vary in the intentionality, where some are accidental, intentional or ambiguous. Participants rate whether the person acted a certain way to them on purpose, how angry it would make them feel and how much they would blame the other person (these three ratings yield a "blame score"). Independent raters score the degree of hostility in the causal responses and aggression in how they would approach the scenario. The AIHQ is unique in that it assesses hostility and includes ambiguous situations, which are not found on the ASQ or IPSAQ. It is critical to assess hostility in schizophrenia because individuals with paranoia have shown to identify hostility in situations where hostility is not evident (Combs, et al., 2009) and the use of ambiguous situations rather than just intentional events is more likely to tap into social cognitive biases. Indeed, individuals who are high in paranoia are more apt to perceive threat in ambiguous situations (Combs et al., 2007). The inclusion of ambiguous situations also bolsters the AIHQ's external validity as many of the daily interactions that one experiences are ambiguous, and do not have definitive closure (e.g., people laughing as you walk by). Thus, attributional style is more comprehensively measured by evaluating not only locus of control, but hostility and aggression in ambiguous situations.

Individuals with schizophrenia, particularly those with greater persecutory delusions, have shown a hostility bias as measured by the AIHQ (Combs et al., 2009). In Combs et al. (2009), the attributional style in individuals high in persecutory delusions (PDs) was

compared to those without PDs. The PD group demonstrated a personalizing bias such that they had more hostility and blame attributions to ambiguous situations and hostility bias was a significant predictor of paranoia. The AIHQ appears sensitive enough to detect treatment effects in schizophrenia; for example following eighteen weeks of Social Cognitive Interaction Training (SCIT), participants had significantly lower hostility and blame subscale scores on the AIHQ compared to before treatment, as well as compared to individuals in the treatment control group (Combs et al., 2007).

Consistent with other areas of social cognition, the aforementioned attributional biases are evident throughout the course of the illness. Similar attributional style has been observed in the prodrome and first-episode (FE) psychosis (An et al., 2010). Interestingly, in An et al. (2010), FE and prodromal individuals both showed a hostility bias on the AIHQ compared to healthy controls, and the prodromal individuals had a significantly higher blame bias (i.e., blaming other for negative outcomes) than the FE group and healthy controls. In the FE and prodromal groups, hostility bias was related to paranoia, and blame was related to level of paranoia in the prodromal group. Further support for attributional style as a vulnerability marker comes from the research not only showing an external attributional style in first-degree of individuals with schizophrenia, but also that it is a predictor of future psychosis onset (Frenkel, Kugelmass, Nathan, & Ingraham, 1995).

Less work has been conducted on the relationship between social functioning and attributional style, but there is tentative data on this relationship (Couture et al., 2008); for example, external attributional style has been linked to aggressive behavior in inpatients with schizophrenia (Waldheter et al., 2005). Lysker et al. (2004) found that attributional style, specifically perceiving life events as unstable and unpredictable, was related to worse social

functioning in individuals with schizophrenia. Lastly, a personalizing bias is related to insecure attachment styles in schizophrenia (Donohoe, et al., 2008). In light of the evidence that attributional style contributes to paranoia, and is possibly related to social functioning and ToM, it is certainly a promising area to target in treatment.

Summary and Implications of Social Cognition and Schizophrenia Research

In summary, individuals with schizophrenia have marked difficulties in social functioning, which are associated with outcome and relapse. Due to social functioning's impact on schizophrenia, it is essential to evaluate more proximal underlying processes, such as social cognition. Individuals with schizophrenia have shown deficits and biases in a variety of social cognitive domains including emotion identification, theory of mind, empathy, social perception, and attributional style. Social cognitive deficits are observed across the course of the illness, as well as in first-degree relatives. Therefore, these deficits are not necessarily a byproduct of medication or disease chronicity, but are more likely associated with disease vulnerability. In addition, social cognitive impairments in schizophrenia are strongly related to social functioning beyond other variables such as neurocognition. These findings underscore the importance of social cognition as a treatment target.

A variety of efforts have been put forth to improve social cognition. While pharmacological approaches have not shown efficacious in remediating social cognitive deficits (Harvey et al., 2006; Penn et al., 2009), psychosocial approaches have been developed with the ultimate goal of improving social functioning (Green et al., 2008; Horan et al., 2008; Kern et al., 2009). Kern et al.'s (2009) review of psychosocial approaches in schizophrenia highlights the benefits of treatments that focus on social cognition. However,

they also point out there are no current medications that similarly improve social cognition or social functioning in schizophrenia. As Kern et al. suggest, pharmacological agents can be useful for initiating engagement in psychotherapy and augmenting its benefits. Additionally, some facilities may not have the resources to properly train clinicians in psychological approaches for individuals with schizophrenia, so pharmacological approaches targeting social cognition could be of great utility in community clinics. Thus, there is a need for pharmacological agents that could be used to facilitate improvements in social cognition and social functioning. One such pharmacological agent is oxytocin. The next section will provide an overview of oxytocin, as well as evidence of its role in social behavior and its potential use in schizophrenia. This review will include research in non-human mammals, humans, and preliminary evidence of its effects on social cognition in non-clinical populations and clinical populations, including schizophrenia.

Oxytocin

Oxytocin: Background and Basic Research

Oxytocin (OT) is a neuropeptide associated with social behavior, such as empathy, attachment, trust and affiliation (Lee, Macbeth, Pagani, & Young, 2009). OT is found throughout the central nervous system and is highly concentrated in the paraventricular and supraoptic nuclei of the hypothalamus (Carter, Boone, Pournajafi-Nazarloo, & Bales, 2009). OT is most commonly known for its uterine contraction and lactation properties (Insel, Young, Wang, 1997) and is implicated in a variety of social behaviors, such as maternal behavior (Pedersen, Ascher, Monroe, & Prange, 1982), emotion recognition, understanding other's mental states, empathy, social affiliation, as well as other behaviors such as anxiety and depression (Lee et al., 2009). There also appears to be gender differences in OT levels,

where some have found that OT expression is higher in females (Carter, 2007; Yamasue, Kuwabara, Kawakubo, & Kasai, 2009).

Animal models of OT, specifically prairie voles, provide much of what we know about the effects of OT on behavior (Carter, Williams, Witt, & Insel, 1992). Prairie voles are often used as models of human social behavior because they are monogamous and display biparental behavior patterns (Carter et al., 2009; Carter et al., 1992). Animal research has shown that levels of OT are related to maternal behavior, where increased OT expression throughout the rat brain is related to increased maternal behavior, such as grooming pups (Lee et al., 2009). Increased OT in plasma is even observed in expectant mice fathers during pregnancy (Gubernick, Winslow, Jensen, Jeanotte, & Bowen, 1995). In prairie voles, OT is involved in mate bonding and increased social contact and exploration of new situations (Carter, et al., 1992).

Interestingly, early experiences (i.e., prenatal and postnatal stages) have implications for later parenting and OT levels (e.g., Carter, Boone, et al., 2009; Pedersen & Boccia, 2002). In rats, prenatal stress is related to OT levels in offspring (Carter et al. 2009). Additionally, Carter et al. (2009) discuss a series of studies where prairie voles were disrupted after the offspring were born (e.g., the voles were moved to different cages in a cup). This disruption was related to later decreased levels of OT in the male offspring, and decreased parental behavior. When OT was directly manipulated in the postnatal stage, such that newborn voles were given either OT or an OT antagonist, the OT males had more pair bonding; whereas, the OT antagonist voles had decreased parental behavior (e.g., not attending to vole pups). Critically, Carter et al. (2009) note that the effects of the OT antagonist and high postnatal family disruption can be reversed; for example, when the voles who were administered the

OT antagonist or whose postnatal experience was disrupted were given OT later in life, they displayed increased social behavior (e.g., increased parental behaviors). While the animal research has provided the scientific community with strong evidence of the role of OT in behavior, the effects on human social behavior and bonding remain mostly unanswered (Lee et al., 2009).

OT and Social Behavior in Humans

Increasingly, researchers are beginning to clarify how the animal OT research translates to human social behavior. OT is related to reducing depressive (Gordon, et al., 2008) and anxious (Heinrichs, Baumgartner, Kirschbaum, & Ehlert, 2003) symptoms in humans. In fact, OT has demonstrated a robust and consistent relationship with stress and anxiety (Lee et al., 2009). OT's mediating effects of stress is supported by evidence that OT is released in the central nervous system (CNS) and peripheral system when humans are stressed (Neumann, Kromer, Toschi, & Ebner, 2000). Additionally, lactation in women is associated with an increase in OT and decrease in the stress hormones adrenocorticotropin (ACTH) and cortisol (Heinrichs, von Dawans, & Domes, 2009). OT has also appears to augment the stress-reducing effects of social support (Heinrichs et al., 2003). Heinrichs et al. (2003) found that individuals administered intranasal OT and given social support during a stress paradigm (giving an impromptu job interview) showed the greatest reduction in stress hormone levels compared to those given an intranasal placebo and without social support, as well as those given the placebo and with social support present during the stress paradigm. These results indicate OT is related not only to anxiety-reduction, but also with increasing the anxiolytic effects of social relationships.

Aside from the antidepressant and antianxiety effects in healthy controls, underlying social cognitive processes are related to OT. A recent review by MacDonald and MacDonald (2010) summarizes the evidence that OT improves social cognition in healthy controls. Specifically, increased levels of OT are associated with increased trust (Kosfeld et al., 2005), correct emotion identification (Domes, et al., 2010) and improved mentalizing (Domes, Heinrichs, Michel, Berger, & Herpertz, 2007) in healthy control samples (Lee et al. 2009).

It should be noted the relationship between OT and emotion identification is somewhat complex. Some have found OT is related to improved emotion recognition for all emotions in healthy control samples (Domes, Heinrichs, Glascher, et al., 2007), while others have found OT is related to improved emotion recognition for specific emotions (Di Simplicio, Massey-Chase, Cowen, & Harmer, 2009; Guastella, Carson, Dadds, Mitchell, & Cox, 2009). While Di Simplicio et al. (2009) did not find OT improved overall emotion accuracy, they did find OT was related to an emotion response bias. Specifically, the OT group was significantly less likely to rate neutral faces with a negative emotion (i.e., neutral faces were less likely categorized as sad or disgusting), and opted to rate them with a positive emotion (e.g., happy). Guastella et al. (2009) found intranasal OT increased recognition of angry faces, as well as increased gaze at the angry facial stimuli. Fischer-Shofty, Shamay-Tsoory, Harari, & Levkovitz (2010) similarly found OT improved identification of only one emotion, namely fear. Improvements in fear recognition as a function of OT have supporting neurological correlates (Kirsch et al., 2005). Kirsh et al. (2005) found reduced amygdalar response in participants given intranasal OT when they were shown fearful faces. It appears OT may have a particular role in regulating fear recognition and response. This is interesting given accurate fear recognition has been linked to better social functioning. Marsh, Kozak, &

Ambady (2007), for example, found fear recognition was the best predictor of social behavior in a healthy control sample. Therefore, it is necessary to evaluate OT's impact on specific emotions, such as fear and anger, as opposed to evaluating emotional accuracy in general.

In addition to emotion recognition, OT has been related to ToM in healthy controls. Domes, Heinrichs, Michel, et al. (2007) found that OT was related to increased performance on the Eyes Test. Specifically, performance improved on the more difficult Eyes Test items (determined by median of item difficulty from a pilot study). One mechanism that may mediate the positive effects of OT on mentalizing is increased attention to critical facial features, such as the eye region. Indeed, Guastella, Mitchell, and Dadds (2008) found a single dose of OT was related to increased gaze to the eye region of human faces in a healthy control sample. This is consistent with the attention training research in schizophrenia, where emotion perception has shown improvements following instruction to attend to the eye regions of faces (Combs et al., 2010).

The effects of OT extend to social perception, specifically trust in others. Increased trust has been repeatedly observed in healthy controls administered intranasal OT (Kosfeld et al., 2005). Kosfeld et al. (2005) found participants administered a single dose of intranasal OT gave more money to another participant during a trust paradigm. Interestingly, when a risk paradigm was implemented (same as the trust paradigm but without the social component), there were no differences between the OT and placebo group in the amount of money transferred. Therefore, OT may not be related to reciprocity in general, but more specifically with increased trust. Perhaps the trust is facilitated by improved ToM and

emotion perception, such that one is more apt to trust another if they can more accurately perceive their cognitive and affective states.

There has also been research looking at the effects of intranasal OT on empathy in humans, which is unsurprising given the association between OT and increased feelings of bonding (Carter et al., 1992). Hurlemann et al. (2010) found intranasal OT improved emotional, but not cognitive empathy. In Hurlemann et al.'s study, OT increased emotional empathy in men to levels comparable to the women in their sample, which were significantly different before the intranasal OT dose. Hurlemann et al. hypothesize that cognitive and emotional empathy may have different neurological underpinnings, where emotional empathy is related to amygdalar functioning. Their results are somewhat inconsistent with research showing OT improves ToM, since cognitive empathy is closely related to ToM; however, Hurlemann et al.'s assessment of cognitive empathy involved social scenes where participants were asked to guess how the people were feeling in the scenes (i.e., participants could not directly see the faces of the individuals in the scenes). This is in contrast to the Eyes Test where the stimuli are the eye regions of faces and participants stare directly at the stimuli. Perhaps participants in Hurlemann et al.'s study did not improve on the cognitive empathy measure because they could directly see the faces and thus were not able to discern the mental states. Clearly more research is needed to elucidate OT's role in empathic processes, but this preliminary research suggests it may indeed have an impact on it.

Given OT's relationship with social cognition, it would reason that OT is associated with social functioning in humans. One study found that intranasal OT improved positive social behavior (e.g., eye contact, validation, non verbal positive behavior) in married couples (Ditzen et al., 2009). OT may also strengthen the processes underlying social

behavior, namely social cognition, and thereby improve social functioning. Of course, the directionality and relationship between OT and social behavior is unknown; for instance, it is possible that the relationship is bi-directional in that social withdrawal could lead to decreased social relationships and a reduction in OT. Lower OT levels, in turn, may have a deleterious impact on social cognitive processes, such as emotion perception, and positive social behavior (i.e., social skills). Such a transactional relationship is supported by OT's association with perceived reward in social interactions (Bell, Nicholson, Mulder, Luty, & Joyce, 2006). That is, lower levels of OT are related to not finding social interactions rewarding. Lack of social reinforcement may prevent individuals from practicing social skills and lead to further impairments in social functioning.

OT in Schizophrenia and Other Clinical Populations

The role of oxytocin in psychiatric disorders has been evaluated in light of the evidence of its anxiolytic, antidepressant (Bell et al., 2006; Ozsoy, Esel, & Kula, 2009) and antipsychotic effects (Caldwell, Stephens, & Young, 2009; Feifel, Shilling, & Belcher, 2012), as well as the aforementioned impact OT appears to have on underlying social cognitive processes. In fact, there has been a recent surge in reviews of OT's role in psychiatric disorders (Bartz, Zaki, Bolger & Ochsner, 2011, Lee et al., 2009; Macdonald & Macdonald, 2010; Marazziti & Catena Dell'osso, 2008). The reviews highlight the predominance of research investigating OT in animal models and healthy controls and indicate there is a need for more research in psychiatric populations, particularly disorders where social behavior is severely compromised such as schizophrenia. Macdonald and Macdonald (2010) discuss the therapeutic implications for clinical populations and the preliminary evidence of OT's therapeutic effects in disorders such as schizophrenia and

autism. Macdonald and Macdonald (2010) argue OT's relevance to a variety of psychiatric disorders does not diminish its utility; rather social relations are frequently affected in psychological disorders, so it reasons OT can be applied to multiple disorders.

Abnormal OT levels have been observed in schizophrenia as compared to healthy controls (Beckmann, Lang, & Gattaz, 1985; Goldman, Marlow-O'Connor, Torres, & Carter, 2008). OT has also demonstrated antipsychotic properties (Bakharev, Tikhomirov, & Lozhkina, 1986; Bujanow, 1974; Caldwell et al., 2009; Feifel et al., 2010; Pedersen et al., 2011) and shown to restore Prepulse Inhibition (PPI; Feifel et al., 2012; Feifel & Rezza, 1999). PPI is a measure of sensorimotor gating, where a reduced startle response to a stimulus is observed when it is preceded by a weaker stimulus. Individuals with schizophrenia display a decreased PPI response and antipsychotics reverse the disrupted PPI seen in schizophrenia (Feifel et al., 2012; Feifel & Rezza, 1999). Interestingly, Feifel et al. (2012) found that OT could similarly restore PPI in rat models of psychosis, which is consistent with the effects of antipsychotics.

Earlier studies (e.g., Bakharev et al., 1986) found some of the first evidence OT could reduce psychotic symptoms, as well as other symptoms such as anxiety in individuals with schizophrenia. In one treatment trial, Bakharev et al. (1986) found intranasal OT was related to decreased negative symptoms (e.g., apathy). Two recent trials have similarly found OT reduces symptoms in schizophrenia (Feifel et al., 2010; Pedersen et al., 2011). Feifel et al. (2010) conducted a three-week, cross-over trial; they administered 20 international units (IUs) of OT for the first week and 40 IUs of OT for the last two-weeks of the trial. They found OT was related to an overall reduction of psychotic symptoms. Interestingly, the treatment effects for positive and negative symptoms were most prominent at the three-week

study visits as compared to the two-week visits. In Pedersen et al.'s (2011) randomized control trial, they found significant reductions in a variety of symptoms (positive, general, anxiety) and a trend reduction in negative symptoms after two-weeks of 24 IUs of intranasal OT. These studies suggest OT has therapeutic implications of for the treatment of schizophrenia-related symptoms.

However, the majority of the OT research has focused on OT's amelioration of the *symptoms* of schizophrenia. Less attention has focused on targeting social cognitive processes, which is surprising in light of the animal and healthy control research linking OT with social cognition (Macdonald & Macdonald, 2010). In the OT and social cognitive research that does exist, autism has been one of the most studied disorders. In fact researchers have begun to explore abnormalities in genes responsible for OT expression in autism (Lee et al., 2009). Lower levels of OT plasma have been found in autism, and there is preliminary evidence intranasal OT can improve affect recognition in autism (Yamusue, 2009). Guastella et al. (2010) found a single dose of intranasal OT in autism spectrum disorders improved ToM as measured by performance on the Eyes Test. OT has also shown to reduce the repetitive, self-stimulating behaviors often observed in autism (Hollander et al., 2003). Overall, the autism literature is promising and suggests that OT can be applied to other populations where social cognition is impaired, such as schizophrenia.

Autism and schizophrenia are often compared because of their similar social cognitive deficits (Couture et al., 2010), and psychological treatments targeting social cognition in schizophrenia, such as social cognition and interaction training (SCIT; Roberts & Penn, 2009; Roberts, Penn, Labate, Margolis, & Sterne, 2010), have previously been adapted to autism (Turner-Brown et al., 2008). Thus, it is theoretically reasonable to apply

OT to social cognition in schizophrenia. Researchers have only begun to postulate about the potential benefits of OT in remediating social cognitive deficits in schizophrenia. Rosenfeld, Lieberman, & Jarskog's (2010) recent review paper discusses OT and social cognitive research, as well as hypothesize that OT can make a significant contribution to our understanding of social cognition in schizophrenia. There have even been a few empirical studies looking at the relationship between OT and social cognition in schizophrenia. In one study, low levels of OT in schizophrenia were associated with decreased emotion perception accuracy (Goldman, Marlow-O'Connor, Torres, & Carter, 2008). Keri et al. (2009) found significantly lower OT levels in those with schizophrenia compared to healthy controls after a trust interaction (writing a secret on a piece of paper and presenting it to the tester). Keri et al. additionally found that low levels of OT were related to negative symptoms and were not related to cognitive functioning or medication.

There have only been three trials evaluating the effects of exogenous OT on social cognition in schizophrenia; two of these have focused on emotion recognition (Averbeck et al., 2012; Goldman et al., 2011) and the other (Pedersen et al., 2011) examined social perception and theory of mind. Averbeck et al. (2012) used a placebo-controlled, cross-over trial to assess the effects of OT on emotion recognition in schizophrenia; specifically, half of the participants first received either OT or PL and then came back for testing a week later and received their second dose of either OT or PL (since they used a cross-over design, participants only received one 24 IU OT dose). Averbeck et al. found overall improvement in emotion recognition and a trend towards significantly improved fear recognition using a subset of Ekman's faces. Goldman et al. (2011) examined multiple OT doses (2 total doses) in a subgroup of individuals with schizophrenia (e.g., polydipsic). Participants received 2

different doses of OT and a placebo three days apart (10 and 20 IUs of OT) and completed the Ekman facial recognition task at each time point. In addition to identifying the emotions displayed, they rated the intensity of the emotions (absent, present, intense). Goldman et al. found that the 20 IU dose lowered intensity ratings in the polydispsic group. In addition, they found that the higher OT dose (20 IU), but not the lower dose (10 IU), increased emotion recognition accuracy. Specifically, the improvements in their study were found for fearful faces in the polydipsic schizophrenia sample. In fact, they found that 10 IUs actually decreased affect recognition in all participants with schizophrenia.

In Pedersen et al.'s (2011) randomized-control trial, participants received daily OT for two weeks and completed a social cognitive battery at baseline and two weeks. Results showed significant improvements on second order false belief ToM (i.e., the ability to discern what an individual is falsely thinking about another's thoughts or intentions) as measured by the Brune Task and a trend towards rating untrustworthy faces (i.e., faces rated as untrustworthy by a normative sample) as trustworthier in the OT group. Notably, Pedersen et al. examined multiple rather than single OT doses; whereas the previous two studies examining OT and social cognition evaluated either one (Averbeck et al., 2012) or two (Goldman et al., 2011) doses. These results are promising and underscore the need to investigate OT in a longer clinical trial assessing a broader range of social cognitive measures.

The Current Study

Given the evidence that antipsychotics do not improve social cognition or functioning (Bellack et al., 2004; Harvey et al., 2006; Penn et al., 2009), there is a need to investigate the effects of OT on social cognition and social functioning in schizophrenia. The current study

evaluated the effects of OT on facial emotion recognition, theory of mind (ToM), empathy, social perception and attribution style. The aims and hypotheses will follow accordingly. Additionally, the effects of OT on social and community functioning were explored in light of the relationship between social cognition and these life domains (Couture et al., 2006; Smith et al., 2012).

Aims & Hypotheses

Aim 1: Evaluate the effects of OT on facial emotion recognition, specifically fear and anger.

