DO SIMILAR NEURAL PROFILES UNDERLIE SOCIAL COGNITIVE DEFICITS IN SCHZOPHRENIA AND HIGH-FUNCTIONING AUTISM?

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ABSTRACT

AMY PINKHAM: Do Similar Neural Profiles Underlie Social Cognitive Deficits in Schizophrenia and High-functioning Autism?
(Under the direction of David Penn, Ph.D.)

Previous research suggests that schizophrenia and autism share similar behavioral deficits in social cognition. This study investigated both neural activation and behavioral performance during a task of complex social cognition in healthy controls, individuals with high-functioning autism, and individuals with schizophrenia. Event-related functional magnetic resonance imaging was utilized as individuals viewed faces and made ratings of trustworthiness. It was hypothesized that both clinical groups would show reduced activation in discrete brain regions comprising a social cognitive neural circuit, which included the amygdala, the fusiform face area (FFA) of the fusiform gyrus, and the superior temporal sulcus (STS). Activation in the ventrolateral prefrontal cortex (VLPFC) was also examined as this area has been implicated in the process of making evaluative judgments. Results largely confirmed the main study hypothesis: both clinical groups showed significant reductions in neural activation while making complex social judgments compared to non-clinical controls. Significant reductions for both clinical groups were evident in the right amygdala and FFA and left VLPFC, and no differences in neural activation were evident between the clinical groups. Behavioral performance on the Trustworthiness task significantly differed only between control individuals and individuals with schizophrenia; the two clinical groups did not significantly differ from one another. These findings suggest

that individuals with schizophrenia and individuals with autism share similar neural abnormalities that may underlie social cognitive deficits.

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CHAPTER I

INTRODUCTION

The direct comparison of schizophrenia and autism enjoys a varied history in which the focus has primarily been differentiating the two disorders diagnostically. Recently however, investigators have shifted their attention to similarities between the disorders that suggest similar underlying pathologies. For instance, Goldstein and colleagues (2002) found similar cognitive profiles for individuals with high functioning autism and individuals with schizophrenia, and Sheitman, Kraus, Bodfish, and Carmel (2004) demonstrated that autistic symptoms can be present in schizophrenia and that these symptoms covary with negative symptoms. Similarly, Konstantareas and Hewitt (2001) noted that half of the autistic individuals in their sample met criteria for disorganized schizophrenia and that individuals with autism are likely to have several negative symptoms such as affective flattening, alogia, and asociality that are present in schizophrenia. These cognitive and symptom similarities provide a firm foundation for continued comparisons and open the door for evaluations across several other domains that may also speak to shared mechanisms underlying the disorders. Two such related areas are social functioning and the cognitive processes that subserve social functioning (i.e. social cognition).

Impairments in social functioning are characteristic of several psychological disorders; but nowhere are they more pronounced than in schizophrenia and autism. Impaired social functioning is a primary criterion for receiving a diagnosis of schizophrenia

(DSM IV; APA, 1994), and individuals with schizophrenia often experience difficulties in multiple areas of social functioning such as interpersonal relationships, work and personal achievement, and self-care (Corrigan & Penn, 2001). Such deficits are present throughout the course of the disorder, including the first-episode, and are often resistant to psychiatric intervention (Addington & Addington, 2000). Additionally, social dysfunction has been found to precede the onset of psychosis and has been identified in individuals with a biological parent who has schizophrenia, both of which suggest that social impairments are vulnerability markers for developing schizophrenia (Davidson et al., 1999; Hans, Auerbach, Asarnow, Styr, & Marcus, 2000). In addition to a contributing role in the development of schizophrenia, poor social functioning has been linked to an increased rate of relapse (Perlick, Stastny, Mattis, & Teresi, 1992). Thus, it appears that impairments in social functioning represent a core behavioral feature of schizophrenia.

Similarly, social dysfunction is primary to autism and Asperger's Syndrome. As with schizophrenia, impairments in social interaction are among the diagnostic criteria for both disorders (DSM-IV; APA, 1994), and adults with autism spectrum disorders show impairments in social relationships, competency at work, independence, and social competence in general (Green, Gilchrist, Burton, & Cox, 2000; Howlin, Mawhood, & Rutter, 2000). Moreover, research examining the Broad Autism Phenotype, a dimensional approach to autistic symptomatology stating that autistic features can be present to a lesser, sub-clinical degree in non-affected relatives of individuals with autism, also demonstrates that social deficits are present in the parents of affected children (Murphy et al., 2000; Piven, Palmer, Jacobi, Childress, & Arndt, 1997), which mirrors the biological vulnerability shown in schizophrenia. These findings further underscore the importance of social dysfunction in

autism spectrum disorders.

In an effort to better understand the processes underlying social dysfunction in both schizophrenia and autism, attention has been given to the role of neurocognitive abilities (e.g. executive function) in supporting social behavior. Although these theories have merit, some findings suggest that they are incomplete. For instance, reviews of the literature do support an association, both cross-sectional and longitudinal, between neurocognition and psychosocial dysfunction in schizophrenia (Green, Kern et al., 2000; Penn et al., 1997); however, this relationship is only modest (Penn et al., 1997). Likewise, neurocognitive theories of autism fall short in explaining how some individuals, in particular, those with HFA or Asperger's, can have intact cognitive abilities but still be socially impaired (Green, Kern et al., 2000). Because of these modest associations and inconsistencies, investigators have more recently sought to examine specific and unique aspects of cognition that underlie social function and that may be distinct from traditional neurocognitive domains. One such aspect that has been targeted in both disorders is social cognition.

Here, I will present an overview of social cognition in schizophrenia and autism and, while placing particular emphasis on the neural mechanisms subserving social cognition, highlight evidence that suggests that a similar neural profile may underlie social cognitive deficits in both disorders. I will begin by reviewing the concept of social cognition and underscoring how social cognition differs from traditional neurocognitive domains. I will then briefly discuss the relevance of social cognitive deficits in both schizophrenia and autism followed by a review of the neural structures implicated in social cognitive processes in both clinical and non-clinical populations. Here, particular emphasis will be placed on the role of the amygdala in making complex social judgments and on research that informs the

possibility of amygdala dysfunction in schizophrenia and autism. Finally, conclusions regarding potential social cognitive and neural similarities between autism and schizophrenia will be discussed, and hypotheses for the proposed study will be provided.

Social Cognition

Social cognition refers broadly to the cognitive processes involved in how individuals perceive, interpret, and process social information. Definitions of social cognition vary widely in complexity and specificity, however two primary definitions include "the mental operations underlying social interactions, which include the human ability to perceive the intentions and dispositions of others" (Brothers, 1990, p. 28) and "the processes that subserve behavior in response to conspicifics, and in particular, to those higher cognitive processes suberving the extremely diverse and flexible social behaviors that are seen in primates" (Adolphs, 1999a). These definitions, and others, firmly link social cognition to social behavior and highlight the potential role that deficits in social cognition may play in social dysfunction. Further, several different specific skills comprise the domain of social cognition and thus support a multidimensional view of the construct. These skills include emotion recognition, social cue perception, theory of mind (ToM), and attributional style.

Evidence for the relative independence of social cognition from traditional neurocognitive skills can be garnered from both lesion studies and examinations of clinical populations. To begin, individuals with either frontal or prefrontal cortex damage show impaired social behavior and functioning despite the retention of intact cognitive skills such as memory and language (Anderson, Bechara, Damasio, Tranel, & Damasio, 1999; Blair & Cipolotti, 2000; Fine, Lumsden, & Blair, 2001). Similarly, individuals with lesions in the somatic marker circuitry show low emotional and social intelligence and disturbances in

social functioning regardless of normative levels of cognitive intelligence (Bar-On, Tranel, Denburg, & Bechara, 2003). The fact that social cognition can become selectively impaired while sparing nonsocial cognition suggests that unique neural circuits subserve social cognition. Additionally, lesions to ventromedial occipital cortex can result in prosopagnosia, a condition in which individuals show selective impairments in the perception of faces but preserved perception for nonsocial stimuli. Such findings have led some to suggest that facial processing is the result of domain specific neural mechanisms (Kanwisher, 2000).

This conclusion is bolstered by studies of clinical populations, specifically individuals with Williams' syndrome (WS) and individuals with autism, that show a dissociation between social cognitive and nonsocial cognitive skills in these groups. Individuals with WS tend to be outgoing and social, despite having below normal intelligence (Jones et al., 2000), and these individuals appear to have relatively preserved basic social cognitive skills (i.e., facial processing and simple Theory of Mind abilities, Karmiloff-Smith, 2000), despite having deficits in spatial cognition (Karmiloff-Smith, Klima, Bellugi, Grant, & Baron-Cohen, 1995; Tager-Flushberg, Boshart, & Baron-Cohen, 1998). Recent work examining specific neural structures in individuals with WS has attempted to explore this dissociation. Reiss and colleagues (2004) used structural neuroimaging to examine volumetric abnormalities in neural structures included in the visual-spatial system and the neural structures most commonly implicated in face and emotion processing. Results indicated that as compared to healthy persons, individuals with WS showed decreased volume and gray matter densities in several regions comprising the visual-spatial system and increased volume and gray matter density in regions thought to subserve face and emotion processing, including the amygdala and superior temporal gyrus. These findings provide striking evidence for the independence

of social and nonsocial cognitive systems.

The partial preservation of social cognition seen in WS is in direct contrast to persons with High Functioning Autism and Asperger's syndrome, who show specific impairments in social cognition and social behavior that may not be related to general cognitive abilities (Heavey, Phillips, Baron-Cohen, & Rutter, 2000; Klin, 2000). As with WS, these findings lend support for the hypothesis that specific neural modules exist that are devoted to the processing of social information, a hypothesis that has also been maintained in the areas of evolutionary biology and primatology (Adolphs, 2001; Cosmides & Tooby, 1994; Frith & Frith, 1999; Penn et al., 1997; Phillips, Drevets, Rauch, & Lane, 2003a; 2003b).

Social cognition has been studied widely in both schizophrenia and autism. The following sections will present a brief review of work exploring social cognitive deficits in schizophrenia and the functional significance of these deficits. The autism literature will then be reviewed using a parallel structure.

Social Cognition in Schizophrenia

Social Cognitive Deficits and Biases in Schizophrenia

The study of social cognition in schizophrenia has generally focused on three primary domains of social functioning: theory of mind, attributional style, and social perception, which includes emotion recognition (Penn, Addington, & Pinkham, 2006). In recent years, each of these three domains has received considerable attention; however, in keeping with the focus of this proposal, the majority of this review will be devoted to social perception whereas theory of mind and attributional style will be covered only briefly.

Theory of Mind

Theory of mind (ToM) refers to the ability to represent the mental states of others

and/or to make inferences about another's intentions. Skills that fall under the rubric of ToM include understanding false beliefs, hints, intentions, deception, metaphor, irony, and faux pas. Relative to non-clinical and clinical control participants (i.e. individuals with depression or mania), individuals with schizophrenia perform poorly on tasks that measure ToM abilities (Corcoran, Mercer, & Frith, 1995; Drury, Robinson, & Birchwood, 1998; Frith & Corcoran, 1996; Marjoram et al., 2005; Pilowsky, Yirmiya, Arbelle, & Mozes, 2000; Sarfati & Hardy-Bayle, 1999; Sarfati, Hardy-Bayle, Brunet, & Widloecher, 1999; Sarfati, Hardy-Bayle, Nadel, Chevalier, & Widloecher, 1997; reviewed in Corcoran, 2001), and on the whole, these deficits are independent of a general cognitive deficit (Brunet, Sarfati, & Hardy-Balye, 2003; Doody, Gotz, Johnstone, Frith, & Cunningham-Owens, 1998; Mazza, De-Risio, Surian, Roncone, & Casacchia, 2001; Pickup & Frith, 2001; Schenkel, Spaulding, & Silverstein, 2005; see Brune, 2003 and Greig, Bryson, & Bell, 2004 for exceptions). Impairments in ToM skills appear to be most profound among individuals with negative features, passivity symptoms, behavioral signs, disorganization, and paranoid symptoms (Corcoran et al., 1995; Greig et al., 2004; Harrington, Langdon, Siegert, & McClure, 2005; Pickup & Frith, 2001); however, increasing evidence suggests that the degree of deficit may vary as a function of symptom and difficulty of ToM task (Frith & Corcoran, 1996; Mazza et al., 2001). This suggests that ToM is sensitive to the heterogeneity of schizophrenia. Finally, evidence is mixed regarding whether these deficits represent trait or state characteristics (Harrington, Siegert, & McClure, 2005). Several studies using a variety of ToM tasks have demonstrated that individuals who are in remission perform comparably to controls (Corcoran, 2003; Drury et al., 1998, Frith & Corcoran, 1996; Pickup & Frith, 2001), which would support a state deficit. In contrast, Herold and colleagues (2002) noted that remitted individuals were

successful on simple ToM tasks but impaired on more complicated tasks, and other studies have found that the first-degree relatives of individuals with schizophrenia perform worse than non-clinical controls on ToM tasks (Janssen, Krabbendam, Jolles, & van Os, 2003; Wykes, Hamid, & Wagstaff, 2001) and that children who later develop schizophrenia perform poorly on measures assessing components of ToM (Schiffman et al., 2004), all of which lend support to a trait hypothesis.

Attributional Style

The majority of work on attributions in schizophrenia has focused on investigating attributional style in individuals with paranoia or persecutory delusions. From this work, two attributional biases have most commonly been observed: a self-serving bias and a personalizing bias. Bentall and colleages (2001) have argued that individuals with persecutory delusions tend to show an exaggerated self-serving bias in which negative outcomes are attributed to others and positive outcomes to one's own actions (for partial failures to replicate this finding, see Kristev, Jackson, & Maude, 1999 and Martin & Penn, 2002), although this effect may be stronger for attributing negative outcomes to others, rather than taking credit for success (Garety & Freeman, 1999). A personalizing bias is evidenced by individuals with paranoia in that for negative interpersonal events, these individuals are more likely to blame others, rather than the situation or circumstances, relative to persons without paranoia and/or persecutory delusions (Bentall, 2001; Craig, Hatton, Craig, & Bentall, 2004; Kinderman & Bentall, 1997). Additionally, this bias may be most pronounced in individuals who are acutely ill rather than individuals whose symptoms are in remission (Randall, Corcoran, Day, & Bentall, 2003).

Social Perception

Studies of social perception in schizophrenia can be broken down into two general areas: facial affect recognition and social cue perception. Reviews of the literature on facial affect recognition (i.e., Edwards, Jackson, & Pattison, 2002; Hellewell & Whittaker, 1998; Kohler & Brennan, 2004; Mandal, Pandey, & Prasad, 1998; Penn et al. 1997) suggest the following conclusions. First, individuals with schizophrenia have deficits in facial affect perception compared to non-clinical control participants. Second, these deficits are present relative to individuals with other psychiatric disorders such as depressive disorder (Wenger, Lange, Ruther, & Irle, 2004); however, results are inconsistent when compared to disorders that include psychotic features such as bipolar disorder. Third, greater impairment is evident for the perception of negative emotional displays compared to positive displays, with perhaps the greatest impairment for the perception of fear (Edwards, Pattison, Jackson, & Wales, 2001; Evangeli & Broks, 2000; Kohler et al., 2003). Fourth, longitudinal studies support a stable deficit in emotion perception (Addington & Addington, 1998; Gaebel & Wolwer, 1992; Kee, Green, Mintz, & Brekke, 2003; Kucharska-Pietura & Klimkowski, 2002); although, there is some evidence that individuals whose symptoms are in remission may perform better on affect perception tasks than individuals in an acute phase of the disorder (Gessler, Cutting, Frith, & Weinman, 1989; Penn et al., 2000). Fifth, there is some evidence that individuals with paranoid schizophrenia are better at facial affect perception than individuals with non-paranoid subtypes of the disorder (Davis & Gibson, 2000; Kline, Smith, & Ellis, 1992; Lewis & Garver, 1995; see Mandal & Rai, 1987 for an exception). Sixth, when viewing faces, individuals with schizophrenia display restricted visual scan paths (Loughland, Williams, & Gordon, 2002a; Streit, Wolwer, & Gaebel, 1997; Williams,

Loughland, Gordon, & Davidson, 1999; Williams, Loughland, Green, Harris, & Gordon, 2003) and spend less time examining salient features of the face (Loughland, Williams, & Gordon, 2002b; Phillips & David, 1997; Phillips & David, 1998; Williams et al., 1999), which may contribute to poor performance (Loughland et al., 2002a; 2002b; Williams et al., 1999). And finally, the jury is still out regarding whether facial affect perception deficits are part of a generalized performance deficit (Baudouin, Martin, Tiberghien, Verlut, & Franck, 2002; Bellack, Blanchard, & Mueser, 1996; Kerr & Neale, 1993; Mueser et al., 1996; Sachs, Steger-Wuchse, Kryspin-Exner, Gur, & Katschnig, 2004; Salem, Kring, & Kerr, 1996) or specific to decoding only facial emotions (e.g., Heimberg, Gur, Erwin, Shatasel, & Gur, 1992; Penn et al., 2000).

