The Neural Basis of Social Cognition and Its Relationship to Social Functioning in Young People at Risk for Schizophrenia

The neural basis of social cognition and its relationship to social functioning in young people at risk for schizophrenia

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Abstract

These three studies seek to contribute to the neurological characterization of the development of schizophrenia as well as begin to branch into understanding how neuroanatomical structure and function may relate to specific deficits in social cognition and social functioning within in this population. Paper #1 investigates the relationship between brain structure in young adults at clinical high risk for schizophrenia and social functioning. Paper #2 expands upon the findings of paper #1 by looking at brain structure, social cognition, and social functioning in children and risk for psychosis. Finally, paper #3 focuses on brain function for theory of mind in typically developing children and its relationship to social cognition and social functioning. Investigating the neural mechanisms underlying social cognitive deficits and social functioning impairment in young adults and children at risk for schizophrenia will contribute to the field's understanding of the development of this disorder.

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Background and Introduction

A complex brain disorder, theories on the etiology of schizophrenia have argued for a disorder of neurodevelopment (Rapoport et al., 2005; Seidman, 1990), others a neurodegenerative disorder that begins in early development (Lieberman, 1999), or perhaps a combination of the two (Ashe et al., 2001). Though there is an extensive body of literature on schizophrenia, its symptoms, treatments, risk factors, and progression from behavioral and biological perspectives, what remains unclear are the questions of what and when in regard to the disruption of the neurobiology. The factors that set the stage for the development of this disorder, likely a combination of biological and environmental variables, are at this time unknown. This dissertation addresses specific aspects of the etiology of the disorder, by focusing on at-risk populations, in different age groups, to make connections between neurobiology, behavior, and symptoms, in order to better understand factors throughout development that may relate to the onset of the disorder. Specifically, we focus on one of the core symptoms of schizophrenia, social impairment, given that this symptoms is seen before the onset of the disorder (Addington et al., 2008b), is predictive of symptom severity (Addington et al., 2003a), and is often unchanged by typical psychopharmacological treatment (Bond et al., 2004; Hamilton et al., 2000). Below I present a targeted review of the relevant literature, and then a statement outlining the specific research questions addressed by this dissertation. What follows are three papers addressing these research questions, and then a summary of the implications of this work.

Social Dysfunction in Schizophrenia Spectrum Disorders

Social dysfunction in schizophrenia is a particularly debilitating symptom, negatively affecting individuals' self-care, interpersonal relationships, and family and occupational functioning. Research has shown that social dysfunction is an early predictor of schizophrenia.

Clinical studies with individuals at risk for schizophrenia have suggested that deficits in social functioning may be one of the earliest key predictive markers for the future onset of psychosis (Addington et al., 2008b). More specifically, global deficits in social functioning are apparent in individuals at a clinical high risk for schizophrenia relative to healthy controls (Addington et al., 2008b) (Ballon et al., 2007). Social functioning deficits before the onset of psychosis are predictive of overall symptom severity, cognitive deficits, and general functioning (Addington et al., 2003b). Additionally, premorbid social functioning is predictive of clinical high risk (CHR) individuals who transition to a psychotic disorder versus those who do not (Tarbox et al., 2013). The goal with this research is to elucidate the underlying factors that contribute to social dysfunction in individuals at risk for schizophrenia.

Social Cognition and Social Functioning in the At-Risk Population

Difficulties in social cognitive processing may underlie social dysfunction in schizophrenia spectrum disorders. Social cognition broadly includes cognitive processes that allow individuals to infer and understand the intentions, beliefs, and feelings, of others. Successful social interactions rely on this ability to predict and interpret other persons' thoughts, emotions, intentions, and behaviors. In turn these interactions help build the foundation for effective interpersonal relationships. Research with individuals with psychiatric disorders, primarily in autism and schizophrenia, demonstrates that deficits in social cognitive processes such as theory of mind (Brune et al., 2007), empathy (Shamay-Tsoory et al., 2007), and affect recognition (Hooker and Park, 2002), may be underlying problems in social functioning in schizophrenia. Individuals with schizophrenia show impairment on social cognitive tasks throughout all stages of the illness, including during psychotic episodes and periods of remission, suggesting that these deficits are not related to specific symptoms (Addington and Piskulic,