The first aim was to evaluate the effects of OT on facial emotion recognition. Averbeck et al.'s (2012) and Goldman et al.'s (2011) findings suggest OT has a role in emotion recognition in schizophrenia. Specifically, OT may improve recognition of the emotions of fear and anger in schizophrenia given the evidence that OT improves recognition of these emotions in healthy controls (Fischer-Shofty, Shamay-Tsoory, Harari, & Levkovitz, 2010; Guastella et al., 2009) and preliminary evidence that it improves fear recognition in schizophrenia (Averbeck et al., 2012; Goldman et al., 2011). This aim is further supported by Morris et al.'s (2009) argument that OT may reduce amygdalar activation to fearful faces in schizophrenia and thereby reduce distress that comes from negative emotional stimuli. Therefore, it was hypothesized that OT would improve recognition of fear and anger in schizophrenia using a well-validated, behavioral facial emotion recognition task, The ER-40 (Carter et al., 2009).

Aim 2: Evaluate the effects of OT on Theory of Mind (ToM).

The second aim was to examine the degree to which OT impacts ToM. As was discussed earlier, ToM is best conceptualized as a multidimensional construct (Sabbagh,

2004; Shamay-Tsoory, Shur, Barcai-Goodman, et al., 2007). Therefore, the current study explored affective and cognitive ToM. OT appears to have beneficial effects on ToM based on the research with healthy controls (Domes et al., 2007) and individuals with autism (Guastella et al., 2010). Pedersen et al.'s (2011) two-week trial provides preliminary evidence OT can improve cognitive ToM. (Note that ten of the participants in the current study are from the Pedersen et al., 2011 trial.) Based on the current body of evidence, it was hypothesized that OT would improve cognitive ToM using a social-reasoning cognitive ToM task, namely the Brune Task. It was also hypothesized OT would improve affective ToM as measured by a behavioral affective ToM task, the Eyes Test.

Aim 3: Evaluate effects of OT on empathy.

The next aim was to evaluate the relationship between OT and empathy in schizophrenia. OT is associated with feelings of closeness (Carter et al., 1992) and evidence with healthy controls suggests OT is associated with increased empathy (Hurlemann et al., 2010). Since empathy is closely related to affective ToM (Derntl, et al., 2009) and emotion perception (Feschbach, 1987; Green et al., 2008), it stands to reason that OT could lead to increased empathic processing in schizophrenia. The current study used a well-established self-report empathy measure, the IRI (Davis, 1983), to assess the effects of OT on cognitive and affective empathy. It was hypothesized that OT would improve self-reported empathy in schizophrenia.

Empathy was also assessed with a newly developed performance-based measure (i.e., a role play test). A performance-based empathy measure may contribute to our understanding of empathy in schizophrenia given the empathic literature is predominated by self-report measures. Since the performance-based measure is newly developed and not yet validated,

performance on the empathy role-play was considered exploratory; however the preliminary psychometric properties of the role-play empathy measure were also assessed.

Aim 4: Evaluate effects of OT on social judgments.

There is initial support that intranasal OT can increase trustworthiness in individuals with schizophrenia (Pedersen et al., 2011). Additionally, Keri et al. (2009) found lower OT plasma levels in individuals with schizophrenia were related to decreased trust during a trustworthiness paradigm. Thus, aim four was to explore how OT impacts social judgment on a behavioral measure of trustworthiness, namely the Trustworthiness Task (Adolphs et al., 1998). It was hypothesized that the OT group would have improved social judgment, such that ratings on the trustworthiness task would be similar to ratings observed in healthy controls. Specifically, it was hypothesized that OT would be related to greater ratings of trustworthiness.

Exploratory Aims

Exploratory Aim 1: Evaluate effect of OT on attribution style.

Since no current research has directly explored how OT affects attribution style in schizophrenia (nor in non-clinical samples in general), the first exploratory aim was to examine the effects of OT on attribution style in schizophrenia using a behavioral task, namely the AIHQ. This is a worthwhile endeavor since there is some evidence that attribution style is related to functional outcome (Couture et al., 2006). It is possible OT can impact attribution biases, such as the personalizing bias, through OTs effects on paranoia (Pedersen et al., 2011). Additionally, OT has shown to reduce reactivity to threat cues (Kirsch et al., 2005), which could manifest in reduced external attributions for ambiguous or negative events.

Exploratory Aim 2: Evaluate effects of OT on social and community functioning.

An additional aim was to examine how OT impacts social functioning using a functional capacity (i.e. role play) measure and community functioning using a self and informant report measure. Since OT has been related to improved social skills in healthy controls (Ditzen et al., 2009), OT may have a similar observable effect on functional capacity in schizophrenia. The relationship between social cognition and social functioning also suggests OT could have an effect on functional capacity. However, the research in this area is lacking in clinical populations, and so the effects of OT on functional capacity were considered exploratory.

In light of research showing improved social functioning is related to better community functioning (Couture et al., 2006; Evert et al., 2003), the impact of OT on community functioning over the course of the present study's treatment trial was additionally explored. Due to potential lack of insight in functioning deficits, both informant and self-reports were administered to examine community functioning.

Exploratory Aim 3: Moderator and Mediators of OT effects on social cognition.

Due to a potentially limited sample size, evaluating mediators and moderators was considered exploratory. Hoyle and Kenny (1999) have found that simple mediation models are indeed possible with small sample sizes. To better characterize possible treatment effects, it was considered critical to evaluate whether there were any variables that may potentially mediate, as well as moderate the effects of OT on multiple domains of social cognition. Specific mediators that were proposed to explore included anxiety and neurocognition. Since OT has known anxiolytic effects (Lee et al., 2009), treatment effects on anxiety could influence performance on social cognitive measures, such that improved social cognitive

performance could be a function of decreased anxiety. Additionally, given the research demonstrating OT is tentatively related to improved cognitive abilities (Macdonald & Macdonald, 2010), neurocognition was also tested as a mediator. Lastly, gender was explored as a moderator; animal studies have shown that OT has a greater effect on social behavior in male than female voles (Carter et al., 2009) and there is an array of studies showing differential effects of OT on social cognition in men and women (e.g. Hurlemann et al., 2010; Rubin et al., 2011). Thus, the current study had proposed to evaluate the possible interaction between gender and OT on social cognition.

CHAPTER II

Methods

Participants

Twenty participants were recruited as part of the Oxytocin Treatment of Social Deficits and Psychotic Symptoms in Schizophrenia study conducted at the Clinical and Translational Research Center (CTRC) at the University of North Carolina Hospitals and the North Carolina Psychiatric Research Center (NCPRC). (Note, five of the participants in the current sample were part of a 12-week OT treatment trial and the other 15 participants were part of the 6-week OT trial; differences in inclusion/exclusion criteria are discussed below.) Participants were recruited from UNC's Department of Psychiatry Schizophrenia Treatment and Evaluation Program (STEP) outpatient clinics, the UNC Hospitals Psychotic Disorders inpatient unit, the inpatient unit at Dorothea Dix Hospital, other studies conducted at UNC Hospitals, as well as flyers in the community and advertisements in the National Alliance of Mental Illness (NAMI) newsletter.

The inclusion criteria for the 6 and 12-week OT trials were generally consistent. For both trials, inclusion criteria included the following: stability of symptom severity; on the same medication(s) and dose(s) for at least one-month prior to study participation; and, low to moderate depressive symptoms. The age criterion for the 6-week trial was 18 to 55 years of age to participate; it was expanded in the 12-week trial to 65 years of age. There were three main differences in inclusion/exclusion criteria for the two trials involving diagnosis,

symptom severity, and baseline social cognition (Table 1). Diagnosis was based on extensive chart review and consultation with the attending psychiatrist. The Structured Clinical Interview for DSM-IV Axis I Disorders (SCID-I; First et al., 2002), Mood Disorders and Psychotic Disorders modules was administered by trained research clinicians or advanced graduate students for participants who not been followed by UNC's Department of Psychiatry or participants whose diagnosis was unclear (e.g., schizophrenia versus schizoaffective disorder).

Exclusion criteria for both trials included low literacy as indicated by an inability to read and understand the consent form and performance on the Wide Range Achievement Test (WRAT; only administered in the 12-week OT trial), dependence on substances other than tobacco or caffeine; positive urine drug screen for illegal substances or drugs that have not been prescribed; debilitating medical conditions; major surgery or trauma in the past year; pregnancy or breast-feeding; having given birth in the past 6 months or breast-feeding in the past 3 months; abnormalities found during medical evaluation during study participation; and, an inability to learn self-administration of intranasal treatments.

Procedures

The current study used a randomized, double-blind, placebo-controlled design. Half of the participants (n=10) received an oxytocin nasal spray and half (n=10) received a normal saline placebo nasal spray. Potential participants were contacted by study staff and completed a telephone screen (described in more detail below) to determine study eligibility. Participants completed a screening visit to further determine eligibility based on the aforementioned inclusion and exclusion criteria. Before the screening visit began, participants read the informed consent document and were asked to answer questions about

the consent to ensure they understood the document. In order to participate in the study, participants must have been able to read and understand the informed consent document.

Baseline measures of social cognition, social functioning, community functioning, neurocognition and psychiatric symptoms were then obtained for eligible participants (measures are described below). The schedule of study visits was different for the 6 and 12-week trials. Both trials collected social cognition, social functioning, and psychiatric symptoms at baseline and 6 weeks. While both studies assessed neurocognition and community functioning at baseline, these areas were only assessed at 6 weeks for the 6-week OT participants (and not the 12-week participants). The participants from the 6-week trial had additional study visits at the 2 and 4-weeks, while the 12-week participants did not complete social cognitive measures at 2 and 4 weeks. The social cognitive, symptom, social and community functioning measures and a flow sheet of the study visit procedures for both trials can be found in the Appendix.

During the baseline visit, participants identified two people that knew them well (e.g., family member, friend, mental health professional) to complete the informant version of the community functioning assessment, the Specific Levels of Functioning (SLOF) scale (described below). Informants who have frequent contact with the study participant (e.g., speak on the phone daily, see each other at least twice a week) were asked to complete the SLOF over the phone with a research clinician or psychology graduate student once at baseline and again at 6-weeks for participants in the 6-week trial only.

Participants received a 60-milliliter (ml) spray vial containing 30 ml of test solution, which was administered twice daily for six weeks (approximately 24 International Units). They were given their first dose immediately after the baseline measures were administered.

Participants were then given new vials at each study visit. Participants in the 12-week trial were given two 30 ml vials at their 2-week visit to ensure they had an adequate amount of spray to last until their 6 week visit. The vials were weighed before the participants took the vials home and then again when they returned so as to track compliance with the study treatment (see flow sheet in Appendix for schedule of compliance tracking).

Participants were called daily for two to seven days after their baseline visit by research staff. These reminder calls were intended to remind participants to take the spray, assess that they were administering it correctly and assess for adverse effects. Participants who had more difficulty remembering to take the nasal-spray or trouble with the administration instructions were called more frequently during the first week. Participants were called weekly for the remainder of the study once they demonstrated that they remembered to take the spray and were familiar with the administration.

The study visits lasted about two hours for the social cognition and social functioning measures. Trained psychology graduate students, research assistants or advanced undergraduate students administered the social cognitive and social functioning measures. Trained psychology graduate students or clinicians administered the symptom measures. Study staff administering the assessments were blind to treatment group. Trained undergraduate research assistants, also blind to treatment group, rated the role-plays and the attributional style measure (i.e., AIHQ; as described below).

Measures

Screening measures.

Telephone Screen.

A telephone screen was developed to screen participants for inclusion criteria, such as diagnosis and substance use in the last year. The telephone screen includes questions tapping into the potential participant's comfort in social situations (e.g., "How do you react to the presence of strangers?"). The potential participant was asked to elaborate on their perceived difficulty in social settings. Based on the telephone screen and consultation with the potential participant's mental health professionals, participants were scheduled for a screening visit.

Psychotic Symptoms.

The Positive and Negative Symptoms Scale (PANSS; White et al., 1997) is a 30-item scale on which an interviewer rates the subject for severity of positive and negative psychotic symptoms and mood and behavioral symptoms after asking a standard series of questions. Items are rated on a scale of 1 (absent) to 7 (severe), and yield three main subscores: positive symptoms, negative symptoms, and general psychopathology. The PANSS was administered by an experienced psychiatric clinician or trained doctoral graduate students blind to treatment group.

Social cognitive measures.

Emotion Perception.

The Emotion Recognition-40 (ER-40; Kohler, Turner, Gur, & Gur, 2004) consists of a series of 40 faces, shown one at a time on a computer screen. Participants choose the correct emotions based on 5 answer choices: happy, sad, anger, fear and no emotion. Participants indicate the word that best describes the emotion each faces expresses. A practice item is administered to ensure the participant understands the task and can see the

stimuli. The stimuli are presented in a randomized order each time they are administered. A scoring program automatically records accuracy and median response time.

The ER-40 faces were derived from the University of Pennsylvania Emotion Recognition Task, 96 faces version, and are balanced for equality and intensity of emotion, age, gender and ethnicity. As mentioned earlier, the ER-40 has showed strong psychometric properties, such as high-levels of test-retest reliability in schizophrenia samples and does not show ceiling effects (Carter et al., 2009). A sample ER-40 stimulus can be found in the Appendix.

Theory of Mind.

In the Theory of Mind Picture Stories Task (Brune, 2003), participants are shown a series of six sets of four cartoon pictures that illustrate interactions between two or more individuals. The cartoon cards were displayed to the participant in a predetermined scrambled order (i.e., they are displayed to each participant in the same scrambled order). Participants are asked to rearrange the pictures in an order that conveys a logical story. Participants are given two practice items and provided with feedback to ensure they understand the task.

The period of time the subject takes to complete the task and the accuracy of the sequencing is recorded. After the participant arranges the cards, the examiner ensures they are in the correct sequence. If they are not in the correct order, the examiner silently arranges them so they are in the logical sequence and never reveals to the participant why they are rearranging the cards; providing feedback as to whether they sequenced the cards correctly may influence the participant's responses to the follow-up questions and increases the likelihood of practice effects. The participant is then asked a series of questions about the

cards, which are meant to tap into different aspects of Theory of Mind, such as first order ToM (e.g., what the character thinking), second order ToM (e.g., what a character is thinking about another character's intentions), second order false belief (e.g., what a character is falsely thinking about another character's intentions), third order false belief (e.g., what a character is thinking that another character is falsely thinking about their intentions), deception (identifying a character's deceptive intentions) and reciprocity (identifying that a character is expecting another character share or reciprocate). The participant's interpretations of the characters' beliefs are scored as correct or incorrect (zero or one), with higher scores indicating better ToM. The scoring of the sequencing of the cards is based on Langdon et al.'s (1997) approach to scoring card sequencing tasks. Two points are given for correctly ordering the first and last card and one point is awarded for each of the two middle cards placed correctly. Thus, participants can receive a total of 36 points for correctly ordering the cards and 23 points for the questions. There is an alternate version of the Brune Task (i.e., six different stories tapping into the same components of ToM). Two participants in the 12-week trial were administered the alternate version at their 6-week visit; all other participants were administered the same original Brune version. A sample story sequence is found in the Appendix.

The Eyes Test (Baron-Cohen, Wheelwright, Hill, Raste, & Plumb, 2001) consists of 36 photographs where participants are asked to guess the mental state (i.e., what the person is thinking or feeling) from among four choice words. Participants are given a practice item to ensure that they understand the task. Each eye region is displayed on a computer screen with the four choice mental states shown in the four corners of the computer screen (one target word and three foil words). A sample stimulus from the Eyes Test is in the Appendix. There

is no time constraint in choosing the mental state. Performance is measured by the number of faces correctly discriminated. Although the Eyes Test was originally designed to assess ToM in Autism (e.g., Baron-Cohen et al., 2001), it has been frequently applied to schizophrenia samples (e.g., Couture et al., 2008; Irani et al., 2006; Kelemen et al., 2005). A glossary of the mental states was made available, if the participants were unsure of the meaning of a word.

Empathy.

The Interpersonal Reactivity Index (IRI; Davis, 1983) is a self-report measure of cognitive and affective empathy. The IRI consists of 28 items where participants rate how well each item describes them using a five-point scale. Participants in the current study were asked to rate the items using the last month as a time-frame (i.e., more recent behavior, etc.). The 28 items yield four subscales: perspective taking (PT), empathic concern (EC), fantasy (F), and personal distress (PD). The PT subscale measures the tendency to take another's point of view (e.g., "I sometimes try to understand my friends better by imagining how things look from their perspective"). The EC subscale measures feelings of sympathy and concern for others (e.g., "I often have tender, concerned feelings for people less fortunate than me"). The F subscale measures the ability to imagine oneself in the role of a fictitious character in books (e.g., "When I am reading an interesting story or novel, I imagine how *I* would feel if the events in the story were happening to me"). The PD subscale measures personal feelings of anxiety and unease in interpersonal settings (e.g., "Being in a tense emotional situation scares me"). The IRI has shown high levels of construct validity (Lawrence, Shaw, Baker, Baron-Cohen, & David, 2004) and internal consistency (Davis, 1983). Additionally, the IRI has been used to assess self-reported empathy in individuals with schizophrenia (e.g., Derntl

et al., 2009; Montag et al., 2007). The IRI has shown to be sensitive to treatment effects in non-clinical samples (e.g. Sands, Stanley and Charon, 2008)

The internal consistency of the IRI in the current study was explored. The majority of the subscales demonstrated adequate reliability; however the Perspective-Taking at baseline and the Distress subscale at baseline and 6-weeks showed poor internal consistency: [(Baseline Cronbach's alphas: Fantasy=.74; Emotional Concern=.80; Perspective Taking=.31; Distress=.15) and (6-week Cronbach's alphas: Fantasy=.75; Emotional Concern=.66; Perspective Taking=.60; Distress=.35)]. Thus, findings regarding these two subscales should be interpreted carefully.

In addition to a self-report measure, a newly developed empathy role-play measure and rating scheme was used to assess empathic abilities. The role-play scenario is meant to elicit an empathic response from the participant. The participant is told that their friend is unhappy and their goal is to find out the reason for their sadness and alleviate their friend's distress. During the role-play, the confederate (played by the research assistant) reveals that they are sad because they were not hired for a job that they thought they were going to receive. The scenarios are slightly different for the 6-week visit to reduce potential practice effects (e.g., in the 6-week visit role-play, the confederate is sad because their friend did not come to visit them).

The role-play lasts 90-seconds and is videotaped. The research assistant informs the participant about the purpose and structure of the role-play before the 90-seconds begins. The research assistant then asks the participant to repeat back the purpose of the role-play to ensure that the participant understands the task before proceeding. The empathy role-play

was performed immediately after an initial social skills role-play (described later under the social functioning measures section).

Performance on the empathy role-play was rated with a newly developed rating scheme informed by the empathy literature. (In addition to empathic abilities, social skills were also assessed in the empathy role-play; this will be discussed later in the social functioning measure section.) Specifically, there is evidence that empathy is most accurately conceptualized as a multidimensional construct, consisting of both affective and cognitive components (Decety & Jackson, 2004) and that empathy is facilitated by mimicking other's behavior and emotional states (Decety & Jackson, 2004; Iacoboni, 2009). Although there are current observer-rated empathy rating schemes, such as those used to evaluate physician empathy with patients (e.g., Evans, Stanley, & Burrows, 1993), there are no current rating systems that similarly deconstruct empathy into its constituent components (i.e., current rating schemes are approached from a one-dimensional perspective).

The rating scheme for the empathy role-play consisted of five items assessing the following components of empathy: cognitive empathy (e.g., how well does the participant communicate to the confederate that they understand how they are feeling, and the degree to which they are able to affectively perspective-take), emotional empathy (e.g., displaying sympathy and concern), ideomotoric empathy (e.g., the level of behavioral mimicking, matching body language), helpfulness (e.g., reassurance and problem-solving) and lastly, a summary empathy item (e.g., how well did the participant display and communicate empathy overall). The items are rated on a one to five rating scale, with higher scores indicating more empathy. Two independent and blind raters were trained to reliability on the empathy rating

measure. One of the raters did not complete all of the tapes in the current study, thus a majority of empathy role-plays (*n*=16) were rated by one trained rater.

Social perception.

The Trustworthiness Task (Adolphs, Tranel, & Damasio, 1998) is comprised of 42 black and white photographs of the faces of unfamiliar people. Participants are shown each picture individually (on a computer monitor) and asked to rate how much they would trust that person (e.g., with their money) on a seven-point scale, ranging from -3 (very untrustworthy) to +3 (very trustworthy). They are provided with a photograph of 0 or an average face (i.e., someone they would neither trust nor distrust) to refer to throughout the task (based on Adolphs et al.'s, 1998 norms). The total score is the sum of the trustworthiness ratings. An additional method of scoring used previously (e.g., Adolphs et al., 1998; Couture et al., 2008) is to create two scales based on the top third of the most trustworthy faces (score of +1 or greater) and the bottom third of untrustworthy faces (score of -1 or below) based on a Adolph et al.'s (2008) normative sample.

Attribution style.

The Ambiguous Intentions Hostility Questionnaire-Abbreviated Version (AIHQ, Combs et al., 2007) evaluates attribution style. The AIHQ-abbreviated version is comprised of five short vignettes that reflect negative events that are ambiguous in intention. Participants are read each vignette, and asked to imagine the scenario happening to them (e.g., "You walk past a bunch of teenagers at a mall and you hear them start to laugh"), and to think of the reason why the other person (or persons) acted that way towards them.

Two independent and reliable raters subsequently rated the responses for hostility ("hostility bias") using a five point Likert scale (higher scores indicating more hostility). The

participant then uses Likert scales to rate whether the other person (or persons) performed the action on purpose, how angry it would make them feel, and how much they would blame the other person (or persons); these responses are averaged to yield a "blame bias." Finally, the participant is asked to write down how they would respond to the situation, which was later rated by the same two independent and reliable raters to compute an "aggression index." Again, the raters use a five point Likert scale, with higher scores indicating more aggression.

The AIHQ has demonstrated high levels of reliability and validity in schizophrenia samples (Combs, Penn, Wicher, & Waldheter, 2007) and been used to assess psychosocial treatment effects for schizophrenia (e.g., Combs, Adams, et al., 2007). In the current study, two independent raters, both blind to condition, were trained to become reliable on the AIHQ.

Social Functioning Measures.

To evaluate social functioning, a role-play measure was administered at the baseline and 6-week visits. Role-plays are routinely used in schizophrenia research to assess social skills and are related to real-world functioning (e.g., Bellack et al., 1990). The current study used two role-play scenarios at each time point (baseline and 6-weeks). One of the role-play scenarios, the empathy role-play, was previously discussed. In addition to the empathy scenario, an initial role-play was conducted where the participant is instructed to have a conversation with their new neighbor. Their goal is to get to know their new neighbor (played by the study confederate). The scenarios are again slightly different at the 6-week visit (e.g., instead of meeting a new neighbor, the participant meets a new friend at a party). The confederate for both the empathy and social functioning role-play were trained research clinicians, doctoral level graduate students, or advanced undergraduate research assistants.