Unlike facial affect recognition stimuli, tasks that assess social cue perception utilize more dynamic stimuli that require multiple sensory modalities, and consistent with work on facial affect perception, individuals with schizophrenia are generally impaired in general social perception (Archer, Hay, & Young, 1994). Bell, Bryson, and Lysaker (1997) evaluated the performance of individuals with schizophrenia on a task of emotion recognition in which an actor portrayed a basic emotion through facial expression, verbal tone, and upper-body movements while reciting one of three standardized monologues. They found that individuals in the schizophrenia sample performed significantly worse than individuals with substance abuse and healthy control participants. Corrigan, Davies-Farmer, and Stolley (1990) also found that individuals with nonparanoid schizophrenia were impaired in accurately recognizing social cues from vignettes of social interactions.

Deficits in social cue perception also appear to be most pronounced for the perception of abstract, rather than concrete, cues. Concrete social cues involve observations of an

actor's behavior (e.g., "what is she doing?") and characteristics (e.g., "what is she wearing?") whereas abstract cues consist of inferences of affect and goals. In a series of studies, Corrigan and colleagues have found that individuals with schizophrenia are more sensitive to, and better able to recognize, concrete social cues rather than abstract ones (Corrigan, Garman, & Nelson, 1996; Corrigan & Green, 1993a; Corrigan & Green, 1993b; Corrigan & Nelson, 1998; Corrigan, Silverman, Stephenson, Nugent-Hirschbeck, & Buican, 1996), a finding consistent with what we would expect from individuals who have difficulties in discerning the intentions of others (i.e., Theory of Mind skills).

A third category of social perception that is just recently receiving attention is the perception of stimuli requiring complex social judgments. As knowledge of basic emotion perception abilities has grown, researchers have become increasingly interested in more complex, real-life social cognitive situations. Thus, assessment methods and stimuli have become more sophisticated, requiring participants to draw upon several social cognitive abilities within the same task. For example, the Eyes Test (Baron-Cohen, Wheelwright, Hill, Raste, & Plumb, 2001) incorporates both emotion perception and ToM abilities. This task consists of still frames of the eye-region of faces depicting various social emotions and complex mental states; therefore, in order to perform well on the task, participants must be able to identify social emotions as well as make inferences about the intentions of the individual shown. A similar task that requires participants to make complex mental judgments is the Trustworthiness/Approachability Task developed by Ralph Adolphs (1998). Here, participants are shown black and white photographs of individuals' faces, and they are asked to rate how trustworthy and approachable they perceive each individual to be.

Due to the relative newness of these tasks, they have not been widely incorporated

into the literature. No studies have investigated the performance of individuals with schizophrenia on the Trustworthiness/Approachability Task, and only two have utilized the Eyes Task. These studies are however largely consistent with the general findings for social perception. Specifically, Craig et al. (2004) found that individuals with paranoid schizophrenia performed significantly worse than healthy controls on the Eyes Task and that this effect remained when controlling for IQ. Likewise, Oguz and colleagues (2003) found similar performance deficits for individuals with schizophrenia and schizoaffective disorder that were not correlated with IQ. Finally, in a later study, Oguz et al. (2005) also found poor performance on the Eyes Task was associated with the severity of negative symptoms.

The Functional Significance of Social Cognition in Schizophrenia

As noted previously, investigators turned their attention to social cognition in the hopes of identifying factors that underlie social functioning, and thus far, several studies have confirmed that a relationship does exist between social cognition and social functioning. To begin, relationships with various aspects of social functioning have been clearly elucidated for affect recognition. For instance, Kee et al. (2003) reported that emotion perception was related to work functioning and independent living, and Poole, Tobias, and Vinogradov (2000) found that errors in affect recognition were correlated with lower quality of life and impoverished interpersonal relations. Hooker and Park (2002) also reported that emotion perception abilities were associated with communication and occupational abilities. Another study found that, for inpatients, affect perception was related to social competence as assessed by social skill and social adjustment on the ward (Mueser et al., 1996). In a similar study, Ihnen, Penn, Corrigan and Martin (1998) concluded that performance on emotion identification tests was associated not only with ratings of overall social skill, but also clarity

(clear enunciation of speech) and conversation involvement as assessed by a role play test. Finally, facial affect perception has also been associated with adaptive ward functioning, particularly hygiene and grooming (Penn, Spaulding, Reed, & Sullivan, 1996).

While sparse, work attempting to link social cue perception to social functioning has also supported a relationship between the two. Corrigan and Toomey (1995) found that sensitivity to social cues was associated with interpersonal problem-solving skills; however, a similar study by Ihnen et al. (1998) that attempted to link social cue perception to social skill found only a weak association. This latter finding is somewhat contradictory to the findings of a study by Bellack and colleagues (1992). Bellack et al. found that social perception was correlated with overall social skill but that this relationship held only in situations involving negative affect. This caveat may explain the discrepancy between these two findings since Ihnen et al. did not examine negative affect situations. Thus, there is some, albeit limited evidence, that social cue perception is related to social functioning.

In addition, there is evidence that social knowledge and general social perception are related to social functioning among persons with schizophrenia. Specifically, the ability to identify the sequence of behavioral steps used in social situations and to place them in the correct order was associated with less irritability on the ward among chronically ill patients (Penn et al., 1996) and persons recovering from an acute psychotic episode (Penn, Ritchie, Francis, Combs, & Martin, 2002). Moreover, Appelo and colleagues (1992) reported that knowledge of social situations accounted for more variance in ward functioning than symptoms.

Finally, although research establishing and describing a ToM deficit in schizophrenia is abundant, only a few studies have examined the functional significance of these deficits.

In Brune (2005), ToM was found to account for 24% of the variance in severe social behavioral problems, and Roncone et al. (2002) found that ToM was related to global social functioning and that this relationship remained when controlling for IQ. Roncone and colleagues also noted that ToM abilities accounted for more variance in social functioning than cognitive factors such as verbal fluency, memory, and executive function. Similarly, Pinkham and Penn (in press) reported that performance on measures of ToM was related to better overall social skill.

Thus, there is growing evidence that social cognition is related to social impairments in schizophrenia, and the foregoing provides strong evidence for the functional significance of social cognition in schizophrenia. Perhaps most impressive is that in a few studies (Corrigan & Toomey, 1995; Penn et al., 1999; Penn et al., 1996; Roncone et al., 2002), the association between social cognition and social functioning could not be accounted for by cognitive deficits. These findings lend support to the hypothesis that social cognition contributes independent variance to functional outcomes beyond non-social cognition alone.

Social Cognition in Autism

Social Cognitive Deficits in Autism

As with schizophrenia, several domains of social cognition have been explored in autism, however, the two domains that have received the most attention are ToM and social perception. Both social cognitive domains have been studied across the developmental course of autism and across the autism spectrum. Where possible, this review will be limited to the literature exploring social cognitive deficits in adults with high-functioning autism and Asperger's syndrome, and the majority of the review will be devoted to social perception.

Theory of Mind

In autism, ToM deficits span the developmental period and remain present in adulthood, a finding which has prompted some to hypothesize that ToM impairments are a core feature of the disorder and the primary deficit in autism (Baron-Cohen, 1989; Baron-Cohen, Leslie, & Frith, 1985; Kleinman, Marciano, & Ault, 2001; Leslie & Frith, 1988; Ozonoff, Pennington, & Rogers, 1991). These deficits are manifest in young children with autism as absent or delayed joint attention behaviors (Dawson et al., 2004; Morgan, Maybery, & Durkin, 2003) and as difficulty with pretend play (Jarrold, 2003; Rutherford & Rogers, 2003). Later, children with autism spectrum disorders show difficulty with false belief tasks (Baron-Cohen, 1995; Yirmiya, et al., 1998) and other more complex ToM abilities such as deception and faux pas (Baron-Cohen, O'Riordan, Stone, Jones, & Plaisted, 1999; Brent, Rios, Happe, & Charman, 2004; Pilowsky et al., 2000). Although ToM abilities remain impaired as compared to age matched typically developing individuals, some improvement over time does occur such that higher functioning adolescents and adults become able to pass first- and second-order false belief tasks (Bowler, 1992; Dahlgren & Trillingsgaard, 1996; Steele, Joseph, & Tager-Flushberg, 2003).

Given that most adults with autism spectrum disorders are able to pass false belief tasks, more complicated tasks have been utilized to examine ToM abilities in older individuals. Unfortunately, as these tasks have become more advanced, their specificity has declined thus making it increasingly difficult to conclude that they measure only ToM. Two commonly used tasks that exemplify this are the Eyes Task mentioned earlier and the Social Attribution Task (SAT; Klin, 2000). Both tasks are used as measures of ToM in the autism literature; however, a convincing argument can be made that they more accurately assess the

ability to make complex social judgments and include multiple social cognitive processes. As noted earlier, the Eyes task incorporates elements of emotion perception as well as ToM, and the SAT necessitates the attribution of biological motion as well as ToM. Despite these complications, studies using these tasks will still be reviewed under the current ToM heading in order to remain consistent with the conclusions put forth by the authors of these studies.

On the whole, studies of ToM abilities in adults with autism spectrum disorders have shown considerable deficits as compared to healthy controls. A series of studies by Baron-Cohen and colleagues has consistently shown that high functioning individuals with autism and Asperger's syndrome are impaired on the Eyes Task (Baron-Cohen, Jolliffe, Mortimore, & Robertson, 1997; Baron-Cohen et al., 2001; Baron-Cohen, Wheelwright, & Jolliffe, 1997). One of these, Baron-Cohen, Jolliffe et al. (1997), also utilized a clinical control group, individuals with Tourettes Syndrome, and still found impairments in ToM. Likewise, other groups have used the Eyes Task in conjunction with other ToM tasks to demonstrate that ToM impairments in autism are not limited to the visual modality (Kleinman et al., 2001) and that these impairments extend beyond attributing a mental state to a face; they are also apparent when trying to infer the true meaning of a hint (Craig et al., 2004). These overall deficits are confirmed by meta-analyses of studies examining ToM and appear to be present not only as compared to healthy individuals but to individuals with mental retardation as well (Yirmiya et al., 1998).

Finally, Klin (2000) expanded Baron-Cohen's work by introducing the SAT that utilizes cartoon animations of geometrical shapes enacting a social plot and requires participants to narrate each animation. Klin found that as compared to healthy controls, individuals with autism and Asperger syndrome were less likely to identify the social

elements of the story and to use ToM or affective terms in their narrations. Moreover, he found that performance was not related to age or verbal ability. These findings not only supported a general deficit in ToM abilities, but also that individuals with autism spectrum disorders may not naturally seek social meaning in the environment.

Attributional Style

Although attributional style is under-researched in autism spectrum disorders, a few studies have attempted to apply the attributional model of paranoia to Asperger's syndrome. Increased rates of paranoia are often seen clinically in individuals with Asperger's syndrome (Hare 1997; Wing 1996), and given this similarity to psychotic disorders, two studies have investigated whether the attributional biases seen in schizophrenia are also be present in individuals with Asperger syndrome (Blackshaw, Kinderman, Hare, & Hatton, 2001; Craig et al., 2004). Both studies found increased rates of paranoia as compared to healthy controls, however both also failed to find evidence of attributional biases. Thus from these limited data, it appears that individuals with Asperger syndrome do not display any attributional abnormalities and that the paranoia seen in such individuals likely stems from mechanisms that differ from those of schizophrenia.

Social Perception

As in schizophrenia research, the study of social perception in autism has focused on several different elements including the detection of biological motion, face perception, emotion perception, and the processing of complex social stimuli. Varying degrees of attention have been devoted to each component of social perception, however, in general, individuals with autism have been found to perform abnormally on tasks assessing these abilities.

The ability to perceive biological motion is most commonly assessed using point-light displays of human figures (i.e. Grossman & Blake, 1999), but other methods such as moving animated characters (Pelphrey, Morris, & McCarthy, 2004) and geometrical shapes moving in conjunction to mimic walking (Pelphrey, Mitchell, et al., 2003) have also been used. To date, only point light displays have been utilized with an autistic sample, and the two studies that have done so have employed children. Moore, Hobson, and Lee (1997) found that children with autism consistently performed more poorly than control participants in differentiating biological motion from the motion of inanimate objects. A similar study confirmed this deficit in perceiving biological motion and found a positive correlation between degree of autistic symptomatology and impairment in detecting biological motion (Blake, Turner, Smoski, Pozdol, & Stone, 2003). Unfortunately, it would be premature to conclude that these deficits will persist into adulthood, but these studies do provide a foundation upon which such a hypothesis could be based.

Beyond perceiving biological motion, investigators have also examined how individuals with autism process human faces. Early work in this area made note of the fact that individuals with autism fail to show an inversion effect for faces (Boucher & Lewis, 1992; Hobson, Ouston, & Lee, 1988a; Langdell, 1978; Tantam, Monaghan, Nicholson, & Stirling, 1989), which in typical development refers to the tendency for individuals to show a processing advantage for faces shown in an upright orientation as opposed to faces shown upside down, or in an inverted orientation (see Teunisse & de Gelder, 2003 for a failure to replicate these findings with high functioning individuals). Individuals with autism also fail to process faces holistically and instead tend to focus on individual features with a particular preference for the features of the lower face (Gross, 2004; Weeks & Hobson, 1987; see

Lahaie et al., 2006 for evidence of enhanced processing of facial features in autism). Examination of the visual scanpaths of individuals with autism also confirms an abnormal featural processing strategy. Klin and colleagues (2002) demonstrated that when viewing social scenes, individuals with autism spend less time examining the eyes of actors in the scene and more time looking at the mouths of the actors or objects in the scene. Pelphrey et al. (2002) also found that individuals with autism devote more time to viewing non-salient features of the face (i.e. the ear or chin) than core features of the face such as the eyes, nose, and mouth. Interestingly, Pelphrey et al. monitored these visual scanpaths within the context of an emotion recognition task, and the behavioral results of this study indicated that individuals with autism correctly identified fewer emotions than controls. Together, these results support the hypothesis that individuals with autism utilize abnormal strategies to process faces and that these strategies may contribute to impairments in face and emotion processing.