2011). If deficits in social cognition exist in all stages of the illness, it suggests that these may be a trait, rather than state characteristic of the disease. This knowledge provides further support for investigating if social cognitive deficits exist prior to the onset of the illness and what role they might play in the known social dysfunction evident before psychosis-onset. While the research is limited, some studies have identified social cognitive impairment in CHR individuals. Research has shown that CHR young adults have deficits on social cognitive tasks relative to healthy controls, including theory of mind (ToM) tasks (Chung et al., 2008) (Bora and Pantelis, 2013; Marjoram et al., 2006), and tasks of emotion identification (Addington et al., 2008a) (Amminger et al., 2012). Identifying whether social cognitive impairments contribute to the social dysfunction before the onset of the disease is a logical next step in characterizing the neurodevelopmental pathway of schizophrenia.

Of note, we recognize that social cognition is a specific type of cognition that is related to understanding the mental states and beliefs of other people in order to engage in effective social interactions. Social cognitive processes, like theory of mind, rely on basic cognitive skills, such as executive function, working memory, and verbal reasoning. Individuals at both a clinical high risk and a genetic high risk (GHR) for schizophrenia demonstrate impairments in general cognitive processes such as executive function (Broome et al., 2009; Koutsouleris et al., 2010), working memory (Broome et al., 2009), verbal memory (Woodberry et al., 2010), and general intelligence (Cullen et al., 2010). Additionally impairments in neurocognition are associated with degree of symptom severity (Cullen et al., 2010), transition status (Woodberry et al., 2010), and are seen in children, as young as seven, who later develop a psychotic disorder (Seidman et al., 2013). At the same time, social cognitive impairments, while related to, exist separately from, neurocognitive deficits also characteristic of schizophrenia (Sergi et al., 2007). Recent research

has suggested that not only is social cognition an important factor in social functional outcome, but it may also mediate the relationship found between neurocognition and functional outcome in patients with schizophrenia (Addington et al., 2006). Social cognition is a type of cognition that is more directly related to social functioning. Additionally social cognition has a specific neural circuitry underlying it, and it is both the neural mechanisms and the process of social cognition and how they relate to social functioning that are the main focus of this project. We will look at the unique contribution of social cognition to social functioning in CHR young adults and adolescents by controlling for the influence of basic cognitive processes.

At this time, we are unaware of any research looking at social cognition and social functioning in adolescents and children at clinical risk for schizophrenia spectrum disorders. While there is some evidence to suggest deficits in social functioning in CHR and GHR children (Gibson et al., 2010), there is no research on social cognition in CHR children. The research in these projects begins to address the question of what might underlie these social functioning deficits, by extending downward previous findings of social cognition deficits in an adolescent group to a younger population to determine if these deficits exist in earlier developmental stages.

The work described in this proposal will investigate whether clinical high-risk individuals have abnormalities in neural systems that support social cognition. Of particular interest are neural systems related to theory of mind. We are interested in structural and functional deficits in regions that support theory of mind processing, including medial prefrontal cortex (mPFC) (including anterior cingulate cortex (ACC)), superior temporal cortex (including temporo-parietal junction (TPJ), superior temporal sulcus (STS), and the superior temporal gyrus (STG)), and somatosensory-related cortex (including postcentral gyrus and insula) (Mar, 2011; Van Overwalle, 2009). We will investigate whether abnormalities in these regions are related to poor

social-cognitive skills and/or poor social functioning. There is strong evidence to support our belief that CHR will demonstrate neurobiological aberrations in these neural regions.