Efforts were made to ensure that the same confederate completed the baseline and week-6 visit for participants; in the event that the same confederate was not available, one of the trained research staff acted as the confederate. The role-play scenarios and confederate instructions were standardized to minimize the potential impact of having a different confederate complete the second role-play.

Both the first role-play (e.g., meeting the new neighbor) and the empathy role-play were coded with a social skills rating manual. A similar coding scheme has been used previously and demonstrated high levels of reliability and validity (e.g., Pinkham & Penn 2006). The social skill manual measures behaviors such as eye-gaze, anxiety, engagement, number of questions asked, fluency of speech (e.g., absence of speech fillers), clarity of speech (e.g., clear enunciation), meshing (e.g., the flow of the conversation), content (e.g., the appropriateness of the content), appropriate affect, flat affect and overall interpersonal skill. One difference between the rating scheme used by Pinkham and Penn (2006) and the current rating scheme is that this study used a five point rating scale as opposed to a nine-point scale so as to further increase inter-rater reliability.

As has been done in previous studies using a similar social skills rating scheme (e.g., Penn, Mueser, Spaulding, Hope, & Reed, 1995; Pinkham, Penn, Perkins, Graham, & Siegel, 2007), the social skills items were grouped by global skills (i.e., content, overall social skill item, social anxiety), specific skills (i.e., questions, fluency, clarity, meshing, involvement) and non-verbal social skills (i.e., gaze, facial affect, appropriate affect). Higher ratings on the rating scale indicate better social skills. Two independent raters (the same raters who completed the empathy ratings) were trained to reasonable levels of reliability on 13 tapes

(e.g., ICCs > .60); however, only one rater completed a majority of the role-plays (*n*=16) in the current study.

Community Functioning.

Specific Levels of Functioning Scale (SLOF; Schneider & Struening, 1983) is a measure of community functioning. The SLOF has an informant and self-report version, both of which were included in the present study. The SLOF measures overall functioning in a variety of domains such as interpersonal relationships (e.g., initiates contact with others), social acceptability (e.g., destroys property), work skills (e.g., has employable skills) and daily living activities (e.g., can handle personal finances) and has shown strong psychometric properties in schizophrenia samples (Bowie et al., 2008). Each item is rated on a 5-point likert scale with anchors describing the frequency of the behavior and/or the patient's level of independence. Higher scores indicate more adaptive community functioning. Since the interpersonal relationships and social acceptability subscales of the SLOF converge on social functioning, these subscales were additionally combined and analyzed to assess the relationship between OT and social functioning.

Anxiety Symptoms.

The Liebowitz Social Anxiety Scale (LSAS; Liebowitz, 1987) is a self-rating instrument that lists 24 social situations that the participant rates for how much fear/anxiety they would experience and how much they would avoid each situation on a scale of zero to three. Higher numbers indicate greater levels of anxiety and frequency of avoidance. The LSAS has previously shown high levels of reliability and validity (e.g., Baker, Heinrichs, Kim, & Hofmann, 2002; Fresco et al., 2001) and has been previously used to assess social anxiety in schizophrenia (e.g., Mazeh et al., 2009; Pallanti, Quercioli, & Pazzagli, 2000).

Cognitive Measures.

In the 6-week trial, the Brief Assessment of Cognition in Schizophrenia (BACS; Keefe et al., 2004) was administered to assess neurocognition. The BACS is an instrument that assesses verbal memory, working memory, motor speed, attention, executive functions and verbal fluency in schizophrenia. In the 12-week trial, the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS; Randolph, 2007) was administered to assess neurocognition. The RBANS measures immediate and delayed memory, attention, language, and visuospatial skills.

CHAPTER III

Data Analytic Plan

Preliminary Analyses Overview

Descriptive statistics were used to evaluate baseline differences between the oxytocin (OT) and placebo (PL) groups. Specifically, Multivariate Analysis of Variance (MANOVA) was used to evaluate differences on demographic, symptoms, compliance, social cognitive and neurocognitive variables for all 19 participants included in the analyses (OT, n=10; PL, n=9). There was one participant in the OT group who was erroneously given a placebo vial rather than an OT vial after his four-week visit. This participant was not included in the 6-week analyses since as-received rather than intent to treat analyses were conducted.

Linear regression analyses were used in each of the primary, exploratory and post-hoc analyses to evaluate the predictive effect of group on each of the outcome variables at 6 weeks. Baseline scores on each of the measures were first added as predictors in the linear models for all analyses so as to control for baseline performance. This allowed for an examination of the additional variance explained for by group (OT versus PL) when added to the model. Then, group was added as a second predictor using the codes 0 and 1 for the PL and OT group, respectively.

Because significant group effects might not be detected due to a small sample size, within group changes were also analyzed. Within group paired samples t-tests were

conducted for the OT and PL groups separately for all primary, exploratory and post-hoc analyses. To assess whether OT compliance was related to performance, Pearson two-tailed correlations were conducted between average compliance over the course of 6 weeks (average compliance for weeks 2, 4 and 6) and change scores (change scores computed by subtracting 6-week performance from baseline scores) on the 6-week social cognitive, social functioning and symptom measures for both conditions.

Statistical significance was set at an alpha level of .05 or below and SPSS was used for all analyses. Cohen's *d* effect sizes were also calculated to measure the magnitude of treatment effects for within and between group analyses (Cohen, 1988). For within group effect size analyses, the correlation between the baseline line and 6- week score was included to correct for dependence between the two means. For the between group effect size analyses, the pooled standard deviation and least square means were used to calculate Cohen's *d*. The specific primary hypotheses and exploratory aims are detailed below:

Primary Analyses

Hypothesis 1: It was hypothesized that OT will improve recognition of fear and anger in schizophrenia.

To evaluate the first hypothesis, linear regression models with total correct responses for fearful and angry faces were entered as the outcome variables. Paired samples t-tests were then conducted to evaluate changes within the PL and OT groups for fearful and angry faces.

Hypothesis 2: It was hypothesized that OT will improve cognitive ToM as measured by the Brune Task and affective ToM as measured by the Eyes Test.

To test hypothesis 2, a linear model was conducted with total mental states correctly identified on the Eyes Test as the outcome variable. Within group analyses were similarly conducted to assess change in Eyes Test accuracy within each of the groups.

To assess change in performance on cognitive ToM as measured by the Brune task, a series of linear regression models were conducted with total Brune score at 6-weeks and subscores (i.e., 1st order ToM, second and third order, deception, and reciprocity detection) as the outcome variables. Then, within group analyses were conducted to evaluate change from baseline to 6-weeks for each of the aforementioned Brune scores.

Hypothesis 3: It was hypothesized OT would improve self-reported empathy, as well as empathic ratings on a role-play measure.

To assess whether OT improves empathy, a series of linear regression models were conducted with the 6-week IRI sum score and each of the four subscale scores (perspective taking [PT]; empathic concern [EC]; fantasy [F]; and personal distress [PD]) as the outcome variables. Paired samples *t*-tests were conducted to assess change over time within each of the groups for the IRI total and subscale scores. The sample size for the IRI was smaller than other measures because the instrument was added after the study began. Thus, the total IRI sample is n=15 (OT, n=7; PL, n=8). Because of the smaller IRI sample size and low internal consistency for the PT subscale at BL and Distress subscale at BL and 6-weeks, these results are more descriptive and should be interpreted carefully.

In order to evaluate the preliminary psychometric properties of the empathy-rating scheme (a new behavioral measure of empathy), the reliability and validity of the instrument was assessed. First, the inter-rater agreement was evaluated using a two-way random effects Intra-Class Correlation (ICC) analysis. Convergent validity was explored with pearson

correlational analyses of the empathy rating scale and the Eyes Test and IRI subscales. Lastly, the internal consistency of the measure was evaluated with Cronbach's alpha. Pending adequate validity and reliability, linear regression analyses were then conducted on each of the empathy items, as well as a sum score. Paired samples t-tests were calculated to evaluate within group changes on the empathy-rating scheme.

Hypothesis 4: It was hypothesized that OT will be related to greater ratings of trustworthiness.

Lastly, a linear regression model was conducted to assess whether OT predicts overall increased trustworthiness ratings at 6-weeks. The dependent outcome on the Trustworthiness Task was the mean trustworthiness rating across all 42 faces. Additionally, trustworthy judgments on two subscales were analyzed. As was discussed earlier, the mean ratings of "trustworthy" faces [i.e., top third of the most trustworthy faces (score of +1 or greater)] and "untrustworthy" faces [i.e., bottom third of untrustworthy faces (score of -1 or below)] based on Adolph et al.'s (2008) normative sample, were entered into linear regression models as outcome variables. Paired samples *t*-tests were then executed to evaluate within group changes on total trustworthy judgments, as well as mostly trustworthy and untrustworthy faces.

Exploratory Analyses

Exploratory Aim 1: Evaluate effect of OT on attributional style.

Exploratory Aim 1 was similarly assessed with linear regression models with AIHQ as the outcome variable. Specifically, the hostility and aggression bias scores (mean rating across two raters) and blame bias (average of the intentionality, anger and blame Likert scale items for each scenario) were entered into the model with baseline performance and group as

the predictors. Paired samples *t*-tests were conducted to examine within group effects for the OT and PL groups.

Exploratory Aim 2: Evaluate effects of OT on social and community functioning.

To address exploratory Aim 2, a linear regression was conducted with social functioning as measured by ratings on a social skill role-play as the outcome variables. Consistent with previous studies (e.g., Pinkham et al., 2007), role-play ratings were combined into three composite scores: global social skill (content, social anxiety, overall social skill items), specific skills (clarity, fluency, meshing, involvement and question items), and non-verbal skills (gaze, appropriate affect, and flat affect items). The social skill composite scores for the two role-plays (i.e., "getting to know your neighbor" and the empathy role-play) were analyzed with *t*-tests to determine if they should be collapsed or analyzed separately (i.e., if the composite scores for the two role-plays were significantly different, then between and within group analyses would be conducted separately for each of the role-plays).

In addition to the social skills role-play ratings, a subjective measure of social and community functioning was measured with the SLOF participant and informant questionnaires. A social subscore was created on the SLOF using the sum of socially relevant SLOF subscales, (interpersonal relationships and social acceptability subscales). In addition to the social subscore, the total SLOF score was analyzed to assess overall community functioning. Both the social subscore and the total score were entered into separate linear regression analyses as the dependent variables, with baseline performance and group as the predictor variables. Note that the SLOF was included after the study began;

therefore, it was not collected for three of the 6-week participants and not collected at the 6-week visit for the five 12-week participants; thus, the sample size is smaller for the SLOF analyses (OT, *n*=6; PL, *n*=5).

Exploratory Aim: Moderator and Mediators of OT effects on social cognition.

Lastly, as part of the post-test analyses, the potential mediators and moderators of OT were evaluated. Specifically, one aim was to evaluate whether gender moderates the relationship between OT and social cognition. An additional aim was to investigate the possible mediating effects of anxiety and neurocognition on social cognition.

CHAPTER IV

Results

Descriptive Analyses

The study groups did not differ on demographic variables (Table 2), baseline dependent measures (Tables 3, 5-7), or on medication compliance ([OT average compliance=77.61%; SD=34.10); PL (average compliance=77.26%, SD=16.75)], $F(1, 16)=.001$, $p=.98$). (Note: the compliance data for one OT participant was not collected.) Additionally, three participants who completed baseline visits did not complete six-week visits. These three participants did not differ on baseline demographic variables from the 19 participants included in the current analyses.

Primary Analyses: Social Cognitive 6-week analyses

Emotion Recognition.

Between group analyses.

In order to evaluate the effect of OT on fear and anger recognition at 6 weeks, linear regression analyses were conducted. When baseline performance and group were entered as predictors into the model, there was no significant effect of treatment group on fear or anger recognition (see Table 3 for raw means, least square means and unstandardized B coefficients). Subsequent post-hoc analyses were conducted to evaluate the effects of OT on other emotions (sad, happy, no emotion; Table 3) and on intensity of emotional expression (mild and extreme intensity; Table 3). Post hoc analyses revealed that the OT condition showed a trend level improvement in the recognition of faces displaying high intensity

emotions [Group B=.65 (95%CI: -.10-1.40), R^2=.86, *p*=.085]; the effect size for this difference was large. Specifically, the OT group showed a .65 increase in recognition of high intensity emotions at 6-weeks as compared to the PL group. There were no significant changes in the other emotion recognition outcome variables for either group (Table 3).

Within-group analyses.

There were no significant with-in group changes for either group for fear or anger. Post hoc within group analyses revealed a significant improvement in recognition of faces with higher (i.e., extreme) intensity emotions in the OT group (*t(9)*=-2.53, *p*=.035) and not in the PL group. Effect sizes reflected a large improvement in the recognition of higher intensity emotions for the OT group. Post-hoc analyses revealed no changes on other emotions or mild intensity faces for either group (Table 3).

Theory of Mind (ToM): Affective and cognitive ToM.

Between group analyses.

There was no significant treatment group effect on affective ToM as measured with the Eyes Test. Similarly, there were no treatment group effects on cognitive ToM as measured by the Brune Task. (See Table 3 for total score and subscore raw means, least squares means, and unstandardized B coefficients).

Within-group analyses.

There were no within group changes on the Eyes Test for either group (Table 3). The OT group significantly improved on overall cognitive ToM as measured by total score on the Brune task (*t(9)*=2.33, *p*=.045). Specifically, the OT group showed a large improvement in overall Brune performance. However, the OT group was still performing worse than the PL group at 6 weeks. The OT group also displayed a significant improvement in detection of

deception (*t(9)*=3.00, *p*=.015); whereas the PL group did not significantly improve. The effect size for improved deception detection was large in the OT group and moderate in the PL group. In addition, the OT group showed a trend level improvement on 2nd order ToM (*t(9)*=2.09, *p*=.066). Similar to the other Brune results, the effect size for improved 2nd order ToM was large in the OT group and small to moderate in the PL group (the OT group was still performing slightly worse than the PL group at 6-weeks). The PL group showed a trend improvement on 1st order ToM (*t(8)*=1.89, *p*=.095); whereas no significant change was seen in the OT group (*t*(9)=.94, *p*=.373). The effect size for improved 1st order ToM was moderate in the PL group and small in the OT group. Neither group showed significant changes in 3rd order false belief or reciprocity detection (Table 3).

Social Perception.

Between group analyses.

There was no effect of treatment group on social perception, as measured by trustworthiness judgments. Additional linear regression analyses were conducted to evaluate change on two trustworthiness subscores: faces judged as mostly trustworthy and as mostly untrustworthy by nonclinical samples using Adolph et al.'s (2008) normative sample. There were no significant effects of group on either of the two trustworthy subscores; however there was a moderate increase in rating untrustworthy faces as more trustworthy in the OT group relative to the PL group [Group B=6.44; $R^{2=}$ .205, *p*=.174]. The OT group showed a 6.44 increase in trustworthiness ratings for faces typically rated as untrustworthy as compared to the PL group. (See Table 3 for raw means, least square means, and unstandardized beta coefficients.)

Within group analyses.

Similarly, there were no significant within group changes on the total sum ratings on the trustworthiness task or two subscores for either group; although, the OT group's effect size was in the expected direction for ratings of all faces and the untrustworthy faces. Specifically, the OT showed a small increase in trustworthiness judgments for untrustworthy faces (i.e., rating untrustworthy faces as more trustworthy; $t(9)=.87$, $p=.406$), while the PL group showed a small decrease in trustworthiness judgments for the same faces (i.e., rating the untrustworthy faces as less trustworthy; $t(8)=-.50$, $p=.630$) (Table 3).

Empathy: Interpersonal Reactivity Index (IRI).

Between group analyses.

The impact of OT on self-reported empathy, as measured by ratings on the IRI, was analyzed. There was a statistically significant improvement of self-reported perspective taking in the OT group [Group B**=**4.30; $R^{2=}$ .780, $p=.022$]. That is, the predicted value of perspective taking increased by 4.30 units at 6 weeks for the OT as compared to the PL group. Furthermore, group (OT, PL) explained 12.7% of the variance in self-reported perspective-taking[1]. The effect size was large for the improved perspective-taking in the OT group as compared to the PL group. There were no significant effects of treatment group on the other IRI subscores (fantasy, emotional concern, distress) or total score (Table 3).

Within group analyses.

Within group paired samples *t*-tests showed significantly improved perspective-taking in the OT group at 6-weeks (Table 3; $t(6)=-2.68$, $p=.037$). Moreover, the effect size

[1](R^2 BL perspective taking, Group=.780)-(R^2 BL perspective taking=.653)=.127.

was large for improved perspective-taking in the OT group. The OT group also showed a trend level decrease in self-reported emotional empathy ($t(6)$=2.189, p=.07), with a large decrease in self-rated emotional empathy. OT was not related to any other changes on the IRI. The placebo group showed a significant decrease in self-reported distress ($t(7)$=3.48, p=.010). The PL group also showed a trend level decrease in total self-reported empathy ($t(7)$=2.00, p=.085). Specifically, the PL group displayed a large decrease in total self-reported empathy at six-weeks (Table 3).

Empathy: Role-play.

Psychometric Properties.

The initial psychometric properties of a new behavioral rating scheme of empathy were evaluated. Two raters, blind to group status, were trained to reliability on 13 cases. They achieved Inter Class Correlations (ICCs) ≥.60 on four of the five empathy role-play items: Emotional empathy ICC=.60; cognitive empathy ICC=.66; ideomotoric empathy ICC=.60; helpfulness ICC=.50; summary empathy item ICC=.75. (Note, 16 of the cases in the present study were rated by one of the raters.) Since the helpfulness item did not reach acceptable levels of inter-rater reliability, it was excluded from the analyses. Internal consistency of the four remaining items (cognitive, emotional, ideomotoric, and the summary empathy item) was then evaluated. The empathy role play showed a reasonable level of internal consistency (Cronbach's alpha=.60). The average correlation between the four empathy items was .28 (range of item correlations: .05-.58; Table 4). The four empathy items were positively correlated with the total empathy score (sum of the empathy items). The cognitive empathy role-play item was significantly correlated with the summary item (i.e.,

participants with higher rated cognitive empathy displayed higher ratings on the overall empathy summary item).

In regard to convergent validity with the IRI, the ideomotoric empathy role play item had a trend positive correlation with the IRI-Total score (p=.07); participants with higher ideomotoric ratings on the role-play reported higher overall empathy on the IRI. In addition, there was a trend positive correlation between the total role-play empathy score and total IRI score (p=.11). That is, participants with higher ratings on the empathy role-play measure reported higher levels of empathy. There were no other significant correlations between the other empathy role-play items, IRI subscales or the Eyes Test (Table 4).

Between group-analyses.

Between group differences at 6 weeks were evaluated for each item on the empathy role-play and the total empathy score. There was no significant effect of treatment group on the empathy role-play; however, there was a trend for group to be a significant predictor of emotional empathy [B=.571, R^2=.352, p=.086]. Specifically, the OT group was trending towards higher emotional empathy scores at 6-weeks relative to the PL group, with a larger emotional empathy rating observed in the OT group as compared to the PL group. The effect sizes were in the expected direction (i.e. improvements for the OT group over time) for all empathy items (Table 5).

Within group-analyses.

Within-group analyses revealed no significant changes for either group at 6 weeks on the empathy role-play items or total score (Table 5).

Exploratory Analyses

Social and Community Functioning.

Social skill role-play: psychometric properties.

Two independent raters, blind to group status, were trained to reliability on 13 cases. They reached acceptable levels of reliability for social skill ratings on both role-plays [i.e., ICCs ≥.60; *Role play 1* ("getting to know your neighbor"): Global ICC=.70, Specific skills ICC=.94, Nonverbal ICC=.63 and *Role play 2* (empathy role-play): Global ICC=.74, Specific skills ICC=.80, Non verbal ICC=.60]. Note: one rater rated 16 of the cases in the present study.

Comparisons between the two role-plays were conducted to determine whether to collapse them in the analyses. Since the global social skill ratings for role-play 1 and 2 were significantly different at baseline [Role Play 1 Mean (SE)=10.75(.37), Role Play 2 Mean (SE)=11.83(.20), $t(19)=-3.228$, $p=.004$], the role-plays were analyzed separately for the subsequent analyses.

Between group analyses.

Linear regression analyses revealed that group was a significant predictor of global social skills for role-play one [B=1.08, $R^2=.461$, $p=.042$]. That is, the predicted value of global social skills for role-play one increased by 1.08 units for the OT as compared to the PL group. Specifically, group (OT, PL) explained 16.5% of the variance in global social skill for the first role-play[2]. Regarding the effect size, the OT group showed larger global social skill ratings compared to the PL group at the 6-week visit. Similarly, group was a significant

[2](R^2 BL Global social skill role play 1, Group=.461)-(R^2 BL Global social skill, role play 1=.296)=.165.

predictor of global social skills for role play two [B=1.32, R^2=.553, p=.05]. That is, participants in the OT showed larger global social skills ratings for role-play 2; the predicted value of global social skills for role-play two increased by 1.32 units at 6 weeks for the OT as compared to the PL group. Group explained 12.6% of the variance in global social skills for role-play 2[3]. Group was not a significant predictor for any other 6-week social skill components (Table 5).

Within group-analyses.

The OT group showed a trend improvement in global social skills ratings for role play1 ($t(9)$=2.108, p=.06); the effect size indicated a large improvement in global social skills ratings at 6 weeks. On the contrary, the PL group showed a significant decrease in global social skills ratings (t(8)= -.858, p=.021) and non verbal social skill ratings (t(8)=-2.296, p=.05) for role play 2. The effect sizes indicated that the PL condition had a large decrease in their global and nonverbal social skills ratings at the 6-week visit. There were no other changes observed in either group (Table 5).

SLOF.

Between group analyses.

Analyses were conducted evaluating changes on community and social functioning as measured by informant and participant ratings on the SLOF. There was no effect of treatment group on the SLOF community or social functioning (Table 6).

[3](R^2 BL Global social skill role play 2, Group=.553)-(R^2 BL Global social skill, role play 2=.427)=.126.

Within group analyses.

Within group analyses in the OT group revealed a significant improvement on the total SLOF score ($t(5)$=2.882, p=.045) and the social subscore ($t(5)$=2.697, p=.05) for participant ratings and no changes for the informant SLOF ratings; however the SLOF participant effect sizes were large in both the OT and PL groups (Table 6).