The literature addressing emotion perception in autism is quite extensive and can be summarized as follows. First, individuals with autism do show impairments in emotion recognition (Bolte & Poustka, 2003; Hall, Szechtman, & Nahmias, 2003; Howard et al., 2000; Pelphrey et al., 2002). Second, these impairments do not appear to be uniform across the autism spectrum; instead, there appears to be an interaction between level of functioning and difficulty of task. Numerous studies have failed to find emotion recognition deficits in high functioning individuals when only basic emotions are used (Adolphs et al., 2001; Baron-Cohen, Spitz, & Cross, 1993; Baron-Cohen, Wheelwright, & Jolliffe, 1997; Ogai et al., 2003; Piggot et al., 2004; Volkmar, Sparrow, Rende, & Cohen, 1989); however, deficits do emerge when more complex emotions are processed (Capps, Yirmiya, & Sigman, 1992;

Grossman, Klin, Carter, & Volkmar, 2000; Pelphrey et al., 2002). Further, Loveland et al. (1997) demonstrated that high functioning individuals performed better on emotion recognition tasks than lower functioning individuals, which has prompted some to conclude that high functioning individuals may be able use compensatory strategies to mask deficits when processing basic emotions (Teunisse & de Gelder, 2001). Third, and as alluded to above, greater impairment is evident for more complex emotions such as fear, surprise, and complex social emotions (e.g. distrustful, accusing, and friendly) (Baron-Cohen et al., 1993; Baron-Cohen et al., 2001; Capps et al., 1992; Pelphrey et al., 2002). Fourth, the evidence is mixed regarding whether this is a specific deficit (Celani, Battacchi, Arcidiacono, & Di-Domenico, 1999; Hobson, 1986a; Hobson, 1986b; Hobson, Ouston, & Lee, 1988b; Weeks & Hobson, 1987) or if it can be accounted for by more generalized deficits in face perception (Critchley, Daly, Bullmore, et al., 2000) or cognitive abilities (Ozonoff, Pennington, & Rogers, 1990).

The last area of social perception is the processing of complex social stimuli. Similar to the current trend in schizophrenia research, autism investigators have recently begun exploring the ability of individuals with autism to process stimuli in a manner that requires complex social judgments. As can be recalled from the ToM review, several studies have utilized the Eyes Task to demonstrate that individuals with autism show deficits in recognizing social emotions and complex mental states. Likewise, in an innovative study, Adolphs and colleagues (2001) administered the Trustworthiness/Approachability task to a sample of high functioning individuals with autism. On average, individuals with autism gave abnormally high ratings of trustworthiness and approachability to unfamiliar faces. From this, Adolphs et al. concluded that individuals with autism may be impaired in the

processes necessary for higher-level social cognition and that they may fail to link social judgments to the perception of a face. Studies such as these are the first of their kind to use tasks that are sensitive to, and that target, subtle impairments in social cognition.

The Functional Significance of Social Cognition in Autism

As compared to schizophrenia, less emphasis has been placed on understanding the impact of social cognition on functioning in autism; however, the studies that have examined this question do support a relationship between social cognitive abilities and social functioning. Specifically, ToM abilities have been linked to social behavior in children with autism (Frith, Happe, & Siddons, 1994; Hughes, Soares-Boucaud, Hochmann, & Frith, 1997), and various elements of social perception have also been shown to correlate with social functioning in individuals with autism and individuals with pervasive developmental disorders (PDD). In the Klin et al. (2002) study examining the visual fixation patterns of individuals with autism while viewing social scenes, the authors found that more time fixating on objects in the scene instead of the actors was related to poorer social adjustment. Additionally, Fein and colleagues (1992) noted that emotion perception abilities were correlated with level of social skill in individuals with PDD, and a similar study by Braverman and colleagues (1989) also reported that deficits in emotion perception were related to greater social impairment.

The Neurobiology of Social Cognition

In 1990, Brothers proposed a neural system of social cognition that was comprised of the orbito-frontal cortex, the superior temporal sulcus, and the amygdala. This seminal paper led to numerous studies that have generally confirmed the role of these neural structures in social information processing (Adolphs, 2001; Adolphs, 2002; Allison, Puce, & McCarthy,

2000; Baron-Cohen et al., 1994; Stone, Baron-Cohen, & Knight, 1998), as well as several others that may play secondary roles (i.e. the right parietal cortex, the insular cortex, the basal ganglia, (Adolphs, 2002) and the temporal-parietal junction at the top of the superior temporal gyrus, and the temporal poles, (Frith, 2001)). Although these neural structures also subserve other cognitive functions (e.g., problem solving; conceptual reasoning), they, and not other neural structures, tend to be most consistently activated in response to social stimuli, thus underscoring their role in neural models of social cognition. In what follows, I will briefly describe the major neural structures and mechanisms that have consistently shown a role in social cognition, particularly those structures implicated in ToM and social perception. An in depth treatment of each brain region would far exceed the scope of this paper; thus, I will limit this discussion to the specific areas proposed by Brothers (1990) and Adolphs (1999a; 2001; 2002) as subserving social cognition: the medial prefrontal cortex, the superior temporal sulcus, the fusiform gyrus, and the amygdala. Finally, in keeping with the focus of this project, research elucidating the role of the amygdala in social perception will be reviewed in the most detail.

The Frontal Cortices and Theory of Mind

There is growing evidence that performance on ToM tasks is associated with activation of specific frontal cortical regions, in particular, the medial frontal cortex and the medial prefrontal cortex. A limited number of studies also support the role of the orbito-frontal cortex in ToM. Early studies that attempted to localize ToM in the brain examined regions that were activated in healthy participants during a ToM task. Fletcher et al. (1995) used positron emission tomography (PET) to reveal a unique activation of Brodmann's areas (BA) 8 and 9 in the left medial frontal cortex during a verbal ToM task that was not present

during similar non-ToM tasks. Similarly, Goel, Grafman, Sadato, and Hallett (1995) found selective activation of the left medial frontal cortex (BA 9) throughout a ToM task in which normal participants were asked to infer the thoughts of a contemporary of Christopher Columbus. Thus, results from these early studies indicated that ToM was specific to the medial frontal cortex (see also Calarge, Andreasen, & O'Leary, 2003; Stuss, Gallup, & Alexander, 2001 for more recent support of the role of the medial frontal cortex in ToM).

More recent studies have used both verbal and nonverbal tasks in their experimental design, and have supported the role of the prefrontal cortex (McCabe, Houser, Ryan, Smith, & Trouard, 2001; Vogeley et al., 2001), specifically the medial prefrontal cortex, including portions of BA 8 and 9, in ToM skills. Gallagher and colleagues (2000) used functional magnetic resonance imaging (fMRI) to assess brain activity while participants read and answered theory of mind questions about a verbal passage, and interpreted and explained the meaning of cartoons that required theory of mind skills. Relative to control conditions, there was unique activation of the medial prefrontal cortex during the ToM tasks. Similar results were found using only a cartoon task (Brunet, Sarfati, Hardy-Bayle, & Decety, 2000). Additionally, the medial prefrontal cortex has also been implicated in ToM tasks that use non-human stimuli and tasks that do not explicitly ask participants to interpret the mental states of others. For example, Castelli and colleagues (2000; 2002) found that the medial prefrontal cortex was selectively activated when the movement patterns of geometric shapes evoked mental state attribution but not during simple action description. German, Niehaus, Roarty, Giesbrecht, and Miller (2004) also found increased activity in the medial prefrontal cortex when subjects viewed pretend actions as opposed to real actions (recall that understanding of pretense is a developmental precursor to ToM).

Additional studies have also implicated the orbito-frontal cortex in ToM skills. Baron-Cohen et al. (1994) used single photon emission computerized tomography (SPECT) to identify areas of activation during performance on a mental state terms task (a ToM task). They found increased cerebral blood flow in the right orbito-frontal cortex of healthy participants during a ToM task, but not during a control task. Lesion studies also lend support to this pattern of findings. Stone et al. (1998) found that individuals with bilateral orbito-frontal lesions performed similarly to individuals with Asperger's syndrome on a task requiring the recognition of a faux pas, a task that requires social reasoning as well as theory of mind. And, Mah, Arnold, and Grafman (2004) found that individuals with lesions to the orbitofrontal/anterior cingulate cortex were impaired in the detection of lies, also a process that requires ToM. Collectively, the these studies suggest that activation of the medial prefrontal cortex, and to some extent, the orbito-frontal cortex, is critical to being able to infer the mental states of others (see Frith, 2001, for two additional brain regions that are activated during ToM tasks but that are not within the scope of this paper).

The Fusiform Gyrus and Superior Temporal Sulcus in Face Processing

Several recent reviews have established that specific regions of the brain are associated with face processing. Among these are the lateral fusiform gyrus (FG) and the superior temporal sulcus (STS) (Adolphs, 2001; Adolphs, 2002; Allison et al., 2000). The lateral FG subserves selective activation to faces (Aylward et al., 2005; Chao, Martin, & Haxby, 1999; Puce, Allison, Asgari, Gore, & McCarthy, 1996; Rhodes, Byatt, Michie, & Puce, 2004) as opposed to objects, and because of this area's specificity and the consistency with which it has been linked to face recognition, it has been dubbed the "fusiform face area" (although the specificity of the FG for faces has been contested, see Blonder et al., 2004;

Gauthier, Curran, Curby, & Collins, 2003; Gauthier, Skudlarski, Gore, & Anderson, 2000). Additionally, the FG activates strongly during tasks focusing on identity and appears to be most involved in the processing of non-changeable, static aspects of the face (Haxby, Hoffmann, & Gobbini, 2000; Winston, Henson, Fine-Goulden, & Dolan, 2004).

In contrast, the STS is more strongly activated during tasks focusing on visual gaze shifts (Kingstone, Tipper, Ristic, & Ngan, 2004; Pelphrey, Singerman, Allison, & McCarthy, 2003; Pelphrey, Viola, & McCarthy, 2004) and is involved in processing the changeable aspects of the face such as the eyes and the mouth (Haxby et al., 2000; Winston et al., 2004). Such a distinction between the static and dynamic features of the face is important because it is the dynamic features that provide the most social information. Changes in the direction of gaze indicate the focus of one's attention, and changes in the shape of the eyes and mouth facilitate emotional expression, and indicate emotions such as happiness and aggression.

The Amygdala and Complex Social Perception

Both lesion and imaging studies have consistently supported the role of the amygdala in detecting threat, recognizing emotions, and making complex social judgments. Specifically, evidence from both primates and humans strongly implicates the amygdala in the evaluation of potential danger (Amaral et al., 2003), and human individuals with damage to the amygdala are also noted to have difficulty recognizing faces and judging the emotional expressions of others, particularly when that expression is fear (Adolphs, Tranel, Hamann et al., 1999; Calder et al., 1996; Haxby et al., 2000; Whalen et al., 2004; Young et al., 1995). Interestingly, this impairment in recognizing fear can be present despite intact face identity recognition (Adolphs, Tranel, Damasio, & Damasio, 1995) and intact recognition of verbally expressed emotion (Adolphs & Tranel, 1999; Anderson & Phelps, 1998), and also extends to

recognizing the intensity of fearful expressions (Adolphs, Tranel, Damasio, & Damasio, 1994). Although these studies and others (Anderson & Phelps, 2000; Broks et al., 1998) support a specific impairment in the recognition of fear, several more recent studies have found similar deficits for other negatively valanced emotions such as sadness and anger. Schmolck and Squire (2001) noted that patients with bilateral amygdala lesions had difficulty discriminating negative emotions and often mistook fear for surprise or anger and sadness for disgust or anger. Similarly, in two different studies, Adolphs and Tranel also found that individuals with bilateral lesions show a specific impairment in recognizing sadness as opposed to happiness (2004), and that individuals with bilateral amygdala damage are more likely to falsely identify anger as happiness (2003).

Functional neuroimaging studies utilizing healthy participants have largely confirmed and extended the findings from lesion studies. Using PET, Morris et al. (1996) found a differential response in the amygdala to fear and happiness. Amygdalar activation was much more pronounced when participants viewed photographs of fearful faces, and there appeared to be an interaction between level of activation and intensity of emotion such that the more fearful a face looked, the greater the level of activation. Using fMRI, Phillips et al. (1997) explored the differential amygdalar response to fear by comparing activation in response to fearful and disgusted facial expression whereas Breiter and colleagues (1996) compared fearful and neutral expressions. Results from both studies indicated that the amygdala was only activated when viewing fearful faces and not when viewing disgusted and neutral faces, respectively. Similarly, Whalen et al. (2004) found significantly greater activation of the amygdala in response to fearful eye whites as compared to happy eye whites.

Other imaging studies have further elucidated the role of the amygdala by

demonstrating that it is maximally engaged during automatic or rapid processing of faces. Whalen et al. (1998) presented photographs of happy and fearful expressions in a backward masking procedure that resulted in the majority of participants being unaware of seeing fearful and happy expressions, and despite lack of conscious awareness, significantly greater amygdalar activation was noted in response to fearful faces. Likewise, Critchley, Daly, Phillips et al. (2000) compared explicit and implicit facial emotion processing and found that implicit processing activated the amygdala to a greater extent than explicit processing. Indeed, Hariri et al. (2000) noted that asking participants to actively label emotional expressions might actually result in deactivation of the amygdala, a finding that has been mirrored in investigations of automatic and controlled social evaluation (Cunningham et al., 2004). Overall, findings from both lesion and imaging studies clearly indicate that the amygdala is important for emotion recognition and suggest that the amygdala may play a disproportionate role in the automatic processing of negative or threatening stimuli (Adophs et al., 1999).

Closely related to basic emotion recognition and threat perception, the amygdala has also been implicated in the process of making complex social judgments such as identifying social emotions and assessing the trustworthiness and approachability of a social other. Social emotions can be distinguished from basic emotions (i.e. happy, sad, angry, afraid, etc.) in that they only make sense within the context of a social relationship, and thus would include emotions such as arrogant, guilty, admiring, and flirtatious. It appears that when required to process social emotions, individuals with amygdala damage show even more severe impairments that those seen when processing only basic emotions, a finding which suggests that the amygdala may be specialized for processing stimuli with important social

significance (Adolphs, Baron-Cohen, & Tranel, 2002). An interesting line of research examining the role of the amygdala in evaluating trustworthiness supports this view; both lesion and imaging studies have established that the amygdala is integral to making such social judgments. First, Adolphs et al. (1998) asked three individuals with complete bilateral amygdala damage and seven individuals with unilateral amygdala damage to rate faces for approachability and trustworthiness. All three bilateral participants judged the faces to be more approachable and trustworthy than control participants, and this was most notable for faces that the control participants rated the least approachable and trustworthy. In contrast, individuals with unilateral lesions performed comparably to control participants. Taken together, these results seem to imply that only unilateral activation of the amygdala, as opposed to bilateral activation, is necessary for accurate processing of trustworthiness stimuli and that this processing is not highly lateralized. A functional imaging study of healthy individuals lends credence to this conclusion. Winston and colleagues (2002) found bilateral activation of the amygdala in response to untrustworthy faces, and interestingly, faces rated as the most untrustworthy evoked greater amygdalar response. Thus, as can be seen from these studies, the amygdala is not limited to the processing of basic emotions but also plays a critical role in complex social judgment.

The Neural Correlates of Social Cognition in Schizophrenia and Autism

The strong link between neural structures and specific social cognitive abilities presents several interesting implications for pathology and raises the possibility that the social cognitive deficits seen in autism and schizophrenia could be related to abnormal functioning in these particular structures. In what follows, studies that explore structural and functional neural abnormalities in schizophrenia and autism will be detailed. To remain

consistent with the focus of this project, only those structures primarily involved in social perception will be reviewed, however, please see Pinkham, Penn, Perkins, and Leiberman (2003) for a review of the frontal cortices and ventromedial prefrontal cortex in schizophrenia.

The FG, STS, and Amygdala in Schizophrenia

Fusiform Gyrus

In general, the fusiform gyrus shows decreased volume and abnormal activation in persons with schizophrenia. First, both McDonald et al. (2000) and Paillere-Martinot et al. (2001) found decreased regional gray matter in the left fusiform gyrus of individuals with schizophrenia as compared to healthy controls, and their findings have been replicated in both chronic (Onitsuka et al., 2003) and first-episode samples (Lee et al., 2002; although see Pinkham et al., 2005 for a failure to replicate). Second, several studies show reduced activation of the FG while viewing faces (see Hempel et al., 2003 for conflicting results). Both Streit et al. (2001) and Quintana et al. (2003) reported that individuals with schizophrenia show reduced activation of the right lateral FG during emotion perception tasks as compared to healthy individuals. Moreover, a study by Williams et al., (2004) found reduced activation of the FG bilaterally as compared to healthy individuals. It is also interesting to note that Malaspina and colleagues (1999) report increased rCBF in the right fusiform gyrus during a visual fixation task. Although the latter finding may initially seem counterintuitive, one must consider that increased rCBF was not present in healthy control participants and in this respect, may indicate an abnormality in individuals with schizophrenia. Additionally, the fact that individuals with schizophrenia display reduced activation during social cognitive tasks and increased rCBF during a nonsocial task would

suggest that the FG of individuals with schizophrenia may not be specialized for social stimuli.