Attributional style.

Between group analyses.

Exploratory analyses were conducted to test the effects of OT on attributional style. There was no effect of group on AIHQ aggression, hostility or blame bias and the effect size analyses indicate no differences between the groups at the 6 week visit (Table 6).

Within group analyses.

The OT group did not show within group changes on AIHQ aggression, hostility or blame bias scores at 6-weeks. The placebo group showed a significant decrease in AIHQ hostility ($t(8)$=-3.125, p=.014) and blame biases ($t(8)$=-2.53, p<.05) (Table 6). Specifically, the PL group had a large decreases in hostility and blame bias scores at 6-weeks. Although non-significant, the OT group demonstrated moderate decreases in hostility and blame biases (Table 6).

Mediation & Moderation Analyses

An additional exploratory aim was to evaluate whether anxiety and neurocognition mediate the relationship between OT and treatment effects. Baron and Kenny's (1986) approach to mediation involves conducting three regression analyses, if all three are significant, then Sobel's Test (1982) is conducted. There was no significant effect of OT on

self-reported anxiety, as measured by the LSAS, between groups [B=.506 (SE=11.18), R^2=.513, *p*=.964) or within the OT group [*t*(9)=1.611, *p*=.142] and no effect of OT on the PANSS anxiety item between groups [*B*=.517(SE=.600), R^2=.273, *p*.=401] or within the OT group [*t*(9)=.537, *p*=.604]. Therefore, the analysis evaluating anxiety as a mediator of OT treatment effects was not supported. Although neurocognition was collected at baseline and 6-weeks for only 10 participants, changes in neurocognition were still explored. A linear regression analysis revealed no effect of group on neurocognition at 6 weeks as measured the total BACS score [*B*=1.76 (*SE*=4.69), R^2=.746, *p*=.721] and no within-group change in neurcognition for the OT condition [*t*(4)=.535, *p*=.621]. Therefore, no further analysis of neurocognition as a mediator was warranted. An insufficient sample of women (i.e., 3 females/19 participants) precluded exploring gender as a moderator.

Post-Hoc Analyses

Symptom measures: 6-week analyses.

Between group analyses.

Post-hoc analyses were conducted to evaluate the effects of OT on clinical symptoms. Linear regression analyses showed a significant effect of group on negative symptoms. Specifically, the OT group had a significant decrease in negative symptoms at 6 weeks compared to the placebo group (B =-3.78, R^2 =.412, *p*=.046). The predicted value of negative symptoms at 6 weeks decreased by 3.78 units for the OT group as compared to the PL group. To determine the additional variance that group contributed when added to the model, the variance for the model with only baseline negative symptoms was subtracted from the variance for the entire model (BL negative symptoms and group); treatment group explained

17.2% of the variance in week 6-negative symptom scores[4]. The effect size showed a large decrease in negative symptoms for the OT group as compared to the PL group. There was no effect of group on the total PANSS score, other PANSS subscores (i.e., positive and general symptoms), the PANSS anxiety item, or self-reported anxiety as measured by the Liebowitz Social Anxiety Scale (Table 7).

Within group analyses.

Within group analyses revealed significant changes over time for the OT group. The OT group had a significant decrease on the PANSS total ($t(9)=-3.63$, $p=.006$) and all PANSS subscores [(positive: $t(9)=-3.42$, $p=.008$; negative: $t(9)=-4.83$, $p=.001$; general psychopathology: $t(9)=-2.27$, $p=.05$)] at 6 weeks (Table 7). The placebo group showed a significant decrease in PANSS positive ($t(8)=-2.95$, $p=.018$) and general psychopathology ($t(8)=-2.70$, $p=.027$) subscores, as well as the PANSS anxiety item ($t(8)=-2.63$, $p=.03$); however there were no changes on the PANSS total or PANSS negative subscores. There was also no change on the Liebowitz Social Anxiety Scale for either group (Table 7).

The effect size analyses revealed a large decrease in negative symptoms for the OT group. The PANSS total score effect size was large in the OT group and moderate in the PL group. The effect sizes were large for both groups on PANSS positive symptoms and PANSS-general scores (Table 7).

Compliance and change scores

[4](R^2 BL negative symptoms, Group=.412)-(R^2 BL negative symptoms=.240)=.172

Post-hoc correlational analyses were conducted to evaluate the relationship between study drug compliance and change scores on the social cognitive, social and community functioning measures, as well as symptom measures. Correlations between mean compliance over the 6 weeks and change scores revealed significant negative correlations between compliance and change in AIHQ Blame scores, PANSS-general symptoms, a significant positive correlation between compliance and overall empathy on the empathy role-play, as well as a trend level negative correlation with change in total PANSS scores for the OT group. That is, participants who were more compliant with OT showed a greater decrease in AIHQ blame bias, PANSS-general symptoms, increased overall empathy and a trend towards overall reduced symptoms (Tables 8-9). The PL group showed a significant negative correlation with the ER-40 change score; participants more compliant with the placebo were less accurate over time on the ER-40 (Table 8). Positive correlations with PL compliance and change on the cognitive empathy, empathy summary role-play item, as well as global social skills ratings for role-play 2 were also observed. Specifically, participants in the PL condition with greater improvements in cognitive empathy, overall empathy and global social skills were more compliant with the placebo (Table 9). There were no other significant relationships with compliance on social cognitive or symptom measures (Table 8) or role-play items (Table 9).

CHAPTER V

Discussion

This is the first multi-day RCT to assess the effects of OT on social cognition, social functioning and community functioning in individuals with a schizophrenia spectrum disorder. It was hypothesized that OT would be associated with improvements in four social cognitive dimensions (emotion recognition, ToM, social perception and empathy). The results showed that participants randomized to the OT condition improved on self-reported cognitive empathy, cognitive Theory of Mind (ToM) and global social skills as compared to participants in the placebo condition. Post-hoc analyses revealed that OT was related to improved identification of intense facial emotions and a reduction in negative symptoms. These results are consistent with others who have found OT improves components of social cognition in schizophrenia (Averbeck et al., 2012; Guastella & MacLeod, 2012; Kuehn, 2011; Rubin et al., 2011; Striepens et al., 2011).

OT, however, was not related to improvements in all aspects of social cognition. There were no significant changes for fear or anger recognition, affective ToM, or social perception. These results suggest that OT may impact social cognition differentially, which is consistent with a recent review of the literature (Bartz et al., 2011). While the current study's results must be tempered due to the small sample size, they are a contribution the limited literature examining OT treatment of social cognition in schizophrenia. A more detailed description of the results, limitations, implications and future directions are discussed below.

Cognitive Theory of Mind (ToM)

One central finding was that the OT group demonstrated significant improvements on overall cognitive ToM, detection of deception and a trend level improvement on second order ToM as measured by the Brune card-sequencing task. However, both groups did improve over time. The effect sizes were large in the OT group and moderate in the PL group for overall Brune score, deception detection and second-order ToM. It must also be noted that the PL group showed a trend improvement in first-order ToM. The OT group also improved on first-order ToM, but not as greatly as PL. Schizophrenia samples, however, have not shown to perform significantly worse on first-order ToM as compared to non-clinical samples (Brune 2005). Thus, first-order belief does not appear to be an area that needs remediation in schizophrenia. Overall, improvements were found in areas of cognitive ToM that have shown to be more compromised in schizophrenia as compared to non-clinical samples (Brune, 2005).

The finding that the OT group displayed an improvement in deception detection is intriguing. The deception questions on the Brune task tap into the participant's ability to accurately identify whether a character is trying to deceive another person who is unaware of the deceptive act (for example "what do you think the person in red intended to do?"). Improved deception detection implies that OT improves accurate discrimination of false and deceitful intentions. The improvement in deception detection addresses concerns that OT could be exploited if it leads to a generalized increase in trust and would possibly make individuals vulnerable to exploitation (e.g., Penney and McGee, 2005). An ability to detect deception suggests otherwise; OT may therefore improve discriminating beliefs about others intensions.

Although there is little research on OT and deception detection, there was a recent study that may shed some light on these results (Krueger et al., 2012). Krueger et al. (2012) used an experimental design to assess OT's impact on attitudes towards perpetrators and victims in a non-clinical sample. The participants completed a series of vignettes involving criminals and their victims; participants were asked to rate the harm endured by the victim. Krueger et al. (2012) found that OT was associated with increased harm ratings as compared to a PL. Although the authors note that their findings suggest OT facilitated increased empathy towards the victims, their results may also point to an increased ability to detect deception (or harm, which was the prompt in their study). Perhaps OT increases understanding of others in distress and consequently accuracy in detecting when someone has been deceived or vice versa. This proposition highlights the overlap between components of social cognition, such as ToM and empathy.

Overall, the current study suggests a relationship between OT and cognitive ToM in schizophrenia. These results are promising for the treatment of social difficulties in schizophrenia. ToM, particularly cognitive ToM, is a robust correlate of functioning in schizophrenia (Fett et al., 2011). Indeed, the therapeutic potential of OT for ToM deficits in schizophrenia has started to gain attention and great interest. In one review, Biedermann et al. (2012) discuss OT's promise in ameliorating ToM deficits and use as an adjunctive treatment with psychotherapeutic approaches.

Affective ToM

Contrary to what was hypothesized, the OT group did not show significant improvements on affective ToM; although, the OT and not the PL demonstrated effect sizes

in the expected direction (i.e., increased performance at 6-weeks compared to baseline for the OT group). This is surprising given that OT has lead to improved performance on the Eyes Test for non-clinical samples (Dome et al., 2007) and individuals with Autism (Guastella et al., 2010). Although OT has shown to be related to improved affective ToM as measured by the Eyes Test, improvements have not been seen on all affective ToM measures. For example, Hurlemann et al. (2010) did not find OT improved identification of guessing the mental states of characters in a non-clinical using the Multifaceted Empathy Task.

Two possible explanations for not finding significant treatment effects on the Eyes Test will be discussed. First, there could be a subgroup of participants who could benefit from OT treatment. Second, there may be particular items on the Eyes Test that are sensitive to treatment effects (e.g., Domes et al., 2007; Luminet et al., 2011). For example, Luminet et al. (2011) found that OT was related to improved performance on the Eyes Test for high alexithymia (a personality style characterized by trouble identifying one's emotions) as compared to low alexithymia participants in a non-clinical sample. Furthermore, the high alexithymia participants showed more pronounced improvements on high intensity and not low intensity stimuli. Since individuals with schizophrenia report higher levels of alexithymia (Yu et al., 2011), the Luminet et al. study suggests that improvements on the Eyes Test may be detected if the intensity of the affective states presented was analyzed. Unfortunately, the intensity of affective states on the Eyes Test was not evaluated in the current study since there are no established subscales based on affective intensity. (Luminet et al. independently created subscales in their study.) Lastly, there may be a subset of individuals with schizophrenia whose affective ToM would improve with OT treatment (e.g., those with increased alexithymia).

Empathy

Consistent with the finding of improved cognitive ToM, self-reported perspective-taking increased in the OT group (cognitive component of empathy); whereas, the placebo group showed a significant decrease in empathic distress and overall trend towards decreased self-reported empathy. The improvement in perspective-taking component of empathy is promising given that schizophrenia samples have repeatedly shown deficits in self-reported perspective-taking as compared to non-clinical samples (Achim et al., 2011; Haker & Rossler, 2009; Montag, Heinz, Kunz, & Gallinat, 2007; Shamay-Tsoory, Aharon-Peretz, et al., 2007). There are no other studies evaluating OT and perspective-taking in schizophrenia; however, improved empathy has been found in non-clinical samples administered OT (Bartz et al., 2010). It should be noted, however, that the IRI was implemented after the study began and only 15 participants completed the measure. In addition, the IRI perspective-taking subscale at baseline and the distress subscale at baseline and 6-weeks demonstrated poor internal consistency. Therefore, these results must be interpreted cautiously.

The perspective-taking items on the IRI tap into an individual's perception of their ability to take the viewpoint of another person (e.g., "Before criticizing someone, I try to imagine how I would feel if I was in their place"). The improved empathic perspective-taking is indeed promising. As noted, individuals with schizophrenia report deficits in this component of empathy. These deficits have shown to worsen as the illness progresses (Achim et al., 2011; Montag et al., 2007) and appear to be independent of symptoms (Smith et al., 2012). Furthermore, self-reported perspective taking has been associated with community functioning in schizophrenia (Smith et al., 2012) and so this may be an important area to target in treatment.

Another finding was that individuals in the OT group showed a large decrease in the emotional concern component of empathy; this is consistent with evidence that empathy is multidimensional (Adolphs, 2009). And, a decrease in emotional concern may not be surprising. The somewhat paradoxical effects of OT have been seen in other studies where increases in non-prosocial emotions are observed (Bartz et al., 2011); for example, Shamay-Tsooray et al. (2009) found that OT was related to increased envy in a non-clinical sample. Another possibility for observing differential effects on components of empathy may be related to dosing. Other studies evaluating OT and empathy have in fact found the effects on empathy are sensitive to the dose of OT administered (e.g., Hurlemann et al., 2010). Hurlemann et al. (2010) assessed cognitive *and* emotional empathy in a non-clinical sample. Hurlemann and colleagues found emotional empathy, as measured by the Multifaceted Empathy Task (MET), increased in the lower (24 IU) but not higher OT doses (48 IU). The authors suggest that higher OT doses may desensitize OT receptors and thereby influence the effects of OT on emotional empathy.

Objective Empathy

In addition to evaluating empathy with a self-report measure, a new objective measure of empathy was developed and assessed. The new behavioral measure of empathy and corresponding rating scheme demonstrated satisfactory initial psychometric properties. Interestingly, there was a trend relationship between overall empathy score and overall self-reported empathy on the IRI for the total sample. This suggests that the rating-scheme and IRI are tapping into a similar construct. A strength of the rating scheme is that it accounts for the multidimensional nature of empathy, which no other current rating scheme of empathy accomplishes. Others have noted the need for behavioral measures of empathy (Smith et al.,

2012) and thus this rating-scheme may be a necessary compliment to the current measures used to evaluate empathy.

There were, however, no significant changes in objective empathic behavior as measured by the behavioral measure of empathy. Although not significant, there was a trend level increase in emotional concern for the OT group (i.e., higher rated emotional concern exhibited in the empathy role-play). This finding is interesting given that improvements were observed in self-reported cognitive but not emotional empathy on the IRI. Perhaps improvements in self-rated cognitive empathy (i.e., perspective taking) translate to increased emotional concern displayed in social interactions.

Social Skills

The OT condition displayed a large improvement in social skills, namely global skills. The global component consists of overall social skill, content (e.g., appropriateness of the content to the discussion) and overall social anxiety. Interestingly, compliance was not related to social skills performance for the OT condition, rather compliance was related to performance for the PL condition.

Studies evaluating the effects of OT on social functioning have used paradigms similar to the social skills task used in the present study (e.g., Ditzen et al., 2009; Hall et al., 2012). These studies have found that certain aspects of social skills, as measured by performance-based measures, improve with exogenous OT. In a recent study, Hall et al. (2012) found eye gaze increased following 24 IUs of OT and decreased social anxiety after 48 IUs of OT in individuals with Fragile X syndrome (a condition associated with interpersonal difficulties). In another social skills and OT study, Ditzen et al. (2009) found

one 40 IU dose of OT was related to an increase in overall positive behavior (positive behavior defined as eye contact, agreement, nonverbal positive behavior, etc.) for couples during a role-play conflict compared to those given a placebo. Thus, there is some preliminary evidence that OT can improve social functioning at an observable level.

In the current study, significant changes were seen in global skills and not in nonverbal or specific social skills. Changes in global skill may be more apparent during a shorter role-play (90 seconds) than other aspects of social skills. Both role-plays in Hall et al. (2012) and Ditzen et al. (2012) were 10 minutes long; it may have been more difficult to observe treatment effects in subtle nonverbal behavior and specific social skills (e.g., eye gaze) during the 90-second role play that was used in the current study.

Global social skills are critical elements for successful interactions. The mechanism of change for improved social skills in the current study is unknown. OT may improve aspects of social cognition, such as ToM and empathy, that in turn improve overall social skills. This proposition is consistent with findings that social cognition is a robust predictor of social functioning (Fett et al., 2011). The improvement in global social skills is certainly a central finding in the current study. Furthermore, the effect size for global social skills in the OT group is similar to the effect sizes found for psychosocial treatments targeting social functioning [see Kurtz and Mueser's (2008) meta-analysis of social skills interventions in schizophrenia]. Overall, these results are preliminary evidence that OT improves social functioning in schizophrenia.

Emotion recognition

High intensity emotions.

Post-hoc analyses revealed significant improvements in the recognition of faces with *extreme* emotional intensity in the OT group. These results are consistent with studies demonstrating that identification of extreme emotions is more difficult for individuals with schizophrenia (Kohler et al., 2003) compared to non-clinical samples and others that have found OT affects perception of emotional intensity in schizophrenia (Goldman et al., 2011). Specifically, Kohler et al. (2003) found that individuals with schizophrenia have more robust difficulties in identification of extreme emotions as compared to non-clinical controls. Kohler et al. do not postulate why extreme emotions would be more compromised for individuals with schizophrenia; but, it is possible that extreme emotions may increase arousal and distress, which has been linked to decreased emotion recognition (Morris et al., 2009). Additionally, a recent study evaluating the effects of OT on emotion recognition in schizophrenia found that OT resulted in decreased intensity ratings of emotions (i.e., Goldman et al., 2011). Although participants were not rating the intensity of emotions in the current study, the present results and Goldman et al.'s findings suggest that OT may impact perception of emotional intensity.

Fear and anger recognition.

There was no change in recognition of fear and anger as was hypothesized. These results are not consistent with others who have found OT is associated with improved emotion recognition of fear in individuals with schizophrenia (Averbeck et al., 2012; Goldman et al., 2011) and anger in non-clinical samples (Fischer-Shofty et al., 2010). Given that recognition of negative emotions, such as fear, is impaired in schizophrenia (Gur et al., 2007), it is surprising that no effect was seen on recognition of these emotions after 6 weeks of OT treatment.

There have only been two published studies that have evaluated OT and emotion recognition in schizophrenia (Averbeck et al., 2012; Goldman et al., 2011). Averbeck et al. (2012) found an overall improvement in emotion recognition and a trend towards significantly improved fear recognition using a subset of Ekman's faces after one 24 IU OT dose. As discussed earlier, Goldman et al. (2011) found that a higher dose (20 IU) of OT, but not a lower dose (10 IU), increased emotion recognition accuracy. Specifically, the improvements in their study were found for fearful faces in a polydipsic schizophrenia sample. In fact, they found that 10 IUs actually decreased accuracy in affect recognition in participants.

The results of Averbeck et al. (2012) and Goldman et al. (2011) suggest that OT may only target specific emotions, particularly fear. In addition, it seems that emotion recognition is sensitive to OT dosage and may be ameliorated in certain individuals with schizophrenia. In comparing these two studies with the present study, it is interesting to consider whether dosage did indeed impact the results in the present study. Perhaps there is a curvilinear dosage response where no treatment effect (or worse performance) is seen in low and higher levels of intranasal OT. (Note, participants were administered approximately 24IUs of OT daily for six-weeks in the current study.)

Aside from differences in dosage, inconsistencies in study designs may account for discrepant results (Bourke et al., 2010). One major difficulty in comparing across studies is that the stimuli administered are not constant. Whereas the current study used the ER-40, others have used different facial stimuli, such as the Ekman faces (e.g., Averbeck et al., 2012; Goldman et al., 2011); although, the Ekman faces task is not as psychometrically sound as the ER-40 (see Carter et al., 2009). In addition, stimuli differ in their presentation.

Some are static (such as the stimuli in the present study), while others have used morphed faces (e.g., Fischer et al., 2010). However, Averbeck et al., (2012) evaluated the effects of OT on morphed and unmorphed faces, and did not find a difference in performance. Another important point is that the duration of the stimuli varies, with some presenting for an unlimited amount of time (Goldman et al., 2011) and others where the stimuli are time-limited (Averbeck et al, 2012). It would behoove researchers to replicate emotion recognition results using the same stimuli and methods across studies. This would elucidate the effects of OT on emotion recognition and help build a more consistent body of evidence.

Social Perception

The hypothesis that OT would impact social perception as measured by trustworthiness judgments was not supported, although there was a moderate (non significant) increase in rating untrustworthy faces as more trustworthy in the OT group. The only other study to assess OT's impact on trustworthy ratings in schizophrenia was Pedersen et al. (2011). Pedersen et al. found a trend towards increased ratings of trustworthiness for untrustworthy faces after two-weeks of OT.

Other researchers evaluating the effect of OT on social perception have found mixed results (Bartz et al., 2011). Specifically, OT has been associated with increased trustworthiness (Kosfeld et al. 2005; Theodoridou et al., 2009) in non-clinical samples. On the contrary, others have found it has actually been associated with increased *mistrust* in certain populations (e.g., Borderline Personality Disorder; Bartz et al., 2010). A recent meta-analysis found that OT was related to increased trust for *in*-group members and there was no effect on trust of *out*-group members (Van Ijzendoorn & Bakermans-Kranenburg, 2011). This implies that the effect of OT on social perception, particularly trust, is nuanced.

One reason for not observing significant and larger changes in social perception may be related to the measure of trustworthiness. Perhaps the current study's trustworthiness design did not tap into real-world trusting behavior; other studies that have found a significant relationship between OT and trust behavior in schizophrenia (e.g., sharing a secret paradigm in Keri et al., 2011) and non-clinical samples (e.g., Zak et al., 2005) have used more ecologically-valid measures. Zak et al. (2005) found OT was related to trust behavior in a non-clinical sample using a cash transfer paradigm. Specifically, the OT group was more trusting when they received money from a person who had *chosen* a certain amount to give as compared to when they received an amount that was randomly chosen. Thus, intention may be important in impacting trusting behavior, which was not assessed in the current study. This suggests that OT may be implicated in reciprocal trust rather than generalized trusting behavior. In sum, further research is necessary to better understand the relationship between OT and trust behavior in schizophrenia. Future studies should consider utilizing more complex and ecologically valid social perceptual measures that assess intention.

Attribution Style

The current study also explored the relationship between OT and attribution style. There was no specific effect of OT on attribution style. Instead, both groups showed moderate to large decreases in blame and hostility biases. In addition, compliance was significantly associated with AIHQ blame bias in the OT condition. That is, greater OT compliance was related to a greater reduction in blame bias--underscoring the importance of accounting for compliance in OT trials.

Subjective social and community functioning

Additional exploratory aims were to evaluate OT's effects on self-reported social and community functioning. Although within group increases in social and community functioning were observed in the OT group, the PL condition also showed moderate to large improvements in these areas. It is noteworthy that the OT group had slightly higher scores on the SLOF at baseline and still improved on social and community functioning (the opposite of what one would expect if regression to the mean was present).

It should be noted that a limited sample completed the SLOF at baseline and 6-weeks (n=11) because the measure was not collected at six-weeks for the participants in the 12-week trial and was not collected for three of the 6-week participants. It is possible that a longer duration than six-weeks is needed to observe treatment effects on community functioning. Regardless, future OT research should consider including the SLOF given its relationship to social cognition (Smith et al., 2012) and social functioning (Bowie et al., 2007).

Symptoms

Although not a preliminary aim in the current study, there were large effect sizes for decreased negative symptoms in the OT group as compared to the PL group at 6 weeks. This is consistent with previous research in the area (e.g., Bakharev et al. 1986; Fiefel et al., 2011; Pedersen et al., 2011). Conversely, the PL group showed an increase (albeit non-significant) in negative symptoms. These results are especially intriguing in that greater negative symptoms are strongly related to decreased social functioning in schizophrenia (Mancuso et al., 2011) and quality of life (Fujimaki et al. 2012). In addition, current antipsychotics do not significantly ameliorate negative symptoms (Bellack et al., 2004).

Although reductions in total, positive, and general symptoms were also found for the OT group, similar reductions were observed in the placebo group. A closer look at the compliance data reveals that compliance was significantly correlated to change in general symptom scores for the OT group and a trend correlation with total PANSS scores; compliance was not related to symptom scores for the PL condition. Thus, greater compliance was associated with a larger reduction in total PANSS and general symptoms; again, underscoring the importance of assessing OT compliance and analyzing its relationship to treatment outcome.

Limitations

A major limitation of the current study is sample size. The small sample size precluded making definitive conclusions about the effects of OT treatment on social cognition in schizophrenia. Similarly, the sample size did not permit exploration of variables that may be related to treatments effects (e.g., subgroups of individuals who show greater benefits from OT). However, the sample size in the current study is similar to the other OT schizophrenia treatment trials that have found significant OT treatment gains [Feifel at al., 2010 (n=15); Goldman et al., 2011 (n=13)]. Regardless, larger sample sizes are needed to further characterize the effects of OT on social cognition.

The current study did not include a thorough evaluation of potential OT mediators, such as neurocognition and anxiety. Neurocognition was only assessed in a portion of the participants and so it is unknown whether OT influenced neurocognition in the current study. Since other research has show OT is related to improved neurocognition (MacDonald & MacDonald, 2010), further research in this area is warranted. Surprisingly, anxiety as measured by the Liebowitz Social Anxiety Scale (LSAS) and PANSS-anxiety item did not

significantly change in the OT condition. The anxiolytic effects of OT are well documented (Lee et al., 2010). Many other studies evaluating anxiety, though, have used more objective and biological measures (e.g., cortisol levels); it is possible that the LSAS and the PANSS anxiety item were not sensitive to treatment effects. Additionally, as noted previously, individuals with schizophrenia have trouble accurately identifying emotional states (Dernt et al., 2009). Perhaps more general measures of anxiety may be appropriate (e.g., the Beck Anxiety Inventory or an evaluation of cortisol levels), since the LSAS focuses on social anxiety, and the PANSS-anxiety item is limited in that it is a single score of anxiety (rated zero to seven). It is prudent for future research to use valid and appropriate measures of anxiety to further investigate whether the anxiolytic effects of OT mediate improvements on social cognition in schizophrenia.

The moderating effects of gender could not be explored due to only having three females in the current study. Other OT treatment trials have similarly recruited mostly males (e.g. Feifel et al., 2010). One reason for the difficulty in recruiting females may be related to this study's inclusion and exclusion criteria. Participants must have had social difficulties (determined by scores on the socially-relevant PANSS items and/or performance on the Eyes Test) to be included in the study. Reviews find that females with severe mental illness exhibit less social impairment as compared to men with severe mental illness (Scott, 2011); therefore, females were less likely to meet the inclusion criteria of the study. While it is possible that men with schizophrenia have a greater need for treatments targeting social cognition, future research should consider exploring this variable further.

Another limitation concerns compliance. Compliance was related to performance on a variety of measures in the current study and therefore future research must pay careful

attention to this issue. Although efforts were made to maintain compliance in the current study (e.g., reminder calls), compliance was still not 100 percent. Medication compliance is a documented problem in schizophrenia (Moritz et al., 2012), so it is not surprising that it would be a consideration for OT treatment. Other approaches to improve compliance, such as daily diary logs may be helpful in alleviating this issue.

An additional limitation is that no follow up data were obtained. It is unclear whether treatment effects persist when the treatment has ended and how long these effects last. Follow-up data could also provide information as to whether effects generalize to other areas (e.g., service utilization, therapeutic alliance). Other OT treatment trials in schizophrenia have similarly not included follow-up (e.g., Feifel et al., 2011), so it is critical for future studies to include follow-up visits in their designs to more thoroughly characterize the effects of OT on social cognition.

Lastly, the IRI self-report measure of empathy is intended to be a *trait* measure (Davis, 1983). In the current study, participants were prompted to focus on their current empathic tendencies in order to try and assess state rather than trait empathy (i.e., participants were asked to respond to the questions using the last month as a timeframe). Although the IRI is intended to be a trait measure, other studies have found treatment effects using the IRI; for example, Sands, et al. (2008) administered the IRI to assess the efficacy of a training program designed to improve empathy in health-care providers. Interestingly, they found increased perspective-taking on the IRI in the providers who received the training. The Sands et al. (2008) study suggests that the IRI is sensitive to treatment effects even-though it is intended to be a trait measure. In addition, the IRI demonstrated poor internal consistency on two of the subscales (Perspective Taking and Distress) in the current study. Although this

measure has been widely used in schizophrenia research, surprisingly its psychometric properties have not been examined in this population. Therefore, it is critical to evaluate the validity and reliability of the IRI in schizophrenia samples and to assess empathy using measures with established psychometric properties.

Conclusions

Overall, the results of the current study suggest that OT improves specific aspects of social cognition, such as cognitive ToM, cognitive empathy, recognition of high intensity emotional stimuli, as well as global social skills and negative symptoms in schizophrenia. While these findings are preliminary, they indicate that OT may be a potential treatment for social functioning difficulties in schizophrenia or as an adjunctive treatment with psychosocial approaches. An additional point worth noting is that OT appears to be well-tolerated; compliance rates were similar between the OT and PL groups and there were no significant adverse events related to OT reported in the current study.

The verdict is still out on OT's mechanism of change. Bartz et al.'s (2011) recent review of OT and social cognition argues that OT is context dependent, which might explain the observed differential effects on social cognition. That is, Bartz et al.'s review found that 63% of the studies reviewed showed individual and situational moderating effects of OT and 43% showed no main effect of OT. Bartz et al. argue that contextual factors, such as the social salience of stimuli, likely moderate the impact of OT. Therefore, it is strongly recommended that individual and context specific factors be accounted for in future studies. Such factors include evaluating those who would most benefit from OT treatment.

In sum, this study indicates that OT may lead to improved social cognition and social functioning in schizophrenia; more research, however, is needed to better understand the magnitude and extent of its effects. While social functioning difficulties are not unique to schizophrenia, they are markedly compromised in this population (Mausbach et al., 2010), and linked to outcome (Niendam et al., 2009). OT has the potential to improve important social processes in schizophrenia and thereby the quality of life of those affected and their families.

Table 1

Inclusion criteria for the 6 and 12-week trials

Criterion	6 week trial	12 week trial
Diagnosis	Schizophrenia	Schizophrenia *or* Schizoaffective Disorder
PANSS Symptoms	4 ≥ suspic/para *or* 3 ≥ suspic/para *and* hostility, passive social avoidance, active social avoidance *or* uncooperativeness *and* 60 ≥ total score	3 ≥ on 2 of the following: suspic/para, passive social avoidance, active social avoidance, *or* uncooperativeness
Eyes Test [a]	N/A	PANSS criteria *or* < 24[b] on total score at screening

PANSS=Positive and Negative Symptoms Scale; suspic/para=suspiciousness/paranoia item on PANSS

[a]Lower scores indicate worse performance on the Eyes Test, test range is 0-36.

[b]There were 5 participants in the 6 week trial who had Eyes Test Scores 24 and greater; however, these 5 participants met the 12-week PANSS symptom requirements so would still have been included in the 12-week trial.

Table 2

Demographic Information

	Oxytocin (*n*=10)		Placebo (*n*=9)		
Demographic variable	***n***	**%**	***n***	**%**	***p* value**
Male	8	80	8	88.9	.596
Caucasian	5	50	5	54.6	.809
Greater than HS education	6	60	5	55.6	.936
Diagnosis					.622
Paranoid sz	8	80	8	88.89	
Undifferentiated sz	1	10	1	11.11	
Schizoaffective	1	10	0	0	
	Mean	**SD**	**Mean**	**SD**	
Age in years	41.20	8.8	36.78	12.0	.369
Years ill	15.25	10.22	14.0	9.5	.786
Hospitalizations	8.2	14.92	6.11	5.2	.695
Neurocognitive Functioning[1]	-.31	.76	.20	1.11	.329

Sz=schizophrenia

Note. Chi-square for comparison of proportions; t-test for age, # of years ill, # of hospitalizations, neurocognitive functioning

[1]z scores; 10 participants completed the Brief Assessment of Cognition (BACS) & 5 completed the Repeatable Battery of Neuropsychological Status (RBANS), 4 participants did not complete a baseline cognitive measure.

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Table 3

Social cognitive measures: BL and 6-week within and between group analyses

	Oxytocin (*n*=10)			Placebo (*n*=9)			Predictor: Group	Cohen's d^2		
Measure	BL Mean (SE)	Week 6 Raw Mean (SE)	Week 6 LS Mean (SE)	BL Mean (SE)	Week 6 Raw Mean (SE)	Week 6 LS Mean (SE)	*B*(SE)	Between Group	Within Group OT	Within Group PL
ER-40	31.20(1.16)	32.50(1.20)	33.14(.86)	33.33(1.25)	34.67(1.00)	34.21(.96)	-.82(1.25)	-.38	.60	.39
Anger	4.90(.38)	4.60(.40)	5.00 (.38)	6.00(.44)	6.00(.47)	5.56 (.336)	-.56(.48)	-.55	-.30	0
Fear	6.00(.49)	6.50(.56)	6.89 (.37)	7.11(.655)	7.11(.539)	6.68 (.39)	.21(.55)	.18	.33	0
Happy	7.60(.22)	7.80(.20)	7.94 (.12)	8.00(.00)	7.89(.11)	7.74 (.13)	.20(.18)	.53	.48	-.33
NO	6.40(.40)	7.10(.35)	7.09 (.29)	6.33(.65)	7.22(.28)	7.23 (.31)	-.14(.43)	-.15	.53	.63
Sad	6.30(.54)	6.50(.58)	6.40 (.48)	5.89(.564)	6.44(.503)	6.55 (.50)	-.15(.70)	-.11	.23	.24
Mild	11.11(.54)	11.22(.66)	11.58 (.59)	12.22(.760)	12.89(.735)	12.53 (.59)	-.96(.85)	-.53	.13	.28
Extreme	13.89(.56)	**14.33(.60)**[a]	14.77 (.24)	14.78(.596)	14.56(.626)	14.12 (.244)	**.65(.35)**[b]	.86	.85	-.27
Eyes Test	20.40(.98)	21.50(1.64)	22.07 (1.63)	21.67(1.86)	21.44(2.59)	20.81 (1.72)	1.3(2.4)	.25	.31	-.04
Brune Tot	18.30(.87)	**20.10(.80)**[a]	20.36 (.74)	19.89(.89)	21.22(.78)	20.93 (.79)	-.56(1.1)	-.24	.74	.41
1st order	3.70(.37)	4.10(.31)	4.13 (.27)	4.00(.289)	4.56(.242)	4.52 (.29)	-.38(.40)	-.47	.30	.64
2nd sum	3.80(.29)	4.50(.17)	4.48 (.21)	4.44(.176)	4.67(.167)	4.69 (.22)	-.21(.32)	-.32	.97	.24
3rd false	2.00(.26)	2.30(.30)	2.32 (.26)	2.56(.176)	2.67(.167)	2.64 (.28)	-.32(.40)	-.39	.26	.14
Rec.	2.70(.15)	2.70(.15)	2.70 (.15)	2.89(.111)	2.78(.147)	2.78 (.16)	-.09(.23)	-.18	0	-.18
Dec.	2.30(.26)	**2.80(.13)**[a]	2.79 (.10)	2.22(.32)	2.56(.176)	2.57 (.11)	.21(.15)	.67	1.39	.59
Trust Tot	4.3(16.48)	7.40(12.06)	9.11 (7.11)	9.78(6.77)	6.11(9.91)	4.21 (7.49)	4.91(10.34)	.22	.15	-.14
Untrust	-10.90(4.85)	-7.10(3.63)	-7.19 (3.29)	-11.56(2.51)	-13.67(3.28)	-13.56 (3.47)	6.37(4.78)	.62	.28	-.17
Trust	11.00(3.63)	9.40(2.38)	10.61 (1.26)	14.67(1.75)	13.22(2.09)	11.88 (1.33)	-1.27(1.86)	-.32	-.40	-.35
IRI total[1]	87.86(4.99)	87.43(5.93)	88.45 (3.49)	90.13(2.99)	83.63(3.38)	82.73 (3.3)	5.72(4.80)	.55	-.05	-.71
Fantasy	21.00(2.44)	21.29(1.87)	22.50 (2.26)	24.88 (2.28)	22.13(2.87)	21.02 (2.10)	1.53(3.16)	.23	.06	-.41
Emotion	27.00(1.58)	24.57(2.11)	23.47 (1.28)	24.25(2.72)	24.38(2.08)	25.34(1.20)	-1.87(1.78)	-.49	-.93	.03
PT	20.71(.94)	**22.86(1.01)**[a]	24.43 (1.18)	23.25(2.11)	21.50(2.85)	20.13 (1.10)	**4.30(1.64**[c]	1.22	1.02	-.67
Distress	19.14(1.08)	18.71(1.63)	18.09 (1.04)	17.75(1.66)	**15.63(1.48)**[a]	16.17 (.97)	1.92(1.44)	.62	-.13	-1.30

Note. The beta coefficients are analyzed controlling for baseline social cognitive performance; LS=Least Squares Means; SE=Standard error; ER-40=Emotion Recognition-40; NO=No emotion/neutral; 1st order sum=Brune 1st order theory of mind total score; 2nd sum= Brune 2nd order theory of mind sum score; 3rd false= Brune 3rd order theory of mind false belief score; Rec.= accurate detection of reciprocity on Brune; Dec.=accurate detection of deception on Brune; Trust overall=overall score on trustworthiness task; Untrust=score on faces judged as mostly untrustworthy by a normative sample; Trust=score on faces judged as mostly trustworthy by a normative sample; IRI=Interpersonal Reactivity Index; PT=Perspective-Taking; B=unstandardized beta coefficient. BL raw means presented; 6 week raw and least squares means presented. Values in bold indicate statistical significance.

[1] *n*=15 for participants completing the IRI.

[2]Effect sizes with positive values are in the expected direction (improvement on social cognitive measures, higher scores in OT group); within group effect size accounts for dependence of baseline and week-6 means; between group effect size uses the pooled standard deviation and least squares means.
[a] indicates significant within group difference from BL to 6 weeks, $p<.05$
[b] indicates significant group beta coefficient, $p<.10$
[c] indicates significant group beta coefficient, $p<.05$

Table 4

Correlations between empathy role-play scores, IRI, and Eyes Test (n=21)

Measure *r(p)*	Total Empathy	Emotion	Cognitive	Ideo	Summary	Eyes	IRI-TOT	IRI-EC	IRI-F	IRI-D	IRI-PT
Total Empathy	-	**.59(.005)****	**.71(.000)****	**.68(.001)****	**.74(.000)****	-.30(.188)	.42(.110)	.38(.151)	.33(.210)	-.12(.672)	.04(.874)
Emotion	**.59(.01)****	-	.05(.836)	.33(.147)	.28(.216)	-.34(.136)	.31(.246)	.39(.141)	.12(.648)	-.20(.451)	.16(.561)
Cognitive	**.71(.001)****	.05(.836)	-	.24(.209)	.58(.006)**	-.10(.679)	.31(.243)	.19(.475).	.32(.222)	.02(.944)	-.04(.871)
Ideo	**.68(.001)****	.33(.147)	.24(.209)	-	.20(.377)	-.18(.439)	.46(.073)	.32(.222)	.37(.162)	.03(.913)	.04(.879)
Summary	**.74(.000)****	.28(.216)	**.58(.006)****	.20(.377)	-	-.22(.338)	.06(.818)	.19(.480)	.05(.857)	-.24(.378)	.01(.963)
Eyes Test	-.30(.188)	-.34(.136)	-.10(.679)	-.18(.439)	-.22(.338)	-	.33(.206)	13(.631)	.17(.523)	.09(.748)	.25(.352)
IRI-TOT	.42(.110)	.31(.246)	.31(.243)	.46(.073)	.06(.818)	.33(.206)	**-**	**.64(.007)****	**.63(.010)****	-.09(.753)	**.54(.029)***
IRI-EC	.38(.151)	.39(.141)	.19(.475).	.32(.222)	.19(.480)	.13(.631)	**.64(.007)****	-	-.11(.694)	**-.63(.009)****	**.79(.001)****
IRI-F	.33(.210)	.12(.648)	.32(.222)	.37(.162)	.05(.857)	.17(.523)	**.63(.010)****	-.11(.694)	-	.36(.175)	-.17(.542)
IRI-D	-.12(.672)	-.20(.451)	.02(.944)	.03(.913)	-.24(.378)	.09(.748)	-.09(.753)	**-.63(.009)****	.36(.175)	-	**-.68(.004)****
IRI-PT	.04(.874)	.16(.561)	-.04(.871)	.04(.879)	.01(.963)	.25(.352)	**.54(.029**)*	**.79(.001)****	-.17(.542)	**-.68(.004)****	-

Total Empathy=Total score on empathy role play; Emotion=emotional empathy role play item; cognitive=cognitive empathy role play item; ideo=ideomotoric item on role play; summary=summary item on role-play; IRI=Interpersonal Reactivity Index; TOT=IRI Total score; EC=Emotional concern; F=Fantasy; D=Distress; PT=Perspective Taking; Higher scores on empathy role play items indicate higher levels of empathy; Higher: IRI-TOT indicate greater self-reported empathy, IRI-EC indicates greater self-reported emotional concern, IRI-F indicates greater reported use of fantasy, IRI-D indicates greater distress when others are distressed, IRI-PT indicates greater self-reported perspective-taking; Higher Eyes Test scores indicates better performance. Values in bold indicate statistical significance.

*significant correlation, pearson two-tailed, $p<.05$

**significant correlation, pearson two-tailed, $p<.01$

Table 5

Role-play measure: BL and 6-week within and between group analyses

	Oxytocin (*n*=10)			Placebo(*n*=9)			Predictor: Group	Cohen's *d*[1]		
Measure	BL Mean (SE)	Week 6 Raw Mean (SE)	Week 6 LS Mean (SE)	BL Mean (SE)	Week 6 Raw Mean (SE)	Week 6 LS Mean (SE)	*B (SE)*	Between Group	Within Group OT	Within Group PL
Empathy										
Cognitive	2.90(.28)	3.10(.38)	3.10(.35)	2.89(.31)	2.83(.311)	2.83(.37)	.266(.51)	.24	.14	-.05
Emotion	3.95(.19)	4.05(.19)	4.01(.21)	3.78(.22)	3.39(.29)	3.44(.23)	**.571(.31)**[d]	.84	.18	-.46
Ideo	2.60(.31)	2.55(.28)	2.54(.23)	2.56(.24)	2.44(.18)	2.45(.24)	.092(.33)	.13	-.05	-.21
Overall	3.20(.13)	3.25(.31)	3.22(.27)	3.00(.29)	2.78(.22)	2.81(.28)	.406(.39)	.48	.05	-.34
Total	12.65(.60)	12.95(.92)	12.82(.73)	12.22(.80)	11.44(.77)	11.59(.77)	1.22(1.06)	.53	.12	-.38
Social Skill-RP1										
Global	10.85(.53)	**11.75(.29)**[b]	11.75(.33)	10.83(.56)	10.67(.53)	10.67(.35)	**1.076(.49)**[c]	.99	.77	-.11
Specific	20.05(1.02)	19.55(.84)	19.16(.70)	18.44(.91)	18.89(.86)	19.32(.74)	-.159(1.04)	-.07	-.28	.14
Nonverbal	12.40(.56)	12.05(.37)	11.92(.40)	11.67(.41)	10.78(.49)	10.92(.42)	1.007(.59)	.80	-.23	-.62
Social Skill-RP2										
Global	11.90(.233)	12.10(.51)	11.99(.43)	11.72(.38)	**10.56(.65)**[a]	10.67(.45)	**1.320(.62)**[c]	.98	.17	-1.20
Specific	19.80(.83)	20.50(.80)	20.27(.71)	18.78(.70)	18.33(.78)	18.60(.75)	1.670(1.04)	.75	.10	-.19
Nonverbal	12.35(.48)	11.75(.34)	11.67(.36)	11.94(.34)	**10.90(.45)**[a]	10.97(.38)	.701(.53)	.61	-.46	-.78

LS=Least Square Mean; Total Empathy=Total score on empathy role play; Emotion=emotional empathy role play item; cognitive=cognitive empathy role play item; ideo=ideomotoric item on role play; summary=summary item on role-play; RP1=role play 1, "getting to know your neighbor"; RP2=role play2, "empathy role play"; Global=global social skill subscore; specific=specific social skill subscore; nonverbal=nonverbal social skill subscore; OT=Oxytocin; PL=placebo; Higher scores on role plays indicate better social skills and higher rated empathy. Bold values indicate statistical significance and trend significance; B=unstandardized beta coefficient

[1]Effect sizes for the empathy and social skill role-play are positive if in the expected direction (i.e., improvement over time or higher score in the OT group); within group effect size accounts for dependence of baseline and week-6 means; between group effect size uses the pooled standard deviation and least squares means.