Superior Temporal Sulcus

Unfortunately, very little work has spoken to either STS volume or functioning in schizophrenia, and the only study that has done so utilized a ToM task instead of a social perception measure. In this study, Brunet, Sarfati, Hardy-Bayle, and Decety (2003) asked participants to choose concluding frames for comic strips that required the understanding of intentions or physical causality. Despite the absence of moving figures or real people, the authors still found activation of the right STS in individuals with schizophrenia during the processing of cartoons that included human figures. This activation was comparable to healthy controls. Thus, from this very limited evidence, it appears that individuals with schizophrenia may display intact STS functioning.

Amygdala

Considerably more information is available on amygdala volume and functioning in schizophrenia. Although initial reports of amygdala volume could not agree on a unilateral or bilateral reduction (see Buchanan et al., 1993 and Pearlson et al., 1997 for examples), more recent studies have supported a bilateral volume reduction (Joyal et al., 2003; Nelson, Saykin, Flashman, & Riordan, 1998; Niu et al., 2004). Additionally, a meta-analysis by Wright et al. (2000) supports this conclusion by reporting that the average volume of the amygdala in an individual with schizophrenia is only 94% of that in a healthy individual. It should be noted quickly however that despite these rather convincing results, some caution is warranted as a few studies have failed to find differences in amygdala volume between individuals with schizophrenia and control individuals (Sumich et al., 2002; Tanskanen et al.,

2005). Additionally, the findings of Sumich et al. also suggest that reductions in amygdala volume may not be consistent across symptom profiles or schizophrenia subtypes. Specifically, in this study, individuals with paranoid schizophrenia were found to have significantly smaller left amygdala volumes than non-paranoid individuals. Thus, the exact nature of these volume reductions may be more subtle than originally thought.

There is also evidence that amygdalar activation is abnormal in individuals with schizophrenia, particularly when negative affect is involved. Schneider and colleagues (1998) used mood induction in both persons with schizophrenia and normal controls and showed that persons with schizophrenia had reduced amygdalar activation during sadness, despite self-ratings of sadness that were comparable to controls. In addition, Taylor, Liberzon, Decker, and Koeppe (2002) found reduced activation of the amygdala in individuals with schizophrenia while viewing non-aversive, but emotionally salient stimuli, and Takahashi et al. (2004) found reduced activation of the right amygdala in individuals with schizophrenia as compared to controls while viewing emotionally unpleasant stimuli despite similar behavioral ratings of the photos. Moreover, a study utilizing an emotion labeling task found significantly less activation of the amygdala bilaterally in individuals with schizophrenia as compared to control participants (Hempel et al., 2003), and a similar study found reduced activation of the left amygdala in patients while discriminating emotional valance (Gur et al., 2002; see Kosaka et al., 2002 for evidence of increased activation when identifying happiness).

Finally, a few innovative studies have begun to examine whether amygdala activation may vary within schizophrenia sub-type. One such study evaluated individuals with paranoid and non-paranoid schizophrenia during an emotion recognition task and showed

that relative to healthy control participants, both groups of individuals with schizophrenia were not only less accurate in identifying emotions, but they also displayed no amygdalar activation to fearful expressions (Phillips et al., 1999). An elegant study combined fMRI and skin conductance arousal measures to further explore potential differences between paranoid and non-paranoid patients. Via this methodology, Williams and colleagues (2004) found that individuals with paranoid schizophrenia reacted with greater levels of arousal to fearful faces than either controls or non-paranoid patients and that despite this increased arousal, these individuals showed reduced amygdala activity. Interestingly, non-paranoid subjects did not differ from controls in level of amygdala activation. Collectively, these studies and those reviewed earlier provide considerable evidence of reduced amygdala activity in schizophrenia although no definitive conclusions can yet be drawn concerning the consistency of this abnormality across schizophrenia sub-types.

The FG, STS, and Amygdala in Autism

Fusiform Gyrus

Given the considerable evidence for face processing deficits in autism and the relative specificity of the FG, this neural structure became an early target for investigators. Schultz and colleagues (2000) were among the first to compare FG activation in individuals with autism to typically developing individuals. In this study, Schultz et al. first identified primary face and object processing areas in a sample of typically developing individuals and then compared these activation patterns to those present in individuals with autism. Results indicated that as compared to controls, individuals with autism showed no activation of the FG but increased activation of those areas typically used for object processing, suggesting that individuals with autism may process faces not as socially relevant stimuli but as objects.

Several subsequent studies have complemented these findings by also reporting a lack of FG activation during face perception (Hubl et al., 2003; Pierce, Muller, Ambrose, Allen, & Courchesne, 2001), explicit processing of facial emotions (Critchley et al., 2000), and affect perception (Hall et al., 2003; Piggot et al., 2004).

Although these results appear convincing, one important confound of these studies deserves note. As mentioned previously, individuals with autism utilize abnormal viewing strategies when processing faces and spend less time viewing the core features of the face (Pelphrey et al., 2002). These findings introduce the possibility that the lack of FG activation seen in these individuals may not be due to a dysfunctional FG per se, but rather a lack of attention to those stimuli that typically elicit FG activation. To address this issue, Hadjikhani and colleagues (2004) controlled for visual focus by adding a fixation point to the center of their stimuli in order to ensure that all participants were attending to the same features. They found that individuals with autism exhibited normal activation of the FG while viewing faces. Despite this rather rudimentary control for visual focus, the results offered compelling evidence for potentially normal activation of the FG in autism. These results were recently expanded upon in a noteworthy study that combined eye tracking and functional magnetic imaging techniques. In this study, Dalton and colleagues (2005) demonstrated that activation in the fusiform gyrus of individuals with autism was positively correlated with the amount of time spent fixating on the eye region of faces, thus suggesting that the lack of activation found in previous studies could be due to abnormal face processing strategies rather than abnormal neural activation. One additional study that warrants mention can be viewed as indirectly supporting the possibility that, under the right conditions, the FG is capable of activation in autism. In this intriguing study, Grelotti et al. (2005) employed faces, objects,

and a visual stimulus in which a participant with autism had a special interest, namely "Digimon" cartoon characters. By visually presenting these stimuli during functional neuroimaging, the authors demonstrated FG activation in response to Digimon stimuli but not to familiar or unfamiliar faces. Here, FG activation required a stimulus in which the participant had a special interest, or expertise, but it is worthwhile to note that FG activation was achieved.

Superior Temporal Sulcus

As with schizophrenia, there is a general lack of information addressing STS volume and functioning in autism, however, the information that is available does suggest both volumetric and functional abnormalities in autism. First, a structural MRI study of children with autism revealed decreased volumes of grey matter in the STS as compared to typically developing children (Boddaert et al., 2004), and second, both functional imaging studies that examined the STS found reduced activation as compared to control participants (Castelli et al., 2002; Pierce et al., 2001). In Castelli and colleagues, reduced activation was found in response to animations of geometrical shapes moving in socially relevant patterns, and Pierce et al. noted reduced activation during face perception.

Amygdala

Reviews examining amygdala volume in autism provide mixed results with some studies showing increased volume as compared to controls whereas others show no differences or reductions in volume (see Brambilla et al., 2003 and Sweeten, Posey, Skekhar, & McDougle, 2002 for reviews). Functional studies, on the other hand, present more consistent results. In 1999, Baron-Cohen, Ring, and colleagues conducted functional brain scans while asking autistic and typically developing participants to complete his Eyes Task.

Analysis of this data revealed no activation of the amygdala in individuals with autism. Similarly, Pierce et al. (2001) failed to find amygdala activation in individuals with autism during a task of face processing, and Critchley, Daly, Phillips et al. (2000) reported a lack of activation of the left amygdala during implicit processing of facial expressions as compared to control participants. Thus far, only one study has failed to find differences in amygdala activation in individuals with autism (Piggot et al., 2004), and although these results are not consistent with previous studies, it is possible that task demands and participant characteristics can account for the null finding. Specifically, this study included only high-functioning individuals with autism and asked them to process only basic emotions. Given that high-functioning individuals often do not show impairments in identifying basic emotions, these results would be consistent with behavioral data. Likewise, these results pose interesting questions about variations in level of amygdala impairment across the autism spectrum and variations in amygdala functioning based on difficulty of social cognitive task.

Integration

It is clear from the literature that there are striking similarities, both behaviorally and neurobiologically, between schizophrenia and autism. Both groups appear to have similar social cognitive profiles with primary deficits in ToM and social perception, and in both groups, these deficits are related to functioning. Most interestingly however, similar neural abnormalities are implicated as the underlying mechanisms of these deficits in both disorders (Figure 1). Specifically, both groups display either reduced or no activation of the FG while viewing faces, and as noted previously, the FG has consistently been cited as integral to face perception and processing. Thus, it is possible that abnormally low levels of FG activation in schizophrenia and autism may be partially responsible for deficits in social perception.

Although, as noted earlier, reduced FG activation in autism may be secondary to inappropriate selective attention.

Likewise, both groups show reduced, or absent, amygdala activation while processing emotion and making social judgments. In schizophrenia, it is unclear whether reductions in activation are unilateral or bilateral, and it is also unclear whether amygdala activation may vary by schizophrenia subtype. For autism, a lack of activation is apparent in both explicit and implicit processing of emotions, and the extent of the deficit remains unclear in that one study found intact activation during the processing of basic emotions (Piggot et al., 2004). Combining these literatures would suggest that individuals with schizophrenia should also show reduced amygdala activation during both explicit and implicit processing of social information and that across both groups, the degree of amygdala activation should negatively correlate with task complexity. Therefore, when processing complex social stimuli, both groups should show reduced amygdala activation. Moreover, this synthesis would also suggest that reduced amygdala activation in schizophrenia and autism should be reflected in abnormal behavioral performances on complex tasks of social perception. If borne out, these speculations would not only clarify similarities between schizophrenia and autism, but could also provide compelling evidence for the hypothesis that neural abnormalities underlie, and are responsible for, deficits in social cognition. Such conclusions would have a considerable impact on intervention techniques for both disorders and could potentially contribute to the development of interventions that target both behavioral and neural functioning.

Unanswered Questions

Despite the numerous parallels between schizophrenia and autism, there is a general dearth of studies directly comparing social cognitive profiles or neural activation across the

two disorders. Thus far, only three studies have directly compared the social cognitive abilities of individuals with schizophrenia to those of autism. Pilowski et al., (2000) found that children with autism performed worse on a deception task than children with schizophrenia but that both clinical groups performed worse than controls on a false belief task. Similarly, Craig et al. (2004) compared ToM abilities in adults with schizophrenia and autism. Using both a hinting task and the Eyes Task, Craig et al. found comparable deficits in each group as compared to healthy controls. Finally, Bolte and Poustka (2003) have been the only investigators to compare these groups on a measure of social perception. In their study, only individuals with autism showed impaired performance on a test of facial affect recognition whereas control participants and individuals with schizophrenia did not differ from each other.

Examined as a whole, these preliminary results suggest an intriguing pattern in which individuals with schizophrenia may outperform individuals with autism on tasks of basic social cognition (i.e. basic emotion perception) but perform similarly to individuals with autism on tasks that require higher levels of social cognitive skill (i.e. the Eyes Task). This raises the interesting question of whether this behavioral pattern remains manifest across a different social perception task that requires complex social judgments (i.e. the Trustworthiness Task) and more importantly, whether these similarities would be reflected in comparable patterns of neural activation. To our knowledge, no studies have used functional imaging to examine neural activation during the Trustworthiness Task in clinical populations, and no study has directly compared the neural profiles of schizophrenia and autism. Additionally, no studies have attempted to directly link activation of the amygdala to social behavior. Therefore, through this dissertation, I hope to elucidate whether a shared neural

profile underlies social cognitive abnormalities in both disorders and to clarify the means by which two disorders with different developmental pathways can have similar social cognitive outcomes. This information may not only shed light on the developmental neural mechanisms of social cognition, but also offers the opportunity to inform our understanding of abnormalities at the level of brain-behavior interactions in schizophrenia and autism.

Thus, the specific hypotheses and goals of this study are as follows. First, based on previous research, it is predicted that individuals with schizophrenia and individuals with autism will show reduced neural activation in key components of the "social brain" during complex social judgments as compared to healthy control participants. Reductions in activation should be apparent for both individuals with autism and individuals with schizophrenia in the amygdala and the fusiform gyrus, and also in the superior temporal sulcus for individuals with autism only. Additionally, the discrepancy between activation levels of the amygdala in the clinical groups and the healthy participants should be most pronounced when stimulus faces are perceived as untrustworthy.

Next, in regard to behavioral performance on the Trustworthiness Task, two competing hypotheses will be tested. First, the work of Adolphs and colleagues (2001) suggests that individuals with autism should rate more faces as trustworthy and that this should occur as a function of hypoactivtion of the amygdala. Work demonstrating hypoactivtion of the amygdala in schizophrenia also suggests that these individuals should rate more faces as trustworthy as compared to controls. Thus, the first hypothesis predicts that both clinical groups will rate more faces than controls as trustworthy. The competing hypothesis, however, considers the clinical characteristic that both disorders tend to show increased rates of paranoid ideation. Paranoid ideation can be defined as "the belief that

someone, some organization, or some force or power is trying to harm oneself in some way" (Wing, Cooper, & Sartorius, 1974, p. 170). Given this definition, it is likely that individuals with paranoia will perceive more stimuli as threatening or untrustworthy. Therefore, the competing hypothesis predicts that both clinical groups should rate fewer faces as trustworthy due to increased paranoia.

Further, in terms of behavior, it is expected that both individuals with autism and individuals with schizophrenia will show impairments in social functioning compared to healthy control participants; however, individuals with autism are expected to show the greatest impairment relative to both other groups. Finally, it is anticipated that more normative activation of the amygdala will be related to better social functioning. Given the lack of research addressing direct brain-behavior relationships with in the domain of social cognition, this last hypothesis should be viewed in an exploratory manner.

CHAPTER II

METHOD

Participants

Participants were individuals recruited from three groups: non-clinical control participants (n=12), individuals with schizophrenia or schizoaffective disorder (SCZ: n=12), and individuals with high-functioning autism or Asperger's disorder (HFA: n=12). To be included in the study, all participants had to be male, between the ages of 18 and 35, be free of neurological impairment, have no metal in his body, be right-handed, have a visual acuity of at least 20/70, and could not meet current criteria for substance abuse or dependence.

Non-clinical control participants were recruited via informational emails soliciting participation in research and from other research studies conducted in our lab. All control participants were screened for personal and family history of psychopathology to ensure that they did not meet past or present criteria for schizophrenia, schizoaffective disorder, or any autism spectrum disorder and that they did not have any first- degree relatives with a psychotic, affective, or developmental disorder.

Individuals in the schizophrenia group were recruited from the Schizophrenia Treatment and Evaluation Program (STEP) at the University of North Carolina Neurosciences Hospital and had a diagnosis of schizophrenia or schizoaffective disorder based on the Structured Clinical Interview for DSM-IV (SCID-P) and chart review. Additionally, given that individuals with HFA often report symptoms of paranoia (Hare

1997; Wing 1996), an attempt was made to recruit individuals who were actively experiencing symptoms of paranoia, so as to match the two clinical groups as closely as possible.