[a] indicates significant within group difference from BL to 6 weeks, $p<.05$

[b] indicates trend within group difference from BL to 6 weeks, $p<.10$

[c] indicates significant group beta coefficient, $p<.05$

[d] indicates trend group beta coefficient, $p<.10$

Table 6

Exploratory analyses: BL and 6 week within and between group analyses

	Oxytocin			Placebo			Predictor: Group	Cohen's d^2		
Measure	BL Mean (SE)	Week 6 Raw Mean (SE)	Week 6 LS Mean (SE)	BL Mean (SE)	Week 6 Raw Mean (SE)	Week 6 LS Mean (SE)	*B(SE)*	Between Group	Within Group OT	Within Group PL
AIHQ										
	2.12(.15)	1.76(.18)	1.78(.15)	2.20(.20)	**1.80(.15)**[a]	1.78(.16)	-.01(.22)	.00	-.53	-1.12
Hostility										
Agg.	1.18(.09)	1.85(.11)	1.85(.09)	1.79(.07)	1.82(.05)	1.83(.09)	.02(.13)	.11	.10	.22
Blame	3.28(.23)	2.85(.27)	2.74(.26)	2.92(.29)	**2.45(.39)**[a]	2.62(.27)	**.**12(.39)	.20	-.45	-.99
[1]SLOF-Participant										
Social	50.80(3.04)	**54.40(3.97)**[a]	49.59(2.03)	43.80(1.69)	47.80(3.58)	52.61(2.03)	-3.02(3.15)	-.67	1.92	.64
Total	129.40(5.58)	**133.40(6.8)**[a]	122.32(3.58)	113.40(3.67)	117.00(7.48)	128.08(3.58)	-5.76(5.70)	-.72	2.15	1.10
SLOF-Informant										
Social	50.80(2.22)	49.60(2.44)	48.86(2.46)	48.80(3.57)	50.40(3.76)	51.14(2.46)	-2.82(3.50)	-.42	-.17	.58
Total	125.80(3.25)	124.80(2.20)	120.49(3.12)	117(6.67)	119 (7.98)	123.31(3.12)	-2.82(4.59)	-.43	-.14	.50

AIHQ=Ambiguous Intentions Hostility Questionnaire; Agg=Aggression; SLOF=Several Levels of Functioning; B=unstandardized beta coefficient.
Bold indicates statistical significance

[1] n=11 for participants completing the SLOF (6 OT; 5 PL)

[2] Effect sizes for the AIHQ with a negative sign are in the expected direction; Effect sizes for the SLOF with a positive sign are in the expected direction; within group effect size accounts for dependence of baseline and week-6 means; between group effect size uses the pooled standard deviation and least squares means.

[a] indicates significant within group difference from BL to 6 weeks, p<.05

Table 7

Symptom Measures: BL and 6-week within and between group analyses

	Oxytocin			Placebo			Predictor: Group	Cohen's d^1		
Measure	BL Mean (SE)	Week 6 Raw Mean (SE)	Week 6 LS Mean (SE)	BL Mean (SE)	Week 6 Raw Mean (SE)	Week 6 LS Mean (SE)	B(SE)	Between Group	Within-Group OT	Within Group PL
Liebowitz	54.90(9.87)	43.60(8.45)	48.71 (7.57)	68.33(8.32)	53.89(12.57)	48.21 (8.00)	.51(11.18)	.02	-.52	-.66
PANSS total	71.50(3.91)	**62.70(2.89)[a]**	63.40 (2.07)	75.00(5.46)	67.78(2.77)	67 (2.18)	-3.61 (3.02)	-.55	-1.25	-.68
Positive	17.10(1.49)	**14.70(1.24)[a]**	15.84 (.84)	20.22(2.11)	**16.89(1.98)[a]**	15.62 (.89)	.22 (1.25)	.08	-1.15	-.99
Negative	20.50(1.30)	**17.80(1.23)[b]**	16.79 (1.15)	17.44(1.20)	19.44(1.61)	20.57 (1.22)	**-3.78(1.74)[c]**	-1.03	-1.54	.42
General	33.90(2.19)	**30.00(1.42)[a]**	30.62 (1.04)	37.33(3.17)	**31.44(1.46)[a]**	30.76 (1.09)	-.13 (1.52)	-.04	-.78	-1.34
Anxiety	2.80(.47)	2.50(.522)	2.61(.41)	3.33(.624)	2.22(.401)	2.10(.43)	.517(.60)	.40	-.17	-1.00

SE=standard error; PANSS=Positive and Negative Symptom Scale; Liebowitz=Liebowitz Anxiety Scale; Anxiety item=single PANSS anxiety item; BL=baseline; PL=placebo; Beta=unstandardized beta coefficient.

Bold indicates statistical significance

[1]Effect sizes with a negative sign are in the expected direction; within group effect size accounts for dependence of baseline and week-6 means; between group effect size uses the pooled standard deviation and least squares means.

[a] indicates significant within group difference from BL to 6 weeks, $p<.05$

[b] indicates significant within group difference from BL to 6 weeks, $p<.001$

[c] indicates significant group beta coefficient, $p<.05$

Table 8

Correlations between compliance and 6 week-change scores on social cognitive, self-report measures, and symptoms

Measure	OT *r*(*p* value)	PL *r* (*p* value)
Social Cognitive		
ER-40	-.02(.961)	**-.71(.03)**[a]
Eyes Test	.25(.510)	.26(.495)
Brune Total	.41 (.270)	-.06(.884)
Trust Overall	-.33 (.385)	.19(.633)
IRI total	-.17(.722)	-.24(.56)
AIHQ-Agg	-.40(.286)	-.09(.815)
AIHQ-Blame	**-.80 (.010)**[a]	-.31(.415)
AIHQ-Host	-.27(.479)	-.12(.753)
Social & Community Functioning		
SLOF-Soc (P)	.02(.977)	-.65(.234)
SLOF-Tot (P)	-.46 (.434)	-.42(.482)
SLOF-Soc (I)	-.36(.555)	-.12(.854)
SLOF-Tot (I)	-.61(.274)	-.02(.97)
Symptoms		
PANSS-Total	-.59(.096)	-.17(.672)
Positive	-.37(.331)	-.52(.15)
General	**-.71(.034)**[a]	-.21(.594)
Negative	.002(.997)	.20(.602)
Anxiety Item	-.49(.18)	-.16(.67)
Liebowitz	.18(.636)	-.08(.845)

OT=oxytocin group; PL=placebo group; ER-40=Emotion Recognition-40; Trust overall=overall score on trustworthiness task; IRI=Interpersonal Reactivity Index; AIHQ=Ambiguous Intentions Hostility Questionnaire; Agg=Aggression Bias; Blame=Blame bias; Host=Hostility bias; SLOF=Several Levels of Functioning; (P)=participant SLOF; (I)=informant SLOF; PANSS=Positive and Negative Symptom Scale; Liebowitz=Liebowitz Anxiety Scale; *Note*: change scores calculated by subtracting BL score from 6-week score; Positive correlations for the ER-40, Eyes Test, Brune, Trust Overall, IRI, and SLOF indicate improved performance at 6 weeks is related to higher compliance; Negative correlations for AIHQ and symptom measures indicate decreased attributional biases and symptoms at 6 weeks is related to higher compliance.
Bold values indicate statistical significance.

[a] statistically significant at $p<.05$

Table 9

Correlations between compliance and 6 week-change scores on role-play measures

Measure	OT *r*(*p* value)	PL *r* (*p* value)
Empathy		
Empathy, cognitive	.33(.392)	**.92(.000)**[a]
Empathy, emotion	.33(.389)	.546(.128)
Empathy, ideo	-.436(.241)	-34(.377)
Empathy, overall	**.854(.003)**[a]	**.796(.010)**[a]
Social Skill		
Global, RP 1	-.283(.461)	.379(.314)
Global, RP 2	.432(.246)	**.747(.021)**[a]
Specific, RP 1	-.444(.232)	.061(.877)
Specific, RP 2	.261(.498)	.586(.097)
Non Verbal, RP 1	-.05(.898)	-.407(.277)
Non Verbal, RP 2	.146(.708)	.259(.500)

OT=oxytocin group; PL=placebo group; empathy, ideo=ideomotoric item; RP=role-play (1="getting to know your neighbor"; 2=empathy roleplay).

Note: change scores calculated by subtracting BL score from 6-week score. Positive correlations indicate improved performance on role-play measures is related to higher compliance. Bold indicates statistical significance

[a] statistically significant, pearson two-tailed correlation, $p<.05$

Appendix

Flow sheet of measures of social cognition, psychiatric symptoms, social and community functioning, neurocognition and compliance

Measure	Screen	Baseline	2	4	6	Screen	Baseline	2	4	6
	6 week trial (*n*=15)					12 week trial (*n*=5)				
Phone Screen	X					X				
Psychiatric Ratings-PANSS	X	X	X	X	X	X	X	X		X
ER-40 and Trustworthiness Tests		X	X	X	X		X			X
Eyes Test		X	X	X	X	X	X			X
Brüne Test, AIHQ		X	X		X		X			X
Role –play (social skills and empathy)		X			X		X			X
BACS[1] (neurocognition)		X	X		X					
RBANS[2] (neurocognition)							X			
IRI[3]		X	X	X	X		X			X
SLOF-P/I[4]		X			X		X			
LSAS		X	X	X	X		X			X
Compliance			X	X	X			X		X

PANSS=Positive and Negative Symptom Scale; ER-40=Emotion Recognition-40; Eyes=Eyes Test; AIHQ=Ambiguous Attributions and Hostility Questionnaire; BACS=Brief Assessment of Cognition in Schizophrenia; RBANS=Repeatable Battery for the Assessment of Neuropsychological Status; IRI=Interpersonal Reactivity Index; SLOF-P/I=Specific Levels of Functioning Patient and Informant Version; BSI-A=Brief Severity Index, anxiety items; LSAS= Liebowitz Social Anxiety Scale. [1]*n*=10, [2] *n*=5; [3] *n*=15, [4] *n*=11

TELEPHONE SCREEN FOR POTENTIAL PARTICIPANTS (6 WEEK TRIAL)

"HI, I'M (STATE NAME) AND I'M CALLING ABOUT A RESEARCH STUDY BEING CONDUCTED AT UNC CALLED OXYTOCIN TREATMENT OF SOCIAL DEFICITS AND PARANOIA IN SCHIZOPHRENIA. I'M A RESEARCH ASSISTANT WORKING WITH DRS. PEDERSEN AND PENN IN THE PSYCHIATRY AND PSYCHOLOGY DEPARTMENTS. YOU CALLED (OR HAVE PARTICIPATED IN PAST STUDIES WITH US AND HAVE AGREED TO BE CONTACTED ABOUT FUTURE STUDIES OR EXPRESSED INTEREST TO YOUR CARE PROVIDER). I'M FOLLOWING UP TO DESCRIBE THE STUDY, SEE IF YOU ARE STILL INTERESTED IN PARTICIPATING AND TO ANSWER ANY QUESTIONS THAT YOU MAY HAVE ABOUT THE STUDY. I WILLALSO ASK YOU SOME QUESTIONS TO SEE IF YOU ARE ELIGIBILE FOR THE STUDY. THIS SHOULD ONLY TAKE ABOUT 5-10 MINUTES. THESE QUESTIONS WILL ASK ABOUT ANY SYMPTOMS OR EMOTIONAL DIFFICULTIES YOU HAD IN THE PAST OR RECENTLY. PLEASE NOTE THAT RESPONDING TO THESE QUESTIONS IS TOTALLY VOLUNTARY. ALSO, ALL INFORMATION WILL BE KEPT STRICTLY CONFIDENTIAL. FINALLY, ONCE YOUR ELIGIBILITY IS DETERMINED, THIS FORM AND ANY INFORMATION OBTAINED FROM IT WILL BE DESTROYED.

I'D LIKE TO GET SOME GENERAL INFORMATION. FIRST, I'LL NEED YOUR NAME, AGE, ETC

Name: _____ Age:_____ (Note: inclusion criteria is 18-55 years of age)

Gender: M F Ethnicity: _____ Where do you live_____?

Would you prefer to be tested at: _____UNC Hospitals in Chapel Hill or _____Central Regional Hospital in Raleigh (Dorothea Dix)

2. HOW DID YOU HEAR ABOUT THE STUDY? (Check correct answer)

From care provider _____ Flyer_____ Previous research participant _____ Other_____

STUDY DESCRIPTION

"NOW I'LL TELL YOU A LITTLE MORE ABOUT THE STUDY. THIS IS A STUDY TO SEE WHETHER TREATMENT WITH OXYTOCIN CAN IMPROVE SOCIAL SKILLS AND REDUCE SYMPTOMS LIKE PARANOIA IN INDIVIDUALS WITH SCHIZOPHRENIA. OXYTOCIN IS MADE NATURALLY IN THE BRAIN AND SEEMS TO INCREASE TRUST AND ACCURATE READING OF OTHERS' EMOTIONS AND TO DECREASE ANXIETY IN PEOPLE.

IF YOU TAKE PART IN THIS STUDY, YOU WILL BE INVOLVED FOR APPROXIMATELY 8 WEEKS. YOU WILL UNDERGO A SERIES OF 6 STUDY VISITS. THE STUDY VISITS LAST BETWEEN 2 AND 3.5 HOURS. THE STUDY VISITS ARE AT AN OUTPATIENT RESEARCH CLINIC (AT UNC IN CHAPEL HILL OR DOROTHEA DIX HOSPITAL IN RALEIGH, NOW CALLED CENTRAL REGIONAL HOSPITAL) AND YOU WILL COMPLETE SOME INTERVIEWS, QUESTIONNAIRES AND OTHER TASKS. AT THE END OF THE SECOND VISIT, YOU WILL TAKE YOUR FIRST TEST DOSE AND BEGIN A 6 WEEK TREATMENT PERIOD DURING WHICH YOU WILL TAKE EITHER OXTOCIN OR

PLACEBO IN A NASAL SPRAY TWICE DAILY. HALF OF THE PEOPLE IN THIS STUDY WILL BE RANDOMLY CHOSEN TO RECEIVE OXYTOCIN AS THE NASAL SPRAY SUBSTANCE AND THE OTHER HALF WILL RECEIVE A NASAL SPRAY THAT HAS THE SAME INGREDIENTS AS THE OXYTOCIN SPRAY EXCEPT FOR THE OXYTOCIN (THIS IS CALLED A PLACEBO). IN THIS STUDY NEITHER YOU NOR ANY OF THE RESEARCH STAFF WHO MEET WITH YOU WILL KNOW WHETHER YOU ARE RECEIVING OXYTOCIN OR PLACEBO. NURSES WILL TEACH YOU HOW TO GIVE YOURSELF INTRANASAL SPRAY TREATMENTS SO THAT YOU FEEL COMFORTABLE DOING IT YOURSELF

YOU WILL RECEIVE A TOTAL OF $200 FOR COMPLETION OF THE ENTIRE STUDY. YOU CAN CHOOSE TO RECEIVE THIS EITHER BY CHECK OR BY WALMART GIFT CARDS. IF YOU DO NOT COMPLETE THE ENTIRE STUDY, YOU WILL BE PAID FOR THE STUDY VISITS YOU DID COMPLETE. DO YOU HAVE ANY QUESTIONS FOR ME ABOUT THIS STUDY?"

CLINICAL QUESTIONS

"NOW I'M GOING TO ASK YOU SOME PERSONAL QUESTIONS REGARDING YOUR PSYCHIATRIC HISTORY AND SOCIAL FUNCTIONING. ANSWERING THESE QUESTIONS IS VOLUNTARY, BUT THEY WILL HELP US TO DETERMINE YOUR ELIGIBILITY FOR THE STUDY".

NOTE: *POSSIBLE* EXCLUSION ITEMS ARE IN BOLD PRINT. PLEASE REVIEW ALL PHONE SCREENS WITH DR. PEDERSEN

1. Has your doctor given you a diagnosis of schizophrenia?
   NO YES

2. Has there been any time in the last year that you had five or more drinks (beer, wine, liquor) on one occasion?
   NO **YES**
   -Explain:

2. Have you used street drugs in the last year (and if yes which drugs, how much and how recently?)
   NO **YES**
   -Explain:

4. Have you been "hooked" on a prescribed medicine or taken more of it than you were supposed to during the last year?
   NO **YES**
   -Explain:

5. Do you have any serious medical conditions? (If yes, explain)
   NO **YES**
   -Explain:

6. Have you had major surgery or were you seriously injured in the past year? (If yes, explain)
   NO **YES**

-Explain

7. Are you unable or unwilling to give yourself intranasal spray treatments on a daily basis?
   No **Yes**

8. *(For women)* Are you pregnant, breast-feeding now or were breast feeding in the past three months, or did you give birth during the past six months?
   NO **YES**

9. Do you often find it difficult to talk to people or feel comfortable around them?
   NO YES
   -Explain:

10. How often will you start a conversation at home, (or if you live alone, with friends or acquaintances)?

Almost Never	**0**
Rarely	**1**
Sometimes	**2**
Often	3

11. How do you react to the presence of strangers?

Avoid them	**0**
Feel nervous	**1**
Accept them	2
Like them	3

12. How often are you able to carry on a conversation when someone starts talking to you?

Almost never	**0**
Rarely	**1**
Sometimes	**2**
Often	3

13. How easy or difficult do you find it talking to people at the moment?

Very difficult	**0**
Quite difficult	**1**
Average	**2**
Quite easy	3
Very easy	4

"THANK YOU FOR YOUR TIME. I WILL SHARE THIS INFORMATION WITH DR. PEDERSEN AND HE OR HIS STUDY COORDINATOR WILL GET BACK TO YOU WITHIN THE NEXT FEW DAYS TO LET YOU KNOW ABOUT YOUR ELIGIBILITY FOR THE STUDY. MAY I HAVE A PHONE NUMBER WHERE YOU CAN BE REACHED DURING THE DAYTIME AND EVENING? MAY I LEAVE A MESSAGE AT THESE NUMBERS? DO YOU HAVE AN EMAIL ADDRESS? MAY I CONTACT YOU THAT WAY? DO YOU HAVE ANY QUESTIONS?"

TELEPHONE SCREEN FOR POTENTIAL PARTICIPANTS (12 WEEK TRIAL)

"Hi, I'm (state name) and I'm calling about a research study being conducted at UNC called**:** Oxytocin treatment of social cognitive and functional deficits in schizophrenia. I'm a research assistant working with Drs. Pedersen and Penn in the psychiatry and psychology departments. You called (or have participated in past studies with us and have agreed to be contacted about future studies or expressed interest to your care provider). I'm following up to describe the study, see if you are still interested in participating and to answer any questions that you may have about the study. I will also ask you some questions to see if you are eligible for the study. This should only take about 5-10 minutes. These questions will ask about any symptoms or emotional difficulties you had in the past or recently. Please note that responding to these questions is totally voluntary. Also, all information will be kept strictly confidential.

I'd like to get some general information. First, I'll need your name, age, etc.

Name: _____Age:_____ (Note: inclusion criteria is 18-65 years of age)

Gender: M F Date of Birth: _____ Ethnicity: _____

Where do you live_____?

Would you prefer to be tested at: _____UNC Hospitals in Chapel Hill or _____Central Regional Hospital in Raleigh (Dorothea Dix)

How did you hear about the study? (Check correct answer)

From care provider _____ Flyer_____ Previous research participant _____ Other_____

STUDY DESCRIPTION

"Now I'll tell you a little more about the study. This is a study to see whether treatment with oxytocin can improve social skills and reduce symptoms like paranoia in individuals with schizophrenia. Oxytocin is made naturally in the brain and seems to increase trust and accurate reading of others' emotions and to decrease anxiety in people.

If you take part in this study, you will be involved for approximately 14 weeks. You will undergo a series of 6 study visits. The study visits last between 2 and 5 hours. The study visits are at an outpatient research clinic (at UNC in Chapel Hill or the outpatient clinic at Central Regional Hospital in Raleigh) and you will complete some interviews, questionnaires

and other tasks. At the end of the second visit, you will take your first test dose and begin a 12 week treatment period during which you will take either oxytocin or placebo in a nasal spray twice daily. Half of the people in this study will be randomly chosen to receive oxytocin as the nasal spray substance and the other half will receive a nasal spray that has the same ingredients as the oxytocin spray except for the oxytocin (this is called a placebo). In this study, neither you nor any of the research staff who meet with you will know whether you are receiving oxytocin or placebo. Nurses will teach you how to give yourself intranasal spray treatments so that you feel comfortable doing it yourself.

You will receive a total of $220 for completion of the entire study. If you do not complete the entire study, you will be paid for the study visits you did complete.

Do you have any questions for me about this study?"

CLINICAL QUESTIONS

"Now I'm going to ask you some personal questions regarding your psychiatric history and social functioning. Answering these questions is voluntary, but they will help us to determine your eligibility for the study".

NOTE: *POSSIBLE* EXCLUSION ITEMS ARE IN BOLD PRINT. PLEASE REVIEW ALL PHONE SCREENS WITH DR. PEDERSEN.

3. Has your doctor given you a diagnosis of schizophrenia or schizoaffective disorder?
   NO YES

2. Has there been any time in the last year that you had five or more drinks (beer, wine, liquor) on one occasion?
   NO **YES**
   -Explain:

3. Have you used street drugs in the last year (and if yes which drugs, how much and how recently?)
   NO **YES**
   -Explain:

4. Have you been "hooked" on a prescribed medicine or taken more of it than you were supposed to during the last year?
   NO **YES**
   -Explain:

8. Do you have any serious medical conditions? (If yes, explain)
   NO **YES**
   -Explain:

9. Have you had major surgery or were you seriously injured in the past four months? (If yes, explain)

NO **YES**
-Explain

10. Are you unable or unwilling to give yourself intranasal spray treatments on a daily basis?
NO **Yes**

8. *(For women)* Are you pregnant, breast-feeding now or were breast feeding in the past three months, or did you give birth during the past six months?
NO **YES**

9. In general, how do you spend your time during the day?

10. Do you participate in activities with others?
If yes, ask: What activities?

If no, ask: Why not?

I have just few more questions.

11. Do you have any allergies to medications? NO YES
If yes, ask: "What are you allergic to"?

12. Do you have a UNC Medical Record number? NO YES
(If NO and subject is scheduled for screening visit, be sure they obtain one)

"Thank you for your time. I will share this information with Dr. Pedersen and we will get back to you within the next few days to let you know about your eligibility for the study. May I have a phone number where you can be reached during the daytime and evening? May I leave a message at these numbers? Do you have an email address? May I contact you that way? Do you have any questions?"

Day phone:_____ Leave message: yes no

Evening phone:_____ Leave message: yes no

Cell phone:_____ Leave message: yes no

Email address:_____ Leave message: yes no

Home address: _____

Positive and Negative Symptom Scale -PANSS

Instructions: Complete the appropriate rating for dimension following the clinical interview. Refer to the rating manual for item definitions, descriptions of anchoring points, scoring procedure, and norms.

Rating Key: 1 = absent 2 = minimal 3 = mild 4 = moderate 5 = moderately severe 6 = severe 7 = extremely severe

Positive Scale

P1_____Delusions

P2_____Conceptual disorganization

P3_____Hallucinatory behavior

P4_____Excitement

P5_____Grandiosity

P6_____Suspiciousness/persecution

P7_____Hostility

Negative Scale

N1_____Blunted affect

N2_____Emotional withdrawal

N3_____Poor rapport

N4_____Passive/apathetic social withdrawal

N5_____Difficulty in abstract thinking

N6_____Lack of spontaneity and flow of conversation

N7_____Stereotyped thinking

General Psychopathology Scale

G1_____Somatic concern

G2_____Anxiety

G3_____Guilt feelings

G4_____Tension

G5_____Mannerisms and posturing

G6_____Depression

G7_____Motor retardation

G8_____Uncooperativeness

G9_____Unusual thought content

G10_____Disorientation

G11_____Poor attention

G12_____Lack of judgment and insight

G13_____Disturbance of volition

G14_____Poor impulse control

G15_____Preoccupation

G16_____Active social avoidance

Total: ____

ER-40 (Kohler, Turner, Gur, & Gur, 2004) Manual Scoring Sheet

Instructions to read to the subject: In this test you will see some faces. Look carefully at each face and decide what emotion is showing. How does this person feel? Once you decide, say aloud the word to the right that best describes the emotion. If the person isn't showing any emotion, say "No Emotion."

Let's try a practice face….

	P.	Happy	Sad	Anger	Fear	No Emotion

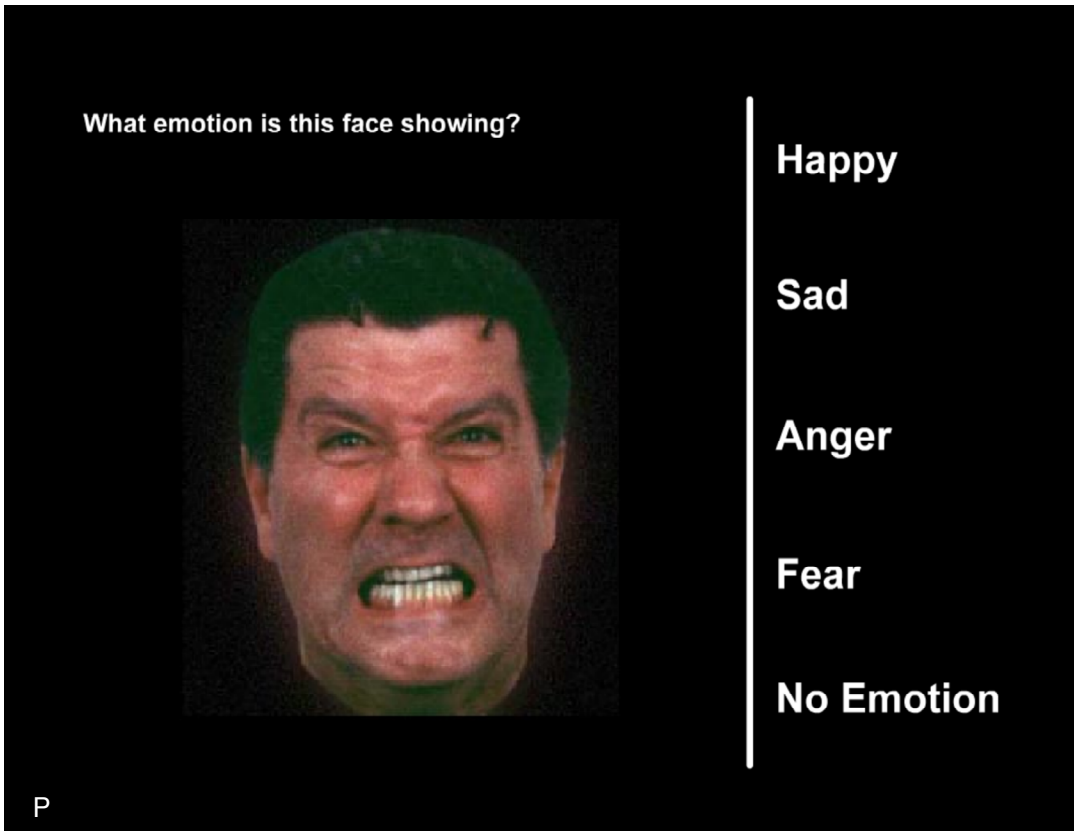
	1.	Happy	Sad	Anger	Fear	No Emotion
	2.	Happy	Sad	Anger	Fear	No Emotion
	3.	Happy	Sad	Anger	Fear	No Emotion
	4.	Happy	Sad	Anger	Fear	No Emotion
	5.	Happy	Sad	Anger	Fear	No Emotion
	6.	Happy	Sad	Anger	Fear	No Emotion
	7.	Happy	Sad	Anger	Fear	No Emotion
	8.	Happy	Sad	Anger	Fear	No Emotion
	9.	Happy	Sad	Anger	Fear	No Emotion
	10.	Happy	Sad	Anger	Fear	No Emotion
	11.	Happy	Sad	Anger	Fear	No Emotion
	12.	Happy	Sad	Anger	Fear	No Emotion
	13.	Happy	Sad	Anger	Fear	No Emotion
	14.	Happy	Sad	Anger	Fear	No Emotion

	15.	Happy	Sad	Anger	Fear	No Emotion
	16.	Happy	Sad	Anger	Fear	No Emotion
	17.	Happy	Sad	Anger	Fear	No Emotion
	18.	Happy	Sad	Anger	Fear	No Emotion
	19.	Happy	Sad	Anger	Fear	No Emotion
	20.	Happy	Sad	Anger	Fear	No Emotion

	21.	Happy	Sad	Anger	Fear	No Emotion
	22.	Happy	Sad	Anger	Fear	No Emotion
	23.	Happy	Sad	Anger	Fear	No Emotion
	24.	Happy	Sad	Anger	Fear	No Emotion
	25.	Happy	Sad	Anger	Fear	No Emotion
	26.	Happy	Sad	Anger	Fear	No Emotion
	27.	Happy	Sad	Anger	Fear	No Emotion
	28.	Happy	Sad	Anger	Fear	No Emotion
	29.	Happy	Sad	Anger	Fear	No Emotion
	30.	Happy	Sad	Anger	Fear	No Emotion
	31.	Happy	Sad	Anger	Fear	No Emotion
	32.	Happy	Sad	Anger	Fear	No Emotion
	33.	Happy	Sad	Anger	Fear	No Emotion

	**34.**	**Happy**	**Sad**	**Anger**	**Fear**	**No Emotion**
	**35.**	**Happy**	**Sad**	**Anger**	**Fear**	**No Emotion**
	**36.**	**Happy**	**Sad**	**Anger**	**Fear**	**No Emotion**
	**37.**	**Happy**	**Sad**	**Anger**	**Fear**	**No Emotion**
	**38.**	**Happy**	**Sad**	**Anger**	**Fear**	**No Emotion**
	**39.**	**Happy**	**Sad**	**Anger**	**Fear**	**No Emotion**
	**40.**	**Happy**	**Sad**	**Anger**	**Fear**	**No Emotion**

ER-40 (Kohler, Turner, Gur, & Gur, 2004): Sample stimuli, practice item



Theory of Mind - Picture Stories

Sequencing score:

- 1st/4th card correct = 2 points each
- 2nd/3rd card correct = 1 point each

1st picture story (apple tree)

correct sequence	H	E	L	P
patient's sequence				
points (max. 6)	2	1	1	2
Sequencing Time (Sec)		Notes:		

Questionnaire:

1a) What does the person with the red shirt believe, the one in blue shirt intends to do?

(2nd order belief) **(pointing to 2nd picture)**

Correct answer: Get apple from tree

Score 0 1

1b) What does the person with the red shirt expect from the person in blue shirt? (reciprocity)

(pointing to 4th picture)

Correct: Give him part of the apple; share with him

Score 0 1

sum of points for Item 1 (max. 8) ☐

2nd picture story (Bug in the Sack)

correct sequence	S	A	C	K
patient's sequence				
points (max. 6)	2	1	1	2
Sequencing Time (Sec)		Notes:		

Questionnaire:

2a) What does the person with the blue shirt believe is in the bag? (false belief) **(pointing to 2nd picture)**

Correct: Gift, present, flower, (bug is incorrect)

Score 0 1

2b) What's in the bag? (reality) **(pointing to 2nd picture)**

Correct: Wasp, bee, insect, or bug

Score 0 1

2c) What does the person in blue shirt believe the person in red intends to do?

(2nd order false belief) **(pointing to 2nd picture)**

Correct: Give him a gift or present

Score 0 1

2d) What does the person in red assume the person with the blue shirt believes, regarding his (the one in red) intentions? (3rd order false belief)

(pointing to 2nd picture)

Correct: Give him a gift or present

Score 0 1

2e) What do you think the person in the red shirt intended to do?

(deception) **(whole story)**

Correct: Scare him, frighten him, shock him

Score 0 1

sum of points for Item 2 (max. 11)

3rd picture story (Steal the Ball)

correct sequence	H	O	L	E
patient's sequence				
points (max. 6)	2	1	1	2
Sequencing Time (Sec)		Notes:		

Questionnaire:

3a) What does the person with the red shirt believe the others intend to do? (2nd order false belief) **(pointing to 3rd picture)**

Correct: Play ball with him

Score 0 1

3b) What do the two characters want the one in red shirt to believe they intend to do? (cheating) **(pointing to 3rd picture)**

Correct: Play ball with him or talk to him

3c) What do they intend to do? (deception) **(whole story)**

Correct: Take his ball or make him fall into a hole

Score 0 1

3d) What does the person in red shirt now think the other two characters intended to do?

(cheating detection) **(pointing to 4th picture)**

Correct: Trick him or take his ball

Score 0 1

Score 0 1

sum of points for Item 3 (max. 10)

4th picture story (Over the wall)

correct sequence	J	A	I	L
patient's sequence				
points (max. 6)	2	1	1	2
Sequencing Time (Sec)		Notes:		

Questionnaire:

4a) What does the bald person think the other person intends to do?

(2nd order belief) **(pointing to 1st picture)**

Correct: Climb over the wall or escape from prison

Score
0 1

4b) What does the bald person expect from the other person? (reciprocity)

(pointing to 3rd picture)

Correct: To pull him up or to help him over the wall

Score
0 1

sum of points for Item 4 (max. 8)

5th picture story (Jack in the Box)

correct sequence	O	P	E	N
patient's sequence				
points (max. 6)	2	1	1	2
Sequencing Time (Sec)		Notes:		

Questionnaire:

5a) What does the blond haired person believe is in the box?
(false belief) **(pointing to 3rd picture)**

Correct: Gift or present

Score 0 1

5b) What's in the box? (reality) **(pointing to 3rd picture)**

Correct: Scary jack in the box or scary toy (monster is also correct)

5c) What does the blond person believe the other person intends to do?
(2nd order false belief) **(pointing to 3rd picture)**

Correct: Give him a gift or present

Score 0 1

5d) What does the the person with the dark hair assume the blond person believes, regarding his (the dark haired person) intentions?
(3rd order false belief) **(pointing to 2nd picture)**

Correct: Give him a gift or present

Score 0 1

5e) What do you think the dark haired person intended to do? (deception) **(whole story)**

Correct: Scare him, or frighten him, or shock him

Score 0 1

sum of points for Item 5 (max. 11)

6th picture story (Bike Accident)

correct sequence	T	A	K	E
patient's sequence				
points (max. 6)	2	1	1	2
Sequencing Time (Sec)		Notes:		

Questionnaire:

6a) What does the person in the blue shirt intends to do?
(intention) **(pointing to 1st picture)**

Correct: Take jar or candy or toys from the store

Score 0 1

6b) What does the shopgirl believe has happened?
(false belief) **(pointing to 3rd picture)**

Correct: An accident on his bike or he fell of his bike, or he is injured

Score 0 1

6c) What do the person in blue and the one in red intend to do?
(cheating) **(pointing to 2nd picture)**

Correct: Distract her and steal her jar

6d) What does the person in red expect from the person in blue?
(reciprocity) **(pointing to 4th picture)**

Correct: To help him steal the jar or to share the jar with him

Score 0 1

6e) What does the shopgirl now think the boys intended to do?
(cheating detection) **(pointing to 4th picture)**

Correct: Steal from her or steal the jar

Score 0 1

Score 0 1

sum of points for Item 6 (max. 11)

Brune Measure (Brune 2003): Sample Stimuli

EYES TEST (Baron-Cohen, Wheelwright, Hill, Raste, & Plumb, 2001)

You will be seeing on the computer screen a series of 36 pictures of individuals expressing a feeling or emotion with their eyes. Your task is to look at each pair of eyes and select the emotion that best fits the actor's facial expression. Please indicate your choice by stating out loud the emotion on that person's face. Once you give your answer, we will go on to the next face. If you do not know what a word means, ask and a definition will be provided for you. Please be aware that we can't go back to faces you've seen already. So, please make sure that your answer for each pair of eyes is a final one. If you are not sure of your answer, please take your best guess.

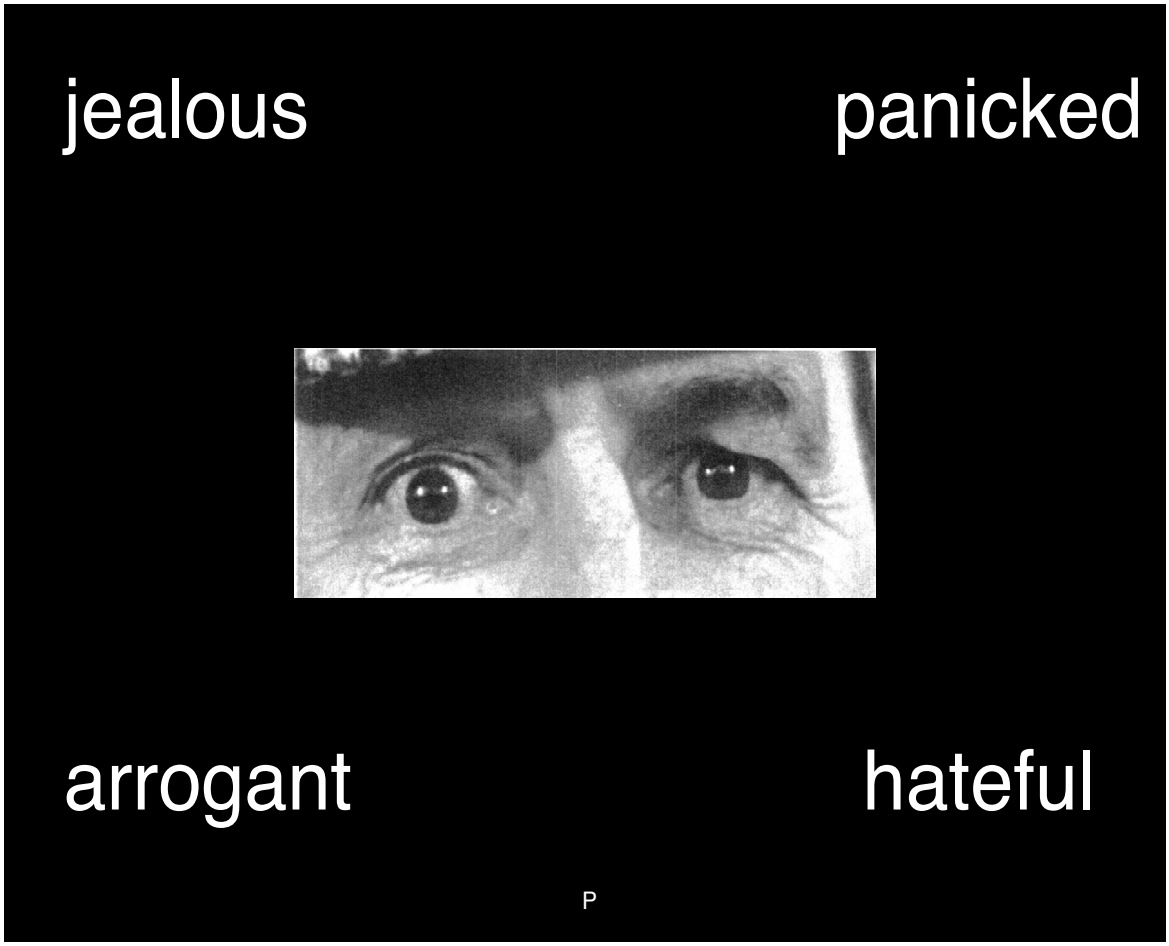
Total Number Correct _____ (*Answers in Italic are Correct Choices)*

P.	Hateful	Jealous	Arrogant	***Panicked***

1.	***Playful***	Comforting	Irritated	Bored
2.	Arrogant	Annoyed	***Upset***	Terrified
3.	Convinced	Flustered	***Desire***	Joking
4.	Amused	Relaxed	Joking	***Insisting***
5.	Friendly	Irritated	***Worried***	Sarcastic
6.	***Fantasizing***	Alarmed	Aghast	Impatient
7.	***Uneasy***	Friendly	Apologetic	Dispirited
8.	Excited	Relieved	Shy	***Despondent***
9.	Annoyed	Hostile	Horrified	***Preoccupied***
10.	***Cautious***	Bored	Aghast	Insisting
11.	Terrified	Flirtatious	Amused	***Regretful***
12.	***Skeptical***	Embarrassed	Dispirited	indifferent
13.	Shy	Decisive	Threatening	***Anticipating***
14.	Irritated	Disappointed	Depressed	***Accusing***
15.	Encouraging	Amused	Flustered	***Contempla-tive***
16.	***Thoughtful***	Irritated	Encouraging	Sympathetic
17.	Playful	Affectionate	Aghast	***Doubtful***
18.	Amused	Bored	***Decisive***	Aghast

19.	Arrogant	Grateful	***Tentative***	Sarcastic
20.	***Friendly***	Horrified	Guilty	Dominant
21.	Panicked	***Fantasizing***	Confused	Embarrassed
22.	***Preoccupied***	Insisting	Imploring	Grateful
23.	Curious	Apologetic	Contented	***Defiant***
24.	***Pensive***	Irritated	Excited	Hostile
25.	Incredulous	Panicked	***Interested***	Despondent
26.	Alarmed	Anxious	Shy	***Hostile***
27.	Arrogant	***Cautious***	Reassuring	Joking
28.	Affectionate	Joking	***Interested***	Contented
29.	Impatient	Aghast	Irritated	***Reflective***
30.	***Flirtatious***	Disappointed	Hostile	Grateful
31.	Joking	Ashamed	***Confident***	Dispirited
32.	Ashamed	Bewildered	Alarmed	***Serious***
33.	***Concerned***	Embarrassed	Guilty	Fantasizing
34.	Aghast	Baffled	Terrified	***Distrustful***
35.	***Nervous***	Contemplat-ive	Insisting	Puzzled
36.	***Suspicious***	Nervous	Ashamed	Indecisive

Eyes Test (Baron-Cohen, Wheelwright, Hill, Raste, & Plumb, 2001): Sample Stimuli, practice item

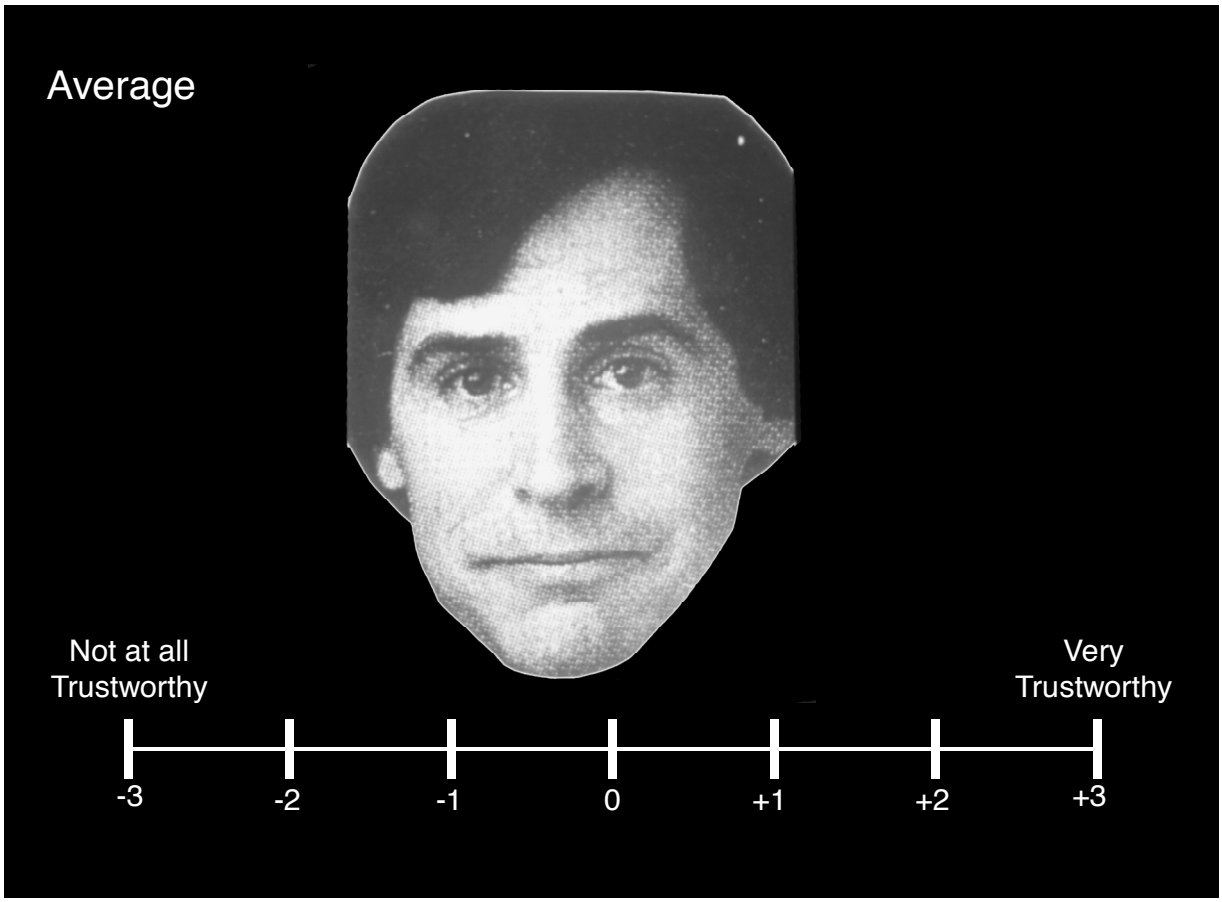


TRUSTWORTHINESS TASK (Adolphs et al., 1998)

"I am going to show you some pictures of faces. Just from looking at each person's face, tell me how much you feel each person can be trusted. You can think of a person you really trust as someone you would trust with your life. You can think of a person you really don't trust as a really big criminal. Now imagine that you were asking each person to hold some money for you. How comfortable would you feel with each one?If you think you would trust them a lot, as if you would let them hold $5,000 of yours, give them a "+3".If you think you would hardly trust them at all, as if you couldn't even trust them to keep 50 cents for you, give them a "-3".If you could sort of trust them, give them a "+2".If you would sort of not trust them, give them a "-2".EXAMPLE: The first person's face you see is right in the middle, or average on both scales. You should consider him to be a "0".*Now, look at this person's face…. How much do you feel this person can be trusted…? What number would you give?*

Image	***Subject's score***	***Image***	***Subject's score***
1. # 37		22. # 28	
2. # 15		23. # 21	
3. # 27		24. # 36	
4. # 35		25. # 25	
5. # 40		26. # 34	
6. # 12		27. # 16	
7. # 33		28. # 11	
8. # 20		29. # 30	
9. # 17		30. # 32	
10. # 19		31. # 29	
11. # 6		32. # 4	
12. # 3		33. # 26	
13. # 38		34. # 41	
14. # 10		35. # 24	
15. # 14		36. # 8	
16. # 18		37. # 2	
17. # 5		38. # 7	
18. # 31		39. # 13	
19. # 1		40. # 22	
20. # 9		41. # 42	
21. # 23		42. # 39	

Trustworthiness Task (Adolphs et al., 1998): Sample Stimuli



Ambiguous Intentions Hostility Questionnaire: AIHQ (Combs et al. 2007)

On the next few pages there are some everyday situations that I will read to you. They will be about people and how they act toward you. Imagine how each situation might happen to you. For each situation, I will ask you for a brief reason for why it happened. Then, I will ask you to rate whether you think the person acted that way toward you on purpose. I will then ask you to rate how angry that situation makes you feel and then how much you blame the other person. Finally, please tell me what you would do about that situation. A response of "I don't know" is not acceptable. You need to describe some type of behavioral response.