Of the 12 participants in the SCZ group, 8 individuals had a diagnosis of schizophrenia and 4 of schizoaffective disorder. Severity of symptoms was assessed with the Positive and Negative Syndrome Scale (PANSS: Kay, Opler, & Fiszbein, 1992), a semi-structured clinical interview designed to measure the full range of psychotic symptomatology. The PANSS was administered by research assistants who had been trained to adequate reliability (ICC of > .80 with a gold standard rater), and symptom severity was rated on a scale from 1 (absent) to 7 (extremely severe). All participants were experiencing significant symptoms of paranoia at the time of testing, scoring at least a 4 or above on the suspiciousness/persecution item, and overall symptom totals were as follows: positive symptom total: M=18.08 (SD = 4.34); negative symptom total: M= 11.83 (SD = 6.16); and general symptom total: M=31.00 (SD = 6.55). Additionally, at the time of testing, all individuals in this group had been adhering to a stable regimen of atypical antipsychotic medications for at least four weeks, and as based on Woods (2003), the mean Chlorpromazine equivalent dose was 404.86 mg/day (SD=249.2).

Finally, individuals with autism spectrum disorders were recruited through the University of North Carolina STAART (Studies to Advance Autism Research and Treatment) Subject Registry Core and the TEACCH (Treatment and Education of Autistic and Related Communication Handicapped Children) programs in Chapel Hill and Asheville, North Carolina. All diagnoses were confirmed with the Autism Diagnostic Interview-Revised (ADI-R; Lord, Rutter, & LeCouteur, 1994) and/or the Autism Diagnostic

Observation Schedule (ADOS; Lord, Rutter, DiLavore, & Risi, 1999) or chart review.

Chi-square tests and a multivariate analysis of variance (MANOVA) were conducted on the demographic variables (see Table 1 for demographic information). No differences existed between the three groups on ethnicity (χ^2=2.4, p=.663) or marital status (χ^2=.3.6, p=.165); however, the groups did significantly differ on the combined variables of age and years of education (Wilks' λ=.587, F(4, 64)=4.886, p=.002). Univariate analyses revealed that the multivariate effect was driven by a significant difference between the groups in years of education (F(2, 33)=10.118, p<.001) but that the groups did not significantly differ on age (F(2, 33)=1.174, p=.322). Overall, the control group had completed more years of education than both the SCZ and HFA comparison groups (p<.001 and p=.001, respectively) who did not differ from one another (p=.819).

Imaging Stimuli and fMRI Experiment

To examine neural activation, functional magnetic resonance imaging (fMRI) was utilized while individuals completed the abbreviated Trustworthiness/Approachability Task (Adolphs et al., 1998). In this task, individuals were asked to view 42 grayscale frontal images of faces and to make a dichotomous decision regarding the trustworthiness of the individual in each photo. It should be noted that the original version of this task requires participants to rate each face on a Likert scale from -3 (not at all trustworthy) to +3 (very trustworthy); however, in order to integrate this task with an imaging paradigm, the rating scale was replaced with a forced choice of trustworthiness. Thus, participants rated each face as either trustworthy or untrustworthy. This procedure was based on Winston et al. (2000). Participants responded by pushing a button corresponding to their rating, and these determinations, as well as reaction time, were recorded and used as a behavioral index of

performance on this task.

In further adapting this task to an imaging paradigm, it was divided into two functional runs, each containing 21 photographs, in which each photograph was displayed for 2 seconds with 16 seconds between each face presentation. While not viewing a face, participants were instructed to keep their eyes focused on a white fixation cross that was presented in the middle of the viewing area. This was done in order to control for visual fixation during the task.

Following the Trustworthiness/Approachability Task, individuals participated in a localizer session designed to isolate the face responsive region of the fusiform gyrus, or fusiform face area. In this task, individuals passively viewed series of grayscale photos of either faces or tools that were presented in six 30 second blocks with a 20 second interval between blocks. Stimulus epochs alternated between the two different conditions (i.e. faces only vs. tools only) and began with a block of face stimuli. During each stimulus epoch, 45 different photos were presented at the rate of one every 670 msec (with the stimulus on for 500 msec and off for 170 msec). Between stimulus block presentations, participants were asked to focus their gaze on a fixation cross to control for visual fixation, and this task was completed in one functional run. This procedure is based on that of Kanwisher, McDermott, & Chun (1997).

Behavioral Tasks/Measures

As noted above, behavioral data was collected during the imaging session in order to assess group differences in social perception. In addition, following the scanning session, all participants were asked to complete several behavioral measures and tasks designed to assess cognitive abilities, symptomatology, and social functioning. Social functioning measures

were used to explore potential impairments in both clinical groups and to explore relationships between neural activation and functioning. Finally, tasks assessing cognitive abilities and symptomatology were utilized to assess "third variable" factors that may have influence performance and contributed to group differences on the social perception and social functioning measures.

Cognitive Assessments

General cognitive ability was assessed with the Wechsler Abbreviated Scale of Intelligence (WASI). This measure provides an estimate of full-scale IQ as well as estimates of verbal and performance IQs. Additionally, an assessment of reading ability was obtained with the reading scale of the Wide Range Achievement Test-III (WRAT-III; Wilkinson, 1993). Previous research has demonstrated that reading ability can be considered a gross estimate of premorbid IQ (Dalby & Williams, 1986; Griffin, Rivera-Mindt, Rankin, Ritchie, & Scott, 2002; Johnstone & Wilhelm, 1996), and thus, the use of this measure allows a comparison of intellectual functioning between groups somewhat independently of clinical status.

Symptomatology

Individuals in all groups were asked to complete the Paranoia Scale (PS; Fenigstein & Vanable, 1992). The PS is comprised of 20 self-report items designed to assess subclinical paranoid thought and that specifically measures self-consciousness and self-attention. Each item is rated on a Likert scale from 1-5, (1 = Not at all applicable; 5 = extremely applicable), and performance is indexed as the total score, with higher scores indicating higher levels of paranoia. The PS has good internal consistency and reliability, α=.84 and .70 respectively, and has been shown to be sensitive to subclinical levels of paranoia in normal populations

(Combs & Penn, 2004) and to correlate well with clinical ratings of paranoia in psychotic populations (Smari, Stefansson, & Thorgilsson, 1994).

Social Functioning

Social functioning was assessed with the Social Functioning Scale (SFS; Birchwood, Smith, Cochrane, Wetton, & Copestake, 1990). The SFS assesses strengths and weaknesses in seven areas of functioning: social engagement, interpersonal communication, pro-social activities, recreation, independence-competence, independence-performance, and employment/occupation. Responses in each section are scored from 3-0, 3 being the highest social functioning rating and 0 being the lowest. Performance is indexed as the percentage achieved of the maximum possible score on each subscale such that higher percentages indicate better social functioning.

Image Acquisition

For the Trustworthiness/Approachability Task, a slow event-related design with a 16 second inter-stimulus interval was utilized. This design allowed the hemodynamic response to return to baseline following each stimulus presentation and allowed the response to each stimulus to be examined as an individual event. Additionally, as mentioned above, a block design incorporating 30 second stimulus epochs interleaved with seven 20 second epochs of fixation was utilized for the localizer task. All functional data was collected using a Siemens Allegra 3T MRI scanner to acquire echo planar T2* weighted images with BOLD (blood oxygenation level dependent) contrast (EPI free induction decay, 2D; 32 slices, voxel size 3.8x3.8x3.8 mm, matrix=64x64; FOV=243x243, TR=2 sec, TE=30ms, Flip angle = 80). In each of the first two functional runs comprising the Trustworthiness Task, 194 images were collected using an interleaved acquisition sequence resulting in a total acquisition time of 398

seconds per run. During the localizer task, 165 images were collected with an interleaved sequence resulting in a total acquisition time of 324 seconds. Each functional run was preceded by two volumes that were discarded to allow for equilibration effects. Following the three functional runs, a structural scan sequence (MPRAGE) was also conducted to obtain a T1 weighted anatomical image (128 slices, voxel size 1x1x1 mm, matrix=256x256, FOV=208x256, TR=1520 ms, TE=4.38 ms) for co-registration and display of functional data. The acquisition time for this scan was 318 seconds. Throughout all MRI data collection, cushioned head restraints were used to control for movement.

Spatial Preprocessing

All images were spatially preprocessed using SPM2 (Wellcome Department of Cognitive Neurology, Queen Square, London, United Kingdom). Data was first corrected for slice-acquisition time and motion. Images were then normalized to an EPI template corresponding to standard MNI (Montreal Neurological Institute) space and smoothed using an 8-mm FWHM (full width at half maximum) Gaussian kernel. In-plane anatomical images were then co-registered to the functional images.

Data Analysis

As the hypotheses of this study included both neural and behavioral outcomes, it should be clarified that imaging data were utilized to test the first hypothesis which stated that HFA individuals would show reduced neural activation in the amygdala, FFA, and STS compared to controls, and that SCZ individuals would show reduced activation in the amygdala and FFA compared to controls. Behavioral data were used for the second hypothesis predicting that both clinical groups would differ from controls on the Trustworthiness task and show significant impairments in social functioning as compared to

controls. And finally, a combination of behavioral and imaging data was used to test the last, and exploratory, area of interest concerning the relationship between amygdala activation and social functioning.

Imaging Data

In testing the hypothesis that both individuals with schizophrenia and individuals with autism would show reduced neural activation during the Trustworthiness Task, region of interest analyses were conducted using a combination of SPM2 and the WFU Pick Atlas (Maldjian, Laurienti, Burdette, & Kraft, 2003). First, for each subject, statistical contrast maps using a hemodynamic response function with the temporal derivative were generated for each within-subject comparison of interest. Contrasts were designed specifically to examine differences in neural activation in response to faces rated as trustworthy and those rated as untrustworthy as well as to examine overall activation during the process of making a complex social judgment regardless of outcome. Consistent effects in regions of interest across subjects within each group were then tested by including these contrast images in a one-sample t-test. Statistical threshold was set at $p<.05$, corrected for multiple comparisons across a small volume of interest (FWE), using ROIs derived as detailed below.

To examine between-group differences, two sample t-tests (conforming to random effects analyses) were then conducted for each combination of group comparison. These tests were performed by using the contrast images of individual subjects as input. Regions of interest (ROI) for the amygdala, STS, and FG, were then defined as detailed below, and ROI analyses were conducted using the WFU Pick Atlas. Significant clusters of activation within each ROI were identified based on a statistical threshold of $p<.01$ (uncorrected) and an extent threshold of 5 contiguous voxels.

Masks Defining Regions of Interest

Regions of interest for the right and left amygdala were defined by drawing a mask around the regions bilaterally using the software package MRIcro (Rorden & Brett, 2000) on a mean anatomical image created by averaging the T1 anatomical images of all participants in the study. Total volume of the amygdala ROI was approximately 12 cm^3. A region of interest for the STS was defined using statistical results from a one sample t-test of activation during trust judgments using all 36 participants ($p<.05$ FWE corrected). These results yielded a significant cluster of 28 voxels (local maxima: $x,y,z = 45, -33,-12$) that corresponded with the right posterior STS and that was subsequently used as the mask for this ROI. Finally, a region of interest for the FFA was defined by use of the localizer task detailed previously. Here again, data were combined across all subjects, and significant activations from a faces > tools contrast ($p<.001$ uncorrected) were examined. Results produced a significant cluster of 10 voxels (local maxima: $x,y,z=45, -51, -27$) within the right fusiform gyrus that is consistent with other reported locations of the FFA (Kanwisher et al., 1997; Winston et al., 2002). As in Winston et al. (2002), this cluster was combined with a sphere of 10 mm radius centered on the local maxima to create a complete ROI for the FFA.

It should also be noted that an ROI corresponding to bilateral ventrolateral prefrontal cortex (VLPFC) was added as a post hoc area of interest. This region has not traditionally been considered part of the social cognitive network; however, recent work has demonstrated that the VLPFC modulates activation of the amygdala such that activity in this region tends to correlate negatively with amygdala activation (Cunningham et al., 2004; Hariri et al., 2000; Hariri, Mattay, Tessitore, Fera, & Weinberger, 2003), and this is particularly true during the process of making evaluative judgments (Cunningham, Johnson, Gatenby, Gore &

Banaji, 2003). Thus, examination of this area may help clarify findings regarding differences in amygdala activation. The ROI for this region was defined via the statistical results for the one sample t-test across all 36 participants. These results yielded two local maxima (right *x,y,z*= 45, 15, -12 and left *x,y,z*= -39, 21, -9) corresponding to right and left VLPFC that were combined with spheres of 15 mm radius centered at each local maxima.

Supplemental Analysis of ROI Time Courses

To augment the analyses described above, the mean response over time of each group within each ROI was extracted using the software package MarsBaR (Brett, Anton, Valabregue, & Poline, 2002). Here, the response for each type of event (i.e. trustworthy faces and untrustworthy faces) was derived via a finite impulse response (FIR) model with 2 second time bins. Where appropriate, time points at the peak of each time course were then statistically tested using paired-sample t-tests and repeated measures ANOVAs with event type as the repeated measure and group membership as the between subjects factor.

Behavioral Data

To test the hypothesis that individuals in both clinical groups would rate faces differently from controls and show lower levels of social functioning, group differences on the number of faces rated as trustworthy during the imaging session were examined with a one-way (Group: control vs. HFA vs. SCZ) ANOVA with Tukey's LSD post hoc tests, and differences in performance on the combined SFS subscales were assessed with a one-way (Group: control vs. HFA vs. SCZ) Multivariate Analysis of Variance (MANOVA) with post hoc tests. Group differences in cognitive abilities and paranoia were also assessed, and the primary analyses were repeated while covarying for significant group differences on these and demographic factors.

Finally, to address the exploratory goal of examining the relationship between neural activation and social functioning, bivariate correlations were conducted between the overall degree of amygdala activation and scores on the SFS subscales for each participant. To do so, degree of amygdala activation was established in two primary ways. One, the spatial extent of activation (i.e. the number of active voxels) within the amygdala ROI for each participant was recorded and used as the first index of amygdala activation. Two, the peak response of the amygdala time course, which represents the greatest amount of percent signal change within the ROI, was selected and recorded as the second index of amygdala activation. These indices were then correlated with performance on the SFS. One tailed tests were utilized given the expectation of a positive association between amygdala activation and social functioning.

CHAPTER III

RESULTS

Imaging Data

To evaluate the first hypothesis that individuals in both clinical groups would show reduced neural activation compared to controls, both within- and between-group comparisons were conducted using the imaging data. Within-group comparisons were used to verify that the Trustworthiness task resulted in activation of the targeted ROIs and to examine differences in neural responses to faces that were rated as untrustworthy compared to faces rated as trustworthy. Between-group comparisons were used to directly test differences in neural activation between the control and clinical groups.

Within-group Comparisons

As expected, completion of the Trustworthiness Task resulted in significant activation in each of the key structures implicated in social perception. Averaged contrasts for the overall effect of completing the Trustworthiness Task, regardless of how a face was rated, revealed that each group showed significant activation within each ROI. That is, all three groups showed significant activation of bilateral amygdala, bilateral VLPFC, right STS, and right FFA ($p<.05$, FWE corrected for comparisons across a small volume of interest; Table 2).

To explore the main effect of trustworthiness rating, averaged contrasts were created for each group for faces that were judged to be untrustworthy relative to those rated as

trustworthy. In this contrast, control participants showed significantly increased BOLD responses in bilateral VLPFC (right, 51, 27, -9; Z=3.77; left, -45, 21, -6; Z=5.39; both $p<.05$ FWE small volume corrected) and right STS (51, -33, -9; Z=3.59; $p<.05$ FWE small volume corrected) indicating that greater responses in these areas were associated with faces judged as untrustworthy. These findings were confirmed via statistical examination of the time courses extracted from each ROI (Figure 2). Activation in the right amygdala and right FFA was also evident in the contrast of untrustworthy to trustworthy faces (AMY, 18, -6, -27; $Z=2.69$; FFA, 51, -48, -24; $Z=2.65$); however, these clusters did not survive correction for multiple comparisons.