1. You've been at a new job for three weeks. One day, you see one of your new co-workers on the street. You start to walk up to this person and start to say hello, but she/he passes by you without saying hello.

A. What do you think was the real reason why your coworker passed by you without saying hello?

B. Do you think your coworker did this to you on purpose?

1	2	3	4	5	6
Definitely No	Probably No	Maybe No	Maybe Yes	Probably Yes	Definitely Yes

C. How angry would this make you feel?

1	2	3	4	5
Not at All Angry				Very Angry

D. How much would you blame the coworker for passing by you?

1	2	3	4	5
Not at All				Very Much

E. What would you do about it?

2. You have an appointment with an important person. When you arrive at your appointment, the secretary informs you that the person is not in; they took the day off.

A. What do you think was the real reason why the person didn't keep the appointment?

B. Do you think the person did this to you on purpose?

1	2	3	4	5	6
Definitely No	Probably No	Maybe No	Maybe Yes	Probably Yes	Definitely Yes

C. How angry would this make you feel?

1	2	3	4	5
Not at All Angry				Very Angry

D. How much would you blame the person for not keeping your appointment?

1	2	3	4	5
Not at All				Very Much

E. What would you do about it?

_____

3. You walk past a bunch of teenagers at a mall and you hear them start to laugh.

A. What do you think was the real reason why the teenagers started to laugh after you walked past them?

B. Do you think the teenagers did this to you on purpose?

1	2	3	4	5	6
Definitely No	Probably No	Maybe No	Maybe Yes	Probably Yes	Definitely Yes

C. How angry would this make you feel?

1	2	3	4	5
Not at All Angry				Very Angry

D. How much would you blame the teenagers for laughing as you walked past them?

1	2	3	4	5
Not at All				Very Much

E. What would you do about it?

4. You are supposed to meet a new friend for lunch at a restaurant but she/he never shows up.

A. What do you think was the real reason why your new friend didn't show up at the restaurant?

B. Do you think your new friend did this to you on purpose?

1	2	3	4	5	6
Definitely No	Probably No	Maybe No	Maybe Yes	Probably Yes	Definitely Yes

C. How angry would this make you feel?

1	2	3	4	5
Not at All Angry				Very Angry

D. How much would you blame your new friend for not showing up at the restaurant?

1	2	3	4	5
Not at All				Very Much

E. What would you do about it?

5. You call a friend and leave a message on their answering machine, asking them to call you back. One week passes and they have not called you back.

A. What do you think was the real reason why your friend didn't call you back?

B. Did your friend not call you back on purpose?

1	2	3	4	5	6
Definitely No	Probably No	Maybe No	Maybe Yes	Probably Yes	Definitely Yes

C. How angry would this make you feel?

1	2	3	4	5
Not at All Angry				Very Angry

D. How much would you blame your friend for not calling you back?

1	2	3	4	5
Not at All				Very Much

E. What would you do about it?

IRI: Interpersonal Reactivity Index (Davis, 1983).

The following statements inquire about your thoughts and feelings in a variety of situations. For each item, indicate how well it describes you by choosing the appropriate number on the scale at the top of the page: 1, 2, 3, 4, or 5. When you have decided on your answer, fill in the number on the answer sheet next to the item number. READ EACH ITEM CAREFULLY BEFORE RESPONDING. Answer as honestly as you can. Thank you.

ANSWER SCALE:

1	2	3	4	5
Does not describe me well				Describes me very well

1. I daydream and fantasize, with some regularity, about things that might happen to me. _____
2. I often have tender, concerned feelings for people less fortunate than me. _____
3. I sometimes find it difficult to see things from the "other guy's" point of view. _____
4. Sometimes I don't feel very sorry for other people when they are having problems. _____
5. I really get involved with the feelings of the characters in a novel. _____
6. In emergency situations, I feel apprehensive and ill-at-ease. _____
7. I am usually objective when I watch a movie or play, and I don't often get completely caught up in it. _____
8. I try to look at everybody's side of a disagreement before I make a decision. _____
9. When I see someone being taken advantage of, I feel kind of protective towards them. _____
10. I sometimes feel helpless when I am in the middle of a very emotional situation. _____
11. I sometimes try to understand my friends better by imagining how things look from their perspective. _____
12. Becoming extremely involved in a good book or movie is somewhat rare for me. _____
13. When I see someone get hurt, I tend to remain calm. _____

14. Other people's misfortunes do not usually disturb me a great deal. _____
15. If I'm sure I'm right about something, I don't waste much time listening to other people's arguments. _____

16. After seeing a play or movie, I have felt as though I were one of the characters. _____
17. Being in a tense emotional situation scares me. _____
18. When I see someone being treated unfairly, I sometimes don't feel very much pity for them. _____

19. I am usually pretty effective in dealing with emergencies. _____
20. I am often quite touched by things that I see happen. _____
21. I believe that there are two sides to every question and try to look at them both. _____
22. I would describe myself as a pretty soft-hearted person. _____
23. When I watch a good movie, I can very easily put myself in the place of a leading character. _____

24. I tend to lose control during emergencies. _____
25. When I'm upset at someone, I usually try to "put myself in his shoes" for a while. _____
26. When I am reading an interesting story or novel, I imagine how I would feel if the events in the story were happening to me. _____

27. When I see someone who badly needs help in an emergency, I go to pieces. _____
28. Before criticizing somebody, I try to imagine how I would feel if I were in their place. _____

Anxiety Items from the Brief Symptom Inventory

Completed by the Test Subject Themselves

(Derogatis, 1975)

0 = Not at all
1 = A little bit
2 = Moderately
3 = Quite a bit
4 = Extremely

Using the numbers above, rate how much you were distressed during the past 7 days by:

1. Nervousness or shakiness inside	0	1	2	3	4
2. Suddenly scared for no reason	0	1	2	3	4
3. Feeling fearful	0	1	2	3	4
4. Feeling tense or keyed up	0	1	2	3	4
5. Spells of terror or panic	0	1	2	3	4
6. Feeling so restless you couldn't sit still	0	1	2	3	4

Leibowitz Social Anxiety Scale

(Leibowitz, 1987)

Fear or Anxiety:	**Avoidance**:
0 = None	0 = Never (0%)
1 = Mild	1 = Occasionally (1-33%)
2 = Moderate	2 = Often (33-67%)
3 = Severe	3 = Usually (67%-100%)

	Fear or Anxiety	Avoidance	#
1. Telephoning in public. (P)			1
2. Participating in small groups. (P)			2
3. Eating in public places. (P)			3
4. Drinking with others in public places. (P)			4
5. Talking to people in authority. (S)			5
6. Acting, performing or giving a talk in front of an audience. (P)			6
7. Going to a party. (S)			7
8. Working while being observed. (P)			8
9. Writing while being observed. (P)			9
10. Calling someone you don't know very well. (S)			10
11. Talking with people you don't know very well. (S)			11
12. Meeting strangers. (S)			12
13. Urinating in a public bathroom. (P)			13
14. Entering a room when others are already seated. (P)			14
15. Being the center of attention. (S)			15
16. Speaking up at a meeting. (P)			16
17. Taking a test. (P)			17
18. Expressing a disagreement or disapproval to people you don't know very well. (S)			18
19. Looking at people you don't know very well in the eyes. (S)			19
20. Giving a report to a group. (P)			20
21. Trying to pick up someone. (P)			21
22. Returning goods to a store. (S)			22
23. Giving a party. (S)			23
24. Resisting a high pressure salesperson. (S)			24

Social Skill and Empathy Rating Sheet for Role-Plays

Content – the appropriateness (or strangeness) of the conversational content

1	2	3	4	5
Discussed bizarre or inappropriate topics	The content seems strange and slightly off; may provide odd answers to questions	Presence of one or two strange statements, but on the whole the conversation is appropriate	Content is appropriate and fits context	Content is very pleasant and appropriate to the topic

Clarity – clear enunciation of speech, includes the amount of verbal slurring and mumbling, volume of speech, and difficulty in understanding speech

1	2	3	4	5
Slurring or mumbling makes the participant barely understandable	Some slurring or mumbling and has an impact on understanding the person	Average slurring/mumbling but does not impact ability to understand	Rare slurring or mumbling	Speech is exceptionally clear and easily understood

Fluency – smoothness of verbal speech (includes stuttering, pauses, or other interruptions in their own speech such as using "um" or other fillers

1	2	3	4	5
Multiple pauses and interruptions negatively impact the conversation	Pauses and interruptions have a minimal impact on conversation	Pauses and interruptions are easily noticeable but do not interfere	Pauses and interruptions are only slightly noticeable	No pauses or interruptions

Meshing – the smoothness of turn taking during the conversation, includes interrupting the other person or long pauses before responding to them, also lulls in the conversation

1	2	3	4	5
Continually interrupts or does not speak following the confederate, making the conversation forced and severely impacts the conversation	Some pauses or interruptions that are noticeable and make the conversation seem halting or stilted resulting in a negative impact on the conversation	Some pauses and interruptions but appear normal and do not impact the conversation	Conversation flows well but there are some barely noticeable pauses and interruptions	Smooth conversation without interruptions, pauses.

Gaze – frequency, duration, and appropriateness of eye contact

1	2	3	4	5
Completely avoids eye contact	Eye contact is sporadic and brief	Eye contact is made occasionally, but is apparent	Eye contact occurs often but is short in duration	Eye contact is natural and has good duration

Involvement – the extent to which they appear involved in the conversation; includes verbal and non-verbal gestures, such as volunteering information and nodding; as well as uninvolved behaviors such as looking away, and checking a watch

1	2	3	4	5
Appears disinterested due to short answers, infrequent nodding and not asking questions; lack of participant effort.	Listens and may nod, but does not ask questions or volunteer information and seems to put forth little effort	Listens and nods and openly offers information, but makes no attempt to engage the confederate (e.g. by asking questions)	Listens attentively, nods and answers questions, asks questions	Highly involved in the conversation and engaged; appears to enjoy the conversation

Asks Questions – number of questions asked by the participant

1	2	3	4	5
Asks one or no	Asks two questions	Asks three	Asks four questions	Asks five or more

questions		questions		

Appropriate Affect – communication of feeling through facial expression, use of gestures and vocal tone that is consistent with the content of the speech and with other forms of emotional expression.

1	2	3	4	5
Inappropriate affect (e.g., smiling during sad content)	Emotional expression is somewhat inconsistent with the topic	Emotional expression is appropriate but slightly out of place (e.g., extreme anger about something only slightly upsetting)	Emotional expression is appropriate	Emotional expression enhances the conversation

Flat Affect – *amount* of communication of feeling through facial expression, use of gestures and vocal tone

1	2	3	4	5
No emotion is displayed	Expression of emotion are infrequent and appear to be stilted, forced, or lacking modulation	Moderate amounts of emotions displayed	Emotional expression appears natural and a range of emotions are apparent	Feelings are communicated freely and frequently

Social Anxiety – the amount of anxiety displayed by the participant during the conversation, evidenced by shaking, voice wavering, sweating, stuttering, squirming, etc.

1	2	3	4	5
Extremely anxious—stuttering, playing with their hands and negatively impacts the conversation	Anxiety is clear and negatively impacts the conversation	Some anxiety but has limited impact on conversation	Very little anxiety, conversation goes smoothly	No anxiety apparent; seems at ease

Overall Social Skill – the person's level of social skill, includes how easy it would be to talk to them, their ability to interact in a meaningful way, and whether or not you would feel comfortable talking to them. Take into account all of your previous ratings, and use this as a "summary" score.

1	2	3	4	5
Extremely poor	Poor	Neither skilled nor unsilled	Good	Extremely skilled

FOLLOWING RATINGS ARE ONLY APPLICABLE TO SCENARIO 2 (ASKING FOR HELP ROLE-PLAYS

Emotional Empathy-- To what extent does the participant *share* the emotional experience of the confederate such that they communicate they notice the confederate is not happy and demonstrate concern; For example they may lower their tone of voice and note "I am sorry this happened to you."

1	2	3	4	5
No emotions shared; appears not to connect emotionally and does not demonstrate concern (e.g. never asks what is wrong)	Does not appear to share the emotional experience of the confederate, but does not appear distant and may ask what is wrong	Emotional experience is shared, but is verbally and visually limited; e.g, they ask how the participant is doing but doing	Demonstrate concern by asking how they are doing and with non-verbal gestures (tone of voice, facial expression)	Communicates concern throughout the role-play, providing multiple examples of emotional empathy.

Cognitive Empathy--To what extent does the participant *understand* what the confederate must be feeling about the situation. Do them seem to be able to put themselves in the other person's shoes? For instance, the participant may reflect back how the confederate feels (e.g., "You feel sad because your friend did not come"). The participant may also indicate they would feel similarly if the situation happened to them (e.g., "I would be sad if my friend did not show").

1	2	3	4	5
No indication or attempt to understand how the confederate must be feeling	Does not appear to understand how the confederate is feeling (e.g., does not provide examples they have felt similarly), but	Some indication they know how the confederate is feeling; e.g., may give one reflection or one example of a time they felt	Indicates they understand how the confederate is feeling	Verbalizes that they understand what the confederate is feeling such that it enhances the conversation

	does not appear distant	similarly.		

Ideomotoric Empathy---The extent that the participant's body language matches the confederate. This may apply to the body (e.g., matching body posture) or face (e.g., sharing a similar facial expression as the confederate).

1	2	3	4	5
No matching body or facial expression and has a negative impact on conversation	Minimal matching of body language or facial expression	Occasional matching of body language and/or facial expression	Matching of body language and/or facial expression for most of the role-play.	Naturally matches body language and/or facial expression throughout the entire role-play such that it communicates understanding and empathy

Helpfulness – How helpful the participant is during the second role-play. Helpfulness is indexed by offering solutions and/or demonstrating reassurance (e.g., "Everything is going to work itself out.")

1	2	3	4	5
Not helpful; does not offer any advice or suggestions or makes suggestions that are unhelpful to the confederate; has negative impact on the conversation	Does not offer any suggestions or show reassurance.	May makes one suggestion or occasional reassurance	Tries to offer two solutions or reassurance	Offers multiple solutions or reassurance (more than once) continuously throughout the role-play

Overall empathy-- The person's level of empathy, includes whether you think they communicated and displayed empathy. Would you describe this person as empathic? Take into account all of your previous empathy ratings, and use this as a "summary" empathy score.

1	2	3	4	5
Unempathic and appears distant	Unempathic but not distant	Moderately empathic	Displays adequate empathy	Effectively displays empathy and it enhances the conversation

Specific Levels of Functioning Scale (Schneider & Struening, 1983): Patient Questionnaire

Instructions: Circle the number that best describes your *typical* level of functioning on each item below. Mark only one number for each item. Be sure to mark all items.

Social Functioning

A. Interpersonal Relationships

Item	Rating				
	Highly Typical	Generally Typical	Somewhat Typical	Generally Untypical	Highly Untypical
1. Accept contact with others	5	4	3	2	1
2. Initiates contact with others	5	4	3	2	1
3. Communicates effectively	5	4	3	2	1
4. Engages in activities without prompting	5	4	3	2	1
5. Participates in groups	5	4	3	2	1
6. Forms and maintains friendships	5	4	3	2	1
7. Asks for help when needed	5	4	3	2	1

B. Social Acceptability

Item	Rating				
	Never	Rarely	Sometimes	Frequently	Always
8. Regularly argues with others	5	4	3	2	1
9. Has physical fights with others	5	4	3	2	1
10. Destroys property	5	4	3	2	1
11. Physically abuses self	5	4	3	2	1
12. Is fearful, crying, clinging	5	4	3	2	1

13. Takes property from others without permission	5	4	3	2	1

Community Living Skills

C. Activities

Item	Totally Self Sufficient	Needs Verbal Advice or Guidance	Needs Some Physical Help or Assistance	Needs Substantial Help	Totally Dependent
14. Household responsibilities (house cleaning, cooking, washing clothes)	5	4	3	2	1
15. Shopping (selection of items, choice of stores, payment at register)	5	4	3	2	1
16. Handling personal finances (budgeting, paying bills)	5	4	3	2	1
17. Use of telephone (getting number, dialing, speaking, listening)	5	4	3	2	1
18. Traveling from residence without getting lost	5	4	3	2	1
19. Use of public transportation (selecting route, using timetable, paying fares, making transfers)	5	4	3	2	1
20. Use of leisure time (reading , visiting friends, listening to music)	5	4	3	2	1
21. Recognizing and avoiding common dangers (traffic safety, fire safety)	5	4	3	2	1
22. Self-medication (understanding purpose, taking as prescribed, recognizing side effects)	5	4	3	2	1
23. Use of medical and other community services (knowing whom to contact, how, and when	5	4	3	2	1

to use)					
24. Basic reading, writing, and arithmetic (enough for daily needs)	5	4	3	2	1

D. Work Skills

Item	Rating				
	Highly Typical	Generally Typical	Somewhat Typical	Generally Untypical	Highly Untypical
25. Has employable skills	5	4	3	2	1
26. Works with minimal supervision	5	4	3	2	1
27. Is able to sustain work effort (not easily distracted, can work under stress)	5	4	3	2	1
28. Appears at appointments on time	5	4	3	2	1
29. Follows verbal instructions accurately	5	4	3	2	1
30. Completes assigned tasks	5	4	3	2	1

Specific Levels of Functioning Scale (Schneider & Struening, 1983): Informant Questionnaire

Instructions: Circle the number that best describes _____'s *typical* level of functioning on each item below. If you are not sure about a certain rating, please give your best guess.Mark only one number for each item. Be sure to mark all items.

Social Functioning

A. Interpersonal Relationships

Item	Rating				
	Highly Typical of This Person	Generally Typical of This Person	Somewhat Typical of This Person	Generally Untypical of This Person	Highly Untypical of This Person
31. Accepts contact with others (does not withdraw or turn away)	5	4	3	2	1
32. Initiates contact with others	5	4	3	2	1
33. Communicates effectively (speech and gestures are understandable and to the point)	5	4	3	2	1
34. Engages in activities without prompting	5	4	3	2	1
35. Participates in groups	5	4	3	2	1
36. Forms and maintains friendships	5	4	3	2	1
37. Asks for help when needed	5	4	3	2	1

B. Social Acceptability

Item	Rating				
	Never	Rarely	Sometimes	Frequently	Always
38. Regularly argues with others	5	4	3	2	1
39. Has physical fights with others	5	4	3	2	1

40. Destroys property	5	4	3	2	1
41. Physically abuses self	5	4	3	2	1
42. Is fearful, crying, clinging	5	4	3	2	1
43. Takes property from others without permission	5	4	3	2	1

Community Living Skills

C. Activities

Item	Totally Self Sufficient	Needs Verbal Advice or Guidance	Needs Some Physical Help or Assistance	Needs Substantia l Help	Totally Dependent
44. Household responsibilities (house cleaning, cooking, washing clothes)	5	4	3	2	1
45. Shopping (selection of items, choice of stores, payment at register)	5	4	3	2	1
46. Handling personal finances (budgeting, paying bills)	5	4	3	2	1
47. Use of telephone (getting number, dialing, speaking, listening)	5	4	3	2	1
48. Traveling from residence without getting lost	5	4	3	2	1
49. Use of public transportation (selecting route, using timetable, paying fares, making transfers)	5	4	3	2	1
50. Use of leisure time (reading , visiting friends, listening to music)	5	4	3	2	1
51. Recognizing and avoiding common dangers (traffic safety, fire safety)	5	4	3	2	1
52. Self-medication (understanding purpose, taking as prescribed, recognizing side effects)	5	4	3	2	1

53. Use of medical and other community services (knowing whom to contact, how, and when to use)	5	4	3	2	1
54. Basic reading, writing, and arithmetic (enough for daily needs)	5	4	3	2	1

D. Work Skills

Item	Rating				
	Highly Typical of This Person	Generally Typical of This Person	Somewhat Typical of This Person	Generally Untypical of This Person	Highly Untypical of This Person
55. Has employable skills	5	4	3	2	1
56. Works with minimal supervision	5	4	3	2	1
57. Is able to sustain work effort (not easily distracted, can work under stress)	5	4	3	2	1
58. Appears at appointments on time	5	4	3	2	1
59. Follows verbal instructions accurately	5	4	3	2	1
60. Completes assigned tasks	5	4	3	2	1

Other Information

61. How well do you know the skills and behavior of the person you just rated? (Circle one)

Very Well		Fairly Well		Not Very Well At All
5	4	3	2	1

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