A different pattern emerged for the two clinical groups on this contrast. For both the HFA and SCZ groups, significant levels of activation were not evident in any regions of interest indicating a lack of greater activation in these areas for untrustworthy faces. To rule out the possibility that these regions showed greater activation when a face was rated to be trustworthy as compared to untrustworthy, a trustworthy > untrustworthy contrast was also examined. Again, no significant activations were evident in any region of interest for either the HFA or SCZ group.

Between-group Comparisons

To explore the main effect of group and test the hypothesis that the clinical groups would show reduced neural activation as compared to controls, two-sample t-tests were conducted for each combination of group comparisons across overall activation in response to the Trustworthiness Task. Examination of the control group relative to the HFA group revealed significantly greater activation for controls in right amygdala, left VLPFC, and FFA (Figure 3). No group differences in STS activation were apparent, and no significantly

greater activation was identified for the HFA group as compared to controls. For the comparison between the control group and this SCZ group, a similar pattern emerged. Control participants showed significantly greater activation than individuals with schizophrenia in right amygdala, left VLPFC, and FFA, and again no differences were apparent in the STS (Figure 3). Likewise, the SCZ group failed to show greater activation than controls in any regions of interest. Finally, the direct comparison of the HFA and SCZ participants across the defined ROIs yielded no significant differences in activation between these two groups.

The interaction between group and trustworthiness rating was tested by comparing groups on the untrustworthy faces > trustworthy faces contrast. These comparisons revealed that when a face was rated as untrustworthy, controls showed significantly greater activation than both clinical groups in bilateral VLPFC (Figure 4). This discrepancy was most pronounced in the comparison between the control group and the SCZ group. No other areas of interest were differentially active in these comparisons.

All imaging results were confirmed via repeated measures ANOVAs on peak time course data extracted from each ROI with trust rating (untrustworthy vs. trustworthy) as the within-subjects factor and group (control vs. HFA vs. SCZ) as the between-subjects factor (Figure 5). Main effects for group were probed with Tukey's LSD post hoc tests. Examination of the time course data from the amygdala revealed a significant main effect for group ($F(2, 33)=4.420$, $p=.02$) such that the control group showed a greater response across all faces as compared to both the HFA group and the SCZ group ($p=.011$ and $p=.02$, respectively) and that the HFA and SCZ group did not differ from one another ($p=.810$). Further, within the amygdala, there was no main effect for trustworthiness ratings ($F(2,$

33)=.235, p=.631), nor was there a significant interaction between trust rating and group (F(2, 33)=.836, p=.442). Similarly, time course data extracted from the FFA demonstrated a significant main effect for group (F(2, 33)=3.906, p=.03). Post hoc tests clarified that the control group showed significantly more activation in this region than either of the clinical groups (HFA: p=.018 and SCZ:p =.026) and that the clinical groups did not differ from each other (p=.877). Both the main effect for trustworthiness ratings (F(2, 33)=3.590, p=.067) and the interaction (F(2, 33)=3.105, p=.058) approached significance. Examination of the interaction revealed that only the control group showed greater activation within the FFA when a face was judged to be untrustworthy. It is important to note, however, that these results were not echoed in the SPM analyses and should therefore be interpreted cautiously. Finally, within the VLPFC, a significant group by trustworthiness rating interaction indicated that the control group showed greater activation of this region than the clinical groups when a face was rated as untrustworthy (F(2, 33)=7.159, p=.003).

Behavioral Data

Behavioral Data during Scanning: Trustworthiness Task

Next, to examine the hypothesis that the control and clinical groups would differ in trustworthiness ratings, a one-way (group: control vs. HFA vs. SCZ) ANOVA conducted on the total number of faces judged as trustworthy on the Trustworthiness Task approached statistical significance (F(2, 33)=3.116, p=.058). Exploratory post hoc tests revealed a significant difference between the control group and the SCZ group (p=.018) indicating that the SCZ group rated significantly fewer faces as trustworthy. No other post hoc tests were statistically significant. Additionally, a one-way (group: control vs. HFA vs. SCZ) ANOVA conducted on reaction time was not significant (F(2, 33)=1.846, p=.174) revealing that the

groups did not differ in the length of time taken to judge each photo as trustworthy or untrustworthy (Table 3).

Social Functioning

For social functioning, a one-way (group: control vs. HFA vs. SCZ) MANOVA on the SFS subscales was significant (Wilk's λ=.309, $F(14,54)$=4.475, p=.001) indicating that the groups differed significantly on overall social functioning (Table 3). Further, significant univariate group differences were observed on all subscales except for Recreation ($F(2,33)$=3.243, p=.052). Non-clinical control participants performed better than both individuals with HFA and individuals with SCZ on the Social Engagement ($F(2,33)$=9.136, p=.001), Interpersonal Communication ($F(2,33)$=7.238, p=.002), and Pro-social Activities scales ($F(2,33)$=6.425, p=.004). Additionally, on both Independence Performance ($F(2,33)$=4.450, p=.019) and Independence Competence ($F(2,33)$=4.354, p=.021), control participants scored higher than HFA individuals and comparably to SCZ individuals. On these subscales, the HFA and SCZ groups did not differ. Finally, on the Employment subscale, the control and HFA groups scored similarly, and both groups scored significantly higher than the SCZ group ($F(2,33)$=8.299, p=.001).

Cognitive Functioning and Symptomatology

Finally, to rule out the potential effects of "third variables," group differences in cognitive ability and paranoia were assessed, and the analyses for the SFS were repeated while controlling for demographic, symptom, and cognitive factors that significantly differed between groups. A one-way (group: control vs. HFA vs. SCZ) MANOVA conducted on the combined cognitive variables of full scale IQ from the WASI and reading ability from the WRAT-III was significant (Wilk's λ=.597, $F(4, 64)$=4.712, p=.002). Univariate and post

hoc analyses revealed that the multivariate effect was driven by significant differences between all groups on full scale IQ ($F(2, 33)=10.81$, $p<.001$) such that non-clinical control participants had the highest score followed by HFA participants and then SCZ participants. The univariate effect for the WRAT-III was not significant ($F(2,33)=1.785$, $p=.184$) indicating that the three groups did not significantly differ in reading ability.

In regard to degree of paranoid ideation, a one-way (group: control vs. HFA vs. SCZ) ANOVA was also significant ($F(2, 31)=4.725$, $p=.016$). Post hoc tests indicated that the control group endorsed significantly fewer paranoid statements than both the HFA and SCZ groups ($p=.011$ for both comparisons) who did not significantly differ from one another ($p=.982$). Means for these comparisons are provided in Table 3.

The MANOVA on the SFS was repeated while covarying for the effects of education, WASI full scale IQ, and degree of paranoia. The resulting multivariate effect remained statistically significant (Wilk's $\lambda=.343$, $F(14,44)=2.224$, $p=.022$). Given the absence of group differences on the Trustworthiness Task, these analyses were not repeated.

Correlational Analyses: BOLD Signal Change and Social Functioning

To examine the exploratory hypothesis that level of amygdala activation would be positively related to social functioning, one-tailed bivariate correlations across all subjects were conducted between the subscales of the SFS and the number of active voxels in the amygdala ROI and the peak response of the amygdala time course (Table 4). All correlations were in the positive direction; however none reached significance at the Bonferroni corrected level of $p\leq.0035$. For descriptive purposes, correlations that were significant at the uncorrected level of $p\leq.05$ (one-tailed) are detailed below.

Activation of a greater number of voxels within the amygdala was significantly

associated with increased ability to live independently. Additionally, performance on the Independence Competence subscale was also significantly correlated with the degree of amygdala activation as measured by height of the time course peak. Finally, higher scores on the social engagement subscale were also related to a higher peak of activation within the amygdala, as were better performances on the Independence Performance and Employment subscales.

CHAPTER IV

DISCUSSION

The primary goal of this study was to compare individuals with high-functioning autism to individuals with schizophrenia at both neural and behavioral levels as they completed a social cognitive task requiring complex social judgments. It was hypothesized that both clinical groups would show reduced activation of the amygdala and fusiform face area, that only the HFA group would show reduced activation of the STS, and that both clinical groups would show abnormal performance on the social cognitive task. To test these predictions, fMRI was utilized to assess neural activation as individuals completed the Trustworthiness Task. Results largely confirmed the main study hypothesis: Individuals in both clinical groups showed significant reductions in activation of the amygdala, fusiform face area, and ventrolateral prefrontal cortex compared to control participants. Contrary to prediction, behavioral performance on the Trustworthiness task significantly differed only between control individuals and individuals with schizophrenia. I also explored the link between amygdala functioning to social behavior. Positive relationships were found between increased amygdala functioning and the ability to live independently, maintain employment, and interact with others. These findings are discussed in detail below.

To begin, a generalized inspection of the (within subject) imaging data revealed that all groups showed significant activation of the amygdala, STS, FFA, and VLPFC while completing the Trustworthiness task. These findings are consistent with the neurobiological

model put forth by Brothers (1990) and lend support to models proposing well-defined neural substrates of social cognition. The idea of a specified neural system that is devoted to the processing of social stimuli is further bolstered by the fact that the same structures were implicated in both non-clinical and clinical groups. In addition, contrary to reports demonstrating a lack of neural activation in the amygdala and FFA in schizophrenia and autism (i.e. Phillips et al., 1999 for schizophrenia and Baron-Cohen, Ring et al., 1999; Pierce et al., 2001; Schultz et al., 2000 for autism), these findings indicate that clinical groups do show activation of these areas and that group differences are a matter of degree rather than a strict absence of activation.

Within-subject comparisons of the imaging data also partially replicate the work of Winston and colleagues (2002) by elucidating differences in neural response associated with perceptions of trustworthiness from faces. Specifically, Winston et al. found that when healthy individuals rated a face as untrustworthy, both the amygdala and STS showed significantly more activation than when a face was rated as trustworthy. As in Winston et al., this study also found increased activation of the STS in non-clinical controls for faces that were rated as untrustworthy; however in contrast, only trend levels of greater amygdala activation for untrustworthy faces were evident. Differential activation of the STS, an area typically implicated in the perception of biological motion, may be somewhat surprising, although, as Winston and colleagues point out, the STS has also been linked to theory of mind inferences. Given that one may attempt to infer the intentions of another as a means of evaluating whether they can be trusted, and that uncertainty about these intentions may lead to a judgment of untrustworthiness, such a process may explain the differential activation seen here.

Methodological differences between this study and Winston et al. may help explain the slight discrepancy between findings regarding amygdala activation. First, this study utilized a longer stimulus presentation and inter-stimulus interval than Winston and colleagues. Recall that the amygdala appears to be maximally engaged in automatic and rapid processing. Therefore, the greater processing time in the present study may not have optimally engaged the amygdala. And second, this study utilized fewer events than Winston et al. and therefore may have had less power to detect differential activation within the amygdala (although the findings were in the expected direction and the results approached statistical significance).

Findings from this study also extend those of Winston et al. (2002) by demonstrating increased activation of the VLPFC in non-clinical controls for untrustworthy faces. This finding suggests that this region is sensitive to differing levels of perceived threat. In addition, greater activation of the VLPFC during untrustworthiness judgments is consistent with work demonstrating that this area modulates and regulates emotional responses (Cunningham et al., 2004; Hariri et al., 2000). Differential activation of the VLPFC is also particularly interesting in light of the trend levels of significantly greater activation of the amygdala in response to untrustworthy faces. Overall, these findings suggest that in controls, untrustworthy faces may initially evoke a relatively more intense emotional response, but that this response is later attenuated by activation in the VLPFC. Such an interpretation is also consistent with work showing that extended cognitive evaluation of emotional stimuli is associated with relative decreases in amygdala response and correlated increases in VLPFC activation, as compared to brief stimulus presentations (Cunningham et al., 2004; Hariri et al., 2003).

In contrast to the pattern of differential activation that was seen in non-clinical controls, there were no differences in neural activation within the examined ROIs for untrustworthy vs. trustworthy faces in either individuals with HFA or individuals with schizophrenia. This lack of differentiation at the neural level suggests that the clinical groups were treating faces the same, irrespective of whether trustworthy or untrustworthy judgments are made. This may be explained by the fact that the amygdala, in addition to its role in social cognition, has also been linked to associating stimuli with social and emotional value (reviewed in Adolphs, 1999b; Adolphs, 2001). It is therefore possible that individuals with HFA and those with schizophrenia failed to assign emotional significance to these stimuli, resulting in a failure to show an accompanying affective response associated with greater neural, and in particular amygdala, activation for untrustworthy faces. This interpretation suggests that individuals with schizophrenia and autism do not process social stimuli in the same manner as controls.

The foregoing within-group analyses were followed by examination of the primary hypothesis, which was confirmed: Both clinical groups showed significant reductions in neural activation while making complex social judgments compared to non-clinical controls. Significant reductions for both clinical groups were evident in the right amygdala and FFA and left VLPFC. Reduced activation in the amygdala and FFA is consistent with several reported studies that investigated these disorders independently. For instance, within schizophrenia research, numerous studies have demonstrated reductions in amygdala activation while processing emotional stimuli (i.e. Gur et al., 2002; Hempel et al., 2003; Taylor et al., 2002), and both Streit et al (2001) and Quintana et al. (2003) found reduced activation of the FFA in schizophrenia during emotion perception. Similarly, the HFA

results are consistent with several studies that suggest dysfunction of the amygdala (Critchley et al., 2000; Pierce et al., 2001) and the FFA (Hall et al., 2003; Piggot et al., 2004) in this population. Moreover, to date, this is the first study that has specifically examined the VLPFC in schizophrenia and autism. Thus, the findings regarding the VLPFC expand upon the current body of research by demonstrating abnormal functioning of a neural region that has been linked to evaluative judgments of social stimuli. These results also extend the current literature by demonstrating reduced activation of the amygdala and FFA in autism and schizophrenia during a task of complex social perception, and by the finding that this neural pattern does not differ between the two clinical groups.

Contrary to the prediction that only individuals with HFA would show reduced activation in the STS, all groups showed comparable levels of neural activation in this region. This finding is consistent with previous research showing intact functioning of the STS in schizophrenia during a ToM task (Brunet et al., 2003) but contradicts the work of Pierce and colleagues (2001) who found reduced STS activation in autism while viewing faces. The discrepancy between the results of this study and Pierce et al. may be explained by considering that only high-functioning individuals with autism were included in this study whereas Pierce et al. (2001) included only lower functioning individuals with autism and that Pierce et al. failed to control for visual fixation. Such an explanation is consistent with work showing that individuals with HFA may achieve normative neural activation under certain experimental circumstances such as performing a basic social cognitive task (Piggot et al., 2004) or manipulating visual focus (Hadjikhani et al., 2004). It should also be noted that only very limited research has been dedicated to understanding STS functioning in autism and schizophrenia and that there is a lack of general knowledge concerning how this region

functions in clinical samples. The results reported here, therefore, are in need of replication.

Group comparisons also showed that the VLPFC had an increased response to untrustworthy faces for controls only. Whereas the group differences detailed above are quantitative, that is, a matter of degree of activation, this finding highlights a qualitative difference in neural response between control and clinical groups. Specifically, controls showed a pattern of responding that was consistent with a heightened perception of threat that was then modulated by prefrontal regions, a pattern not demonstrated by the two clinical groups. Such a finding demonstrates that abnormalities in neural functioning go beyond simple comparisons of amount of activation and that future studies should also aim to examine more subtle and complex differences in patterns of neural functioning.

The behavioral results of this study also offer interesting insights into the comparison of schizophrenia and autism. First, it is interesting to note that both clinical groups showed significantly greater levels of paranoia than controls, and in fact, each scored almost identically on the paranoia scale. This finding is consistent with clinical reports of paranoid ideation in HFA and supports empirical studies showing heightened paranoia in individuals with Asperger's syndrome (Blackshaw et al., 2001; Craig et al., 2004). Furthermore, these results extend previous work by calling attention to an understudied similarity between the disorders.

Second, the hypothesis that both clinical groups would perform differently from controls on the Trustworthiness Task was only partially supported. While both clinical groups rated more faces than controls as untrustworthy, only the difference between the SCZ group and control group was statistically significant. The finding that both clinical groups rated faces more negatively than controls is consistent with the hypothesis that increased

paranoia is related to an increased tendency to rate more faces as untrustworthy. This finding, however, is in direct contrast to both previous work using the Trustworthiness task with autism (Adolphs, Sears, et al., 2001) and the expected behavioral pattern associated with reduced amygdala activation. Previous lesion and imaging studies suggest that a reduction in amygdala functioning is associated with increased ratings of trustworthiness; but here, the pattern of findings is reversed. Thus, the counterintuitive finding of reduced amygdala activation with increased ratings of untrustworthiness suggests that in order to complete the Trustworthiness task, the clinical groups may have employed some compensatory mechanism(s) that were not assessed in this study.

Third, as hypothesized, individuals with autism and individuals with schizophrenia demonstrated impairments in social functioning as compared to healthy controls. Of particular interest is that individuals with HFA and individuals with schizophrenia were comparably impaired on subscales of the SFS directly assessing social skill and social involvement (i.e. social engagement, interpersonal communication, and pro-social activities). This finding underscores a key similarity between these disorders and emphasizes the centrality of social interaction impairments in both disorders. In contrast, more variability was evident on subscales that addressed independent living and employment. On scales assessing independent living, individuals with HFA showed the greatest degree of impairment among the groups, a finding that is consistent with the protracted developmental course of autism that can delay learning and attainment of functional living skills. Interestingly however, both controls and individuals with HFA scored significantly higher on the employment subscale than individuals with schizophrenia. This finding may be explained by several factors including the recurrent and persistent nature of schizophrenia

symptoms that often render individuals unable to maintain steady employment, the fact that several individuals with schizophrenia receive disability benefits and therefore do not work, or that this study utilized a sample of high-functioning individuals with autism, many of whom were in school or received supportive employment services through TEACCH. Taken together, these findings are in accord with conceptualizations that social dysfunction is core feature of both disorders and again highlights comparable levels of impairment between schizophrenia and autism.

Finally, this study attempted to elucidate brain-behavior relationships by directly linking neural activation of the amygdala to social functioning. Although no correlations remained statistically significant after applying Bonferroni correction, uncorrected results do provide tentative support for a relationship between increased amygdala functioning and independent living abilities; however, any direct link to behavior should be interpreted cautiously. It is possible that the lack of a strong relationship between the amygdala and behavior could be due to the amygdala's primary role as a perceptual brain structure. That is, the amygdala is most often implicated in social perception which suggests that this area is utilized early in the process of perceiving and reacting to social stimuli. This suggests that association areas that interpret perceptual information (e.g., orbitofrontal cortex) may provide a better basis for assessing brain-behavior relationships. Thus, additional brain regions both within the social cognitive network (i.e. the medial prefrontal cortex) and beyond the social cognitive network (i.e. the frontal cortices) that integrate social information might show more consistent relationships with social functioning. Future work should develop methodologies that can better assess the complex relationships between neural and behavioral functioning and should continue to explore these relationships in both clinical and non-clinical samples.

Overall, the results provide evidence for considerable overlap between schizophrenia and autism that spans the domains of neural functioning, social cognition, social functioning, and symptoms. As mentioned previously, this study is the first to directly compare these two disorders on neural activation, and results suggest that similar neural abnormalities may underlie complex social judgments in both disorders. This study also contributes to a more general body of work showing similar behavioral patterns of social cognitive deficits in schizophrenia and autism (Craig et al., 2004; Pilowski et al., 2000). In regard to social functioning, here again striking similarities were seen between the two disorders with the exception that individuals with schizophrenia may be more able to live independently. Finally, both individuals with autism and individuals with schizophrenia showed increased levels of paranoid ideation as compared to controls.

The comparable levels of paranoia in both clinical groups may explain the observed neural and behavioral similarities in current study. In fact, only minimal differences in social cognition have been observed between individuals with autism and those with schizophrenia when the latter group was higher in paranoid symptoms. Specifically, Craig et al. (2004) recruited only individuals who were experiencing paranoid delusions and found comparable deficits across both schizophrenia and HFA on two different ToM tasks. Similarly, the schizophrenia sample in Pilowsky et al. (2000) was comprised of predominately children with a diagnosis of paranoid schizophrenia, and this study found comparable deficits in both clinical disorders across a simple task of ToM. In contrast, Bolte and Poustka (2003) failed to find similar degrees of impairment on an emotion perception task; however, the symptom presentation of the schizophrenia sample was not detailed, and an effort to recruit only individuals with paranoid symptoms was not reported.

Heightened paranoia may also help explain the similar reductions in neural activation seen in both disorders and the apparent disconnect between reduced amygdala activation despite more negative ratings of trustworthiness. It may be the case that individuals with paranoia have a higher threshold of threat for amygdala activation and may require extremely threatening stimuli in order to evoke a response from this brain region. Given that paranoid individuals are perceiving threat frequently and regularly in their daily lives, it is possible that their amygdalae may have habituated to these high levels of threat and are therefore not showing sensitivity to lesser threats such as judging trustworthiness from a face. Thus, it is also possible that if given a threatening enough stimulus, paranoid individuals may show normative amygdala activation; however, this hypothesis is merely speculative and requires further investigation.

These results also potentially underscore the need for a symptom based approach in the study of clinical disorders. As Bentall et al. (1988, 2001) point out, studies characterizing samples based on a simple diagnosis of schizophrenia have done little to inform the etiology of the disease process. Additionally, the absence of a unique biochemical or structural marker that is specific to schizophrenia (Brune, 2004), and the considerable symptomatic heterogeneity present in schizophrenia, suggest that a diagnostic approach may not be optimal for exploring developmental pathways. As applied here, a symptom based approach may propose that paranoid ideation and a long standing paranoid perceptual process may serve as the mechanism for the equifinality found between the two disorders in neural activation and social cognitive outcome.

The present study has several limitations. First, all individuals in the schizophrenia group were taking neuroleptic medication which may have affected neural activation. Future

work should seek to explore the overall effects of atypical antipsychotic medication on the BOLD response and should specifically seek to understand how these medications may influence functioning of the social cognitive circuit. Additionally, this study examined only specified regions of interest that have previously been implicated in social cognition. It is possible that whole brain analyses may have gleaned more information regarding similarities and differences between schizophrenia and autism; however, the lack of differences found here would suggest that larger sample sizes would be needed to adequately test all neural regions. Finally, perhaps the main limitation of this study is that the reductions in neural activation seen in the clinical groups cannot be specified as being solely due to problems in social information processing. One could argue that individuals with schizophrenia and HFA would show reduced neural activation during any task and that these reductions could be evident across all neural regions. Future studies would benefit from the inclusion of a non-social control task that could be used to establish normative levels of activation in clinical groups that could then clarify differential deficits when processing social stimuli.

In conclusion, this study investigated both neural activation and behavioral performance during a task of complex social cognition in healthy controls, individuals with high-functioning autism, and individuals with schizophrenia. The two clinical groups showed reduced neural activation in the amygdala, fusiform face area, and the ventrolateral prefrontal cortex. No differences in neural activation or behavioral performance were noted between the clinical groups. These findings suggest that individuals with schizophrenia and individuals with autism share similar neural profiles that may underlie social cognitive deficits. Future work should continue to explore similarities and differences between schizophrenia and autism, and may particularly benefit from a symptom based approach that

might offer the best means of exploring etiology and developmental pathways.

Table 1

Descriptive Statistics for Sample Characteristics

	Controls (*n*=12) Mean (SD)	SCZ (*n*=12) Mean (SD)	HFA (*n*=12) Mean (SD)
Ethnicity			
Caucasian	10	10	10
African American	2	2	1
Other	0	0	1
Marital Status			
Single	8	11	11
Married	4	1	1
Age	27.08 (3.98)	26.42 (5.25)	24.08 (5.71)
Education	16.92 (1.98)	13.29 (2.73)	13.5 (1.83)

Table 2

Cerebral foci of activation within each ROI in response to the Trustworthiness Task

	Side	Coordinates (mm)* x	y	z	Cluster Size	Z Score
Control Group						
AMY	right	15	-6	-21	72	4.89
	left	-21	-3	-21	58	4.68
STS	right	51	-39	-9	28	3.91
FFA	right	45	-54	-36	120	5.05
VLPFC	right	42	21	-18	26	4.23
	left	-42	21	-9	144	4.53
HFA Group						
AMY	right	24	0	-30	22	4.00
	left	-27	-3	-21	6	3.69
STS	right	45	-30	-12	4	3.03
FFA	right	42	-51	-36	54	4.01
VLPFC	right	39	18	0	91	4.45
	left	-48	15	-12	88	4.48
SCZ Group						
AMY	right	21	-3	-24	46	4.02
	left	-18	-6	-21	38	4.14
STS	right	54	-36	-15	24	3.55
FFA	right	39	-51	-33	104	4.38
VLPFC	right	39	24	-9	112	4.79
	left	-42	18	-9	34	4.17

All values, $p<.05$, FWE corrected for multiple comparisons across a small volume of interest.
* The cluster with the largest number of voxels with each ROI is reported. Talairach coordinates refer to the voxel with the maximum signal change in each cluster.

Table 3

Descriptive Statistics for Behavioral Measures

	Controls (*n*=12) Mean (SD)	SCZ (*n*=12) Mean (SD)	HFA (*n*=12) Mean (SD)
Trustworthiness Task			
Number rated as trustworthy	25.33 (4.98)	19.41 (6.01)	22.83 (6.41)
Reaction Time (sec)	1.669 (.655)	2.135 (.902)	2.335 (1.10)
Social Functioning Scale			
Social Engagement	.867 (.065)	.656 (.117)	.667 (.195)
Interpersonal Communication	.991 (.032)	.694 (.242)	.713 (.278)
Pro-social Activities	.535 (.169)	.328 (.159)	.319 (173)
Recreation	.572 (.127)	.433 (.119)	.493 (.153)
Independence – Competence	.981 (.031)	.906 (.113)	.859 (.132)
Independence – Performance	.823 (.108)	.716 (.152)	.654 (.155)
Employment/Occupation	.992 (.029)	.617 (.411)	.950 (.117)
Cognitive Abilities			
WASI Full Scale IQ	122.75 (9.57)	100.00 (14.6)	112.42 (11.28)
Reading Ability	112.58 (9.27)	103.83 (14.24)	110.00 (10.91)
Paranoia Scale	27.6 (5.27)	48.08 (20.48)	48.25 (21.18)

Table 4

Correlations between Amygdala Activation and Social Functioning Across All Groups

	Spatial Extent of Activation	Time Course Peak
Social Functioning Scale		
Social Engagement	.234	.287*
Interpersonal Communication	.146	.244
Pro-social Activities	.075	.082
Recreation	.099	.101
Independence – Competence	.353*	.415*
Independence – Performance	.161	.333*
Employment/Occupation	.182	.338*

* $p < .05$

Figure Captions

Figure 1. Behavioral and neural similarities between schizophrenia and autism.

Figure 2. Unique response of VLPFC and STS in controls for untrustworthy faces. A: statistical parametric map (SPM) overlaid on mean T1 anatomical image showing activation in ventrolateral prefrontal cortex. Left peak at *x,y,z* = -45, 21, -6; Z = 5.39, right peak at *x,y,z* = 51, 27, -9; Z = 3.77. Results are displayed using the ROI mask for the VLPFC. B: mean response profiles for different event types from the VLPFC and STS ROIs. Data derived from a finite impulse response (FIR) model with 2 second time bins. For both, the peak time point for untrustworthy faces is significantly greater than the peak for trustworthy faces at $p<.05$. C: SPM overlaid on mean T1 anatomical image showing activation in the STS that is unique to faces judged as untrustworthy. Peak at *x,y,z* = 51, -33, -9; Z = 3.59. Results are displayed using the ROI mask for the STS.

Figure 3. Group differences in neural activation during trustworthiness judgments. The first column shows statistical parametric maps overlaid on the mean T1 anatomical image showing activation in the right amygdala (*x,y,z* = 15, -9, -21; Z=3.22), right fusiform face area (FFA; *x,y,z* = 48, -57, -30; Z=2.88), and left ventrolateral prefrontal cortex (VLPFC; *x,y,z* = -30, 18, -21; Z=3.13) in which control participants showed significantly greater activation than HFA participants. The second column shows activation in the right amygdala (*x,y,z* = 18, -3, -21; Z=3.11), right FFA (*x,y,z* = 45, -57, -33; Z=2.88), and left VLPFC (*x,y,z* = -30, 24, -18; Z=2.91) in which the control group showed significantly more activation than the schizophrenia group. All SPM results are displayed using the appropriate ROI mask. The last column shows the means response profiles for each event type extracted from the amygdala, FFA, and VLPFC ROIs. Data was derived from a FIR model with 2 second time

bins. For both the amygdala and FFA, peak time points for the control group were significantly higher than the peaks for both clinical groups at $p<.05$. For the VLPFC, the main effect of group was not significant ($p=.275$); however, the interaction between trust and group was significant and likely contributed to the SPM results.

Figure 4. Interaction between trust rating and group. Statistical parametric maps overlaid on mean T1 anatomical images show that when a face is rated as untrustworthy, only control participants show greater activation of bilateral VLPFC (right maxima: x,y,z = 39, 27, -3; Z=3.24; left maxima: x,y,z = -39, 27, 0; Z=5.42). Results are displayed using the VLPFC mask.

Figure 5. Peak response of event time courses from the amygdala, FFA, and VLPFC.

Figure 1. Social Cognition in Schizophrenia and Autism

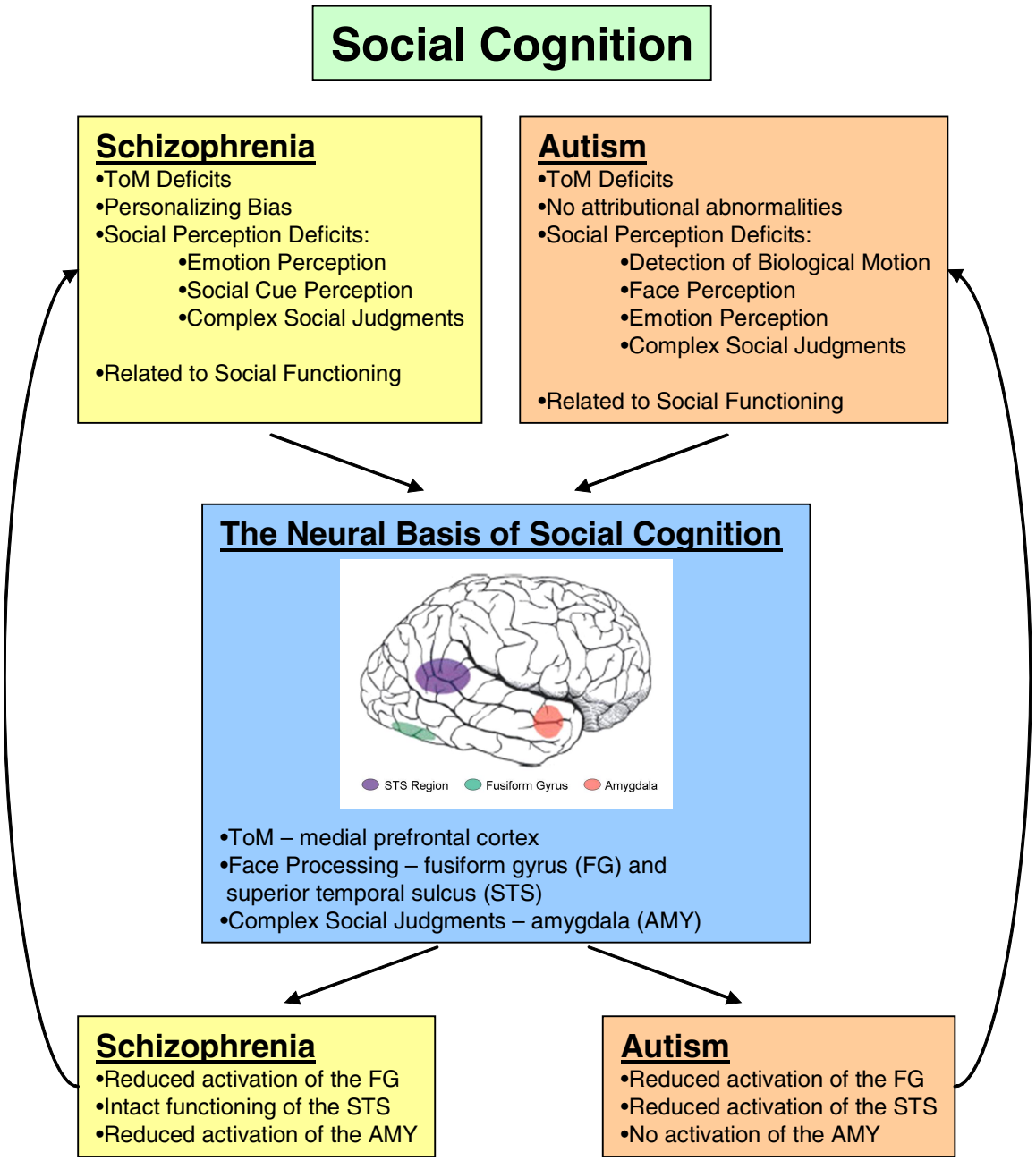


Figure 2. Unique Response of VLPFC and STS in Controls for Untrustworthy Faces

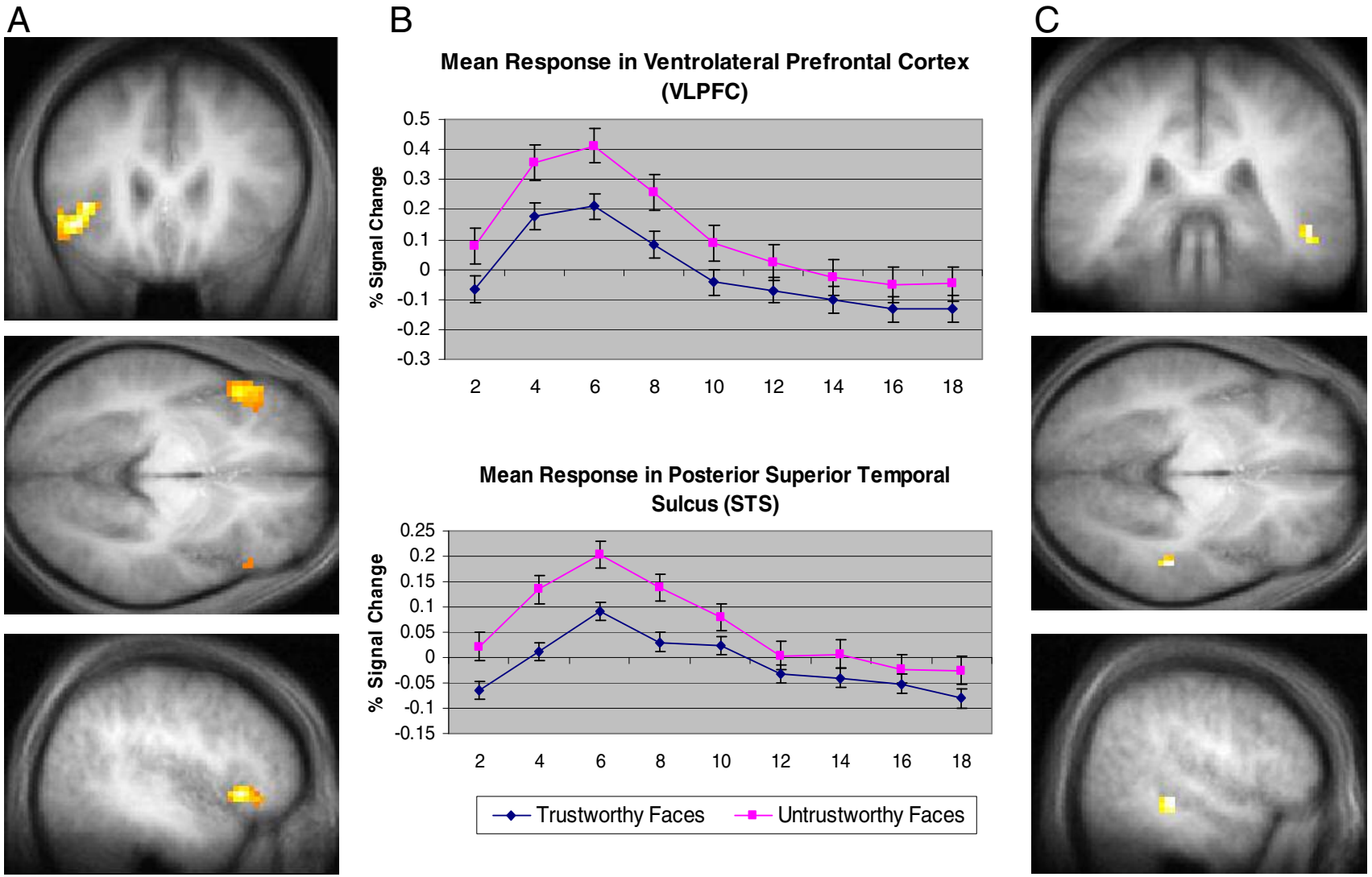


Figure 3. Group Differences in Neural Activation During Trustworthiness Judgments

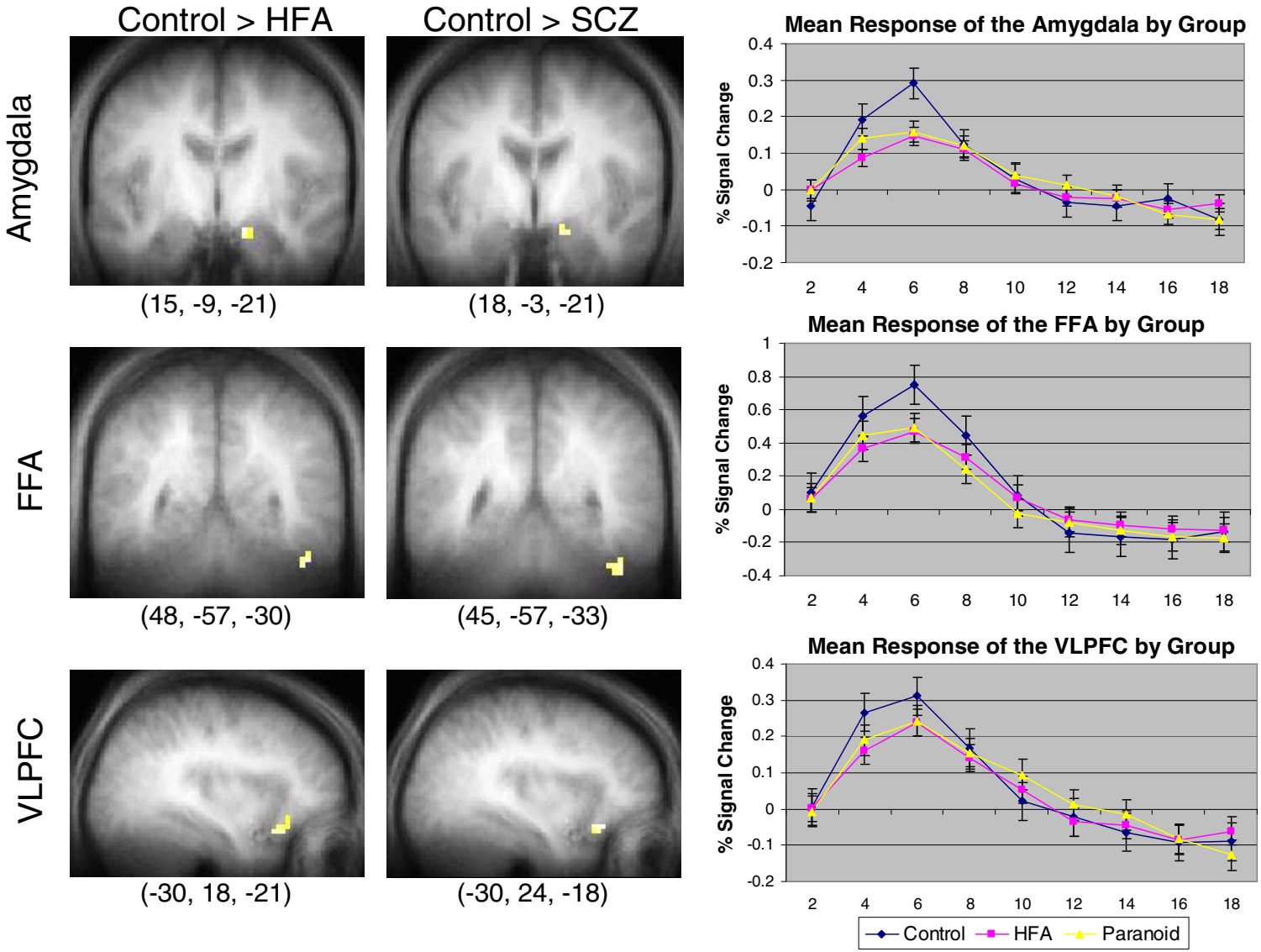


Figure 4. Interaction between Trust Rating and Group

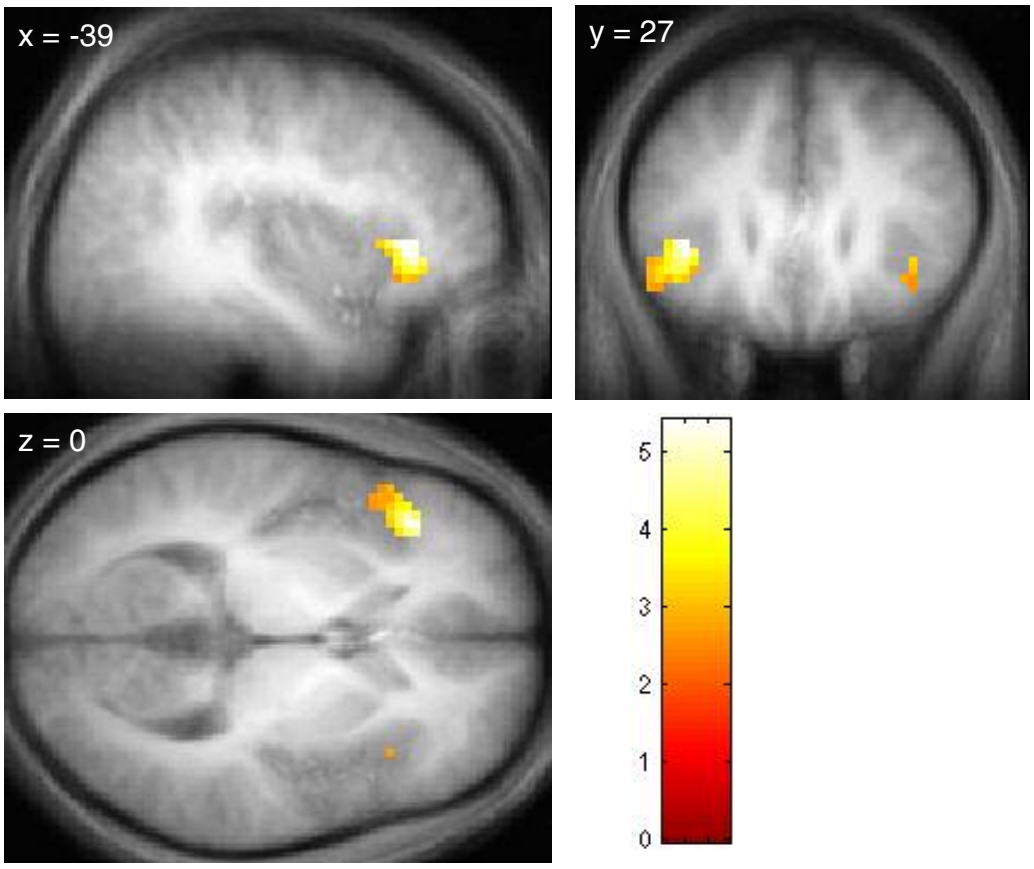
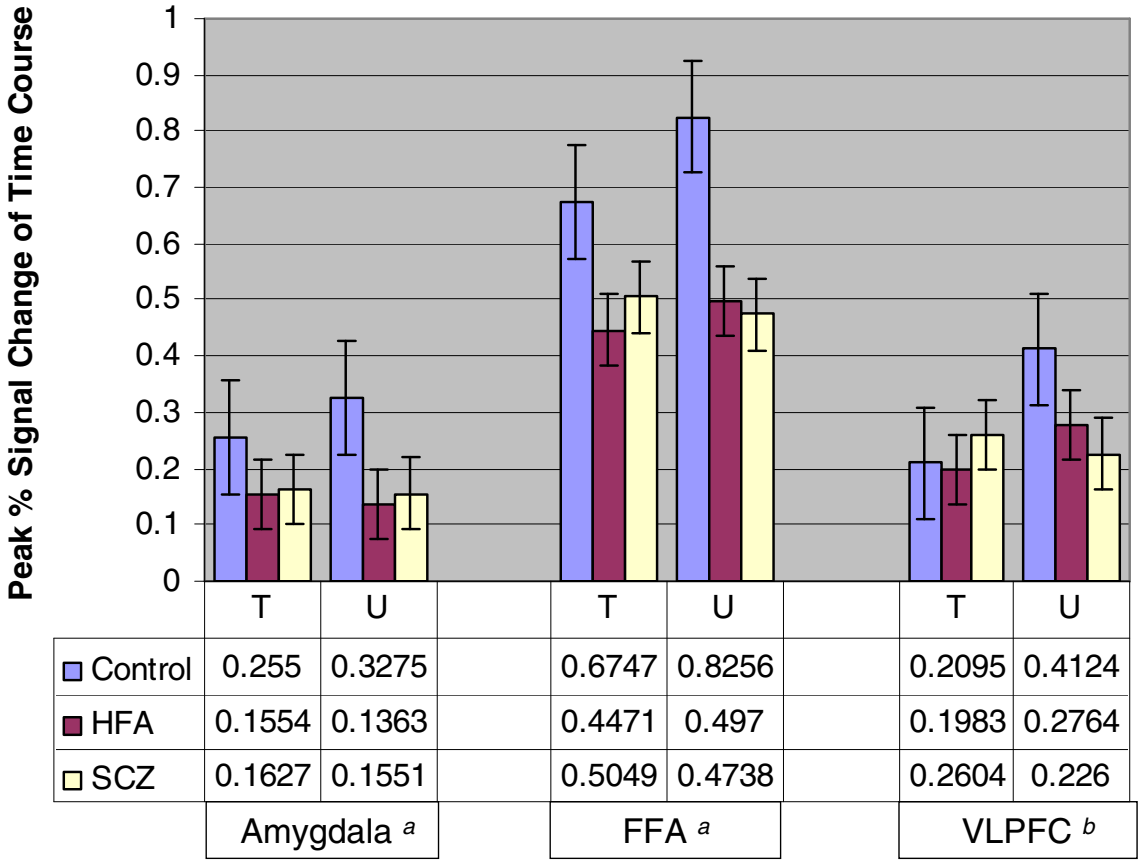


Figure 5. Peak Response of Event Time Courses



	Amygdala [a]		FFA [a]		VLPFC [b]	
	T	U	T	U	T	U
Control	0.255	0.3275	0.6747	0.8256	0.2095	0.4124
HFA	0.1554	0.1363	0.4471	0.497	0.1983	0.2764
SCZ	0.1627	0.1551	0.5049	0.4738	0.2604	0.226

T = trustworthy faces; U = untrustworthy faces

[a] Significant main effect for group at $p<.05$

[b] Significant interaction between trust rating and group at $p<.05$

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