Neurobiology of Social Cognition

Research has identified the neurobiological basis of ToM, highlighting a network of regions that is consistently recruited for a variety of ToM tasks across the life span (Moriguchi et al., 2007). This research has led to a better understanding of the development of ToM, both neurobiological mechanisms and behavioral abilities, across the lifespan. Neurodevelopmental changes, particularly as they relate to social cognition, between childhood and adolescence, beginning with the onset of puberty, are relevant and necessary changes to understand in typically developing children in order to fully understand and identify abnormalities. A network of regions have been identified in healthy adults and children as areas associated with social cognitive processing such as affect recognition, theory of mind, and face recognition. These regions include the TPJ, STS, mPFC, inferior frontal gyrus (IFG), ACC, STG, amygdala, anterior insula, and somatosensory related cortices (Adolphs, 2003a; Blakemore, 2008a) Adolescence, often marked with the start of puberty, is a period of time that is characterized both by interest and increased time with social groups resulting in enhanced social skills, reasoning, and interactions, as well as a maturation of brain regions related to social processing (Blakemore, 2008b). Previous research has demonstrated that specific regions involved in social cognitive processing change in response to social stimuli with age. Work by Rebecca Saxe and colleagues (Saxe et al., 2009) showed age related effects to specificity of the TPJ in response to a theory of mind task. Other work by Frith & Frith (2003) shows differential activation in the mPFC in response to a mentalizing task between adolescents and adults (Frith and Frith, 2003). Studies have shown a relationship between neural activity during social cognitive tasks and performance

on behavioral measures of social cognition, but to our knowledge no work exists looking at whether neural activity in response to a social cognitive tasks is related to social functioning in children. We aim to investigate the neurobiological mechanisms related to social functioning in typically developing children, which will allow us to then apply this knowledge in the future to children and adolescents with psychiatric disorders.

Neurobiology in Clinical At-Risk

Structural imaging studies of patients with schizophrenia throughout various stages of the illness have consistently demonstrated neuroanatomical abnormalities within this population. The most consistently replicated findings have been increased ventricular volume, decreased grey matter volume in the STG, and prefrontal areas such as the IFG, and the insula, and the limbic/paralimbic regions such as the hippocampus, amygdala, and the ACC (Wright et al., 2000) (Shenton et al., 2001). Additionally, grey matter volume (GMV) deficits in areas such as the ventromedial prefrontal cortex (VMPFC) are related to performance on advanced theory of mind tasks and self-reported abilities of perspective-taking and empathy (Hooker et al., 2010). A review by Borgwardt, McGuire, and Fusar-Poli (Borgwardt et al., 2011) summarized the literature looking at GMV in individuals at risk for psychosis. They conclude that literature on individuals with a high risk for schizophrenia (either clinical or genetic) have grey matter abnormalities that are similar, though generally less severe, to patients with schizophrenia. Particularly consistent findings have been reductions in the limbic and prefrontal cortices (Borgwardt et al., 2007), lateral and medial temporal lobe, and areas of the cingulate cortex (Meisenzahl et al., 2008a). These findings indicate that grey matter volume abnormalities may be vulnerabilities for psychosis. Additionally, some studies (Borgwardt et al., 2008; Smieskova et al., 2010; Takahashi et al., 2009b) have found even greater reductions between individuals

who were recognized as prodromal and transitioned to a psychotic disorder versus those recognized as prodromal and did not transition. Specifically decreased GMV in the insula, prefrontal cortex, the cingulate cortex, and overall GMV in the cerebellum were predictive of those individuals at-risk who transitioned to psychosis versus the at-risk individuals who did not transition (Smieskova et al., 2010). These findings suggest that while some abnormalities in grey matter volume suggest an increased vulnerability for psychosis, other structural changes may be directly related to the process of transition to psychosis (Borgwardt et al., 2011). Gogtay and colleagues (Gogtay et al., 2007) found that unaffected siblings of children with early onset schizophrenia had overall decreased grey matter volume relative to healthy controls. Their findings suggest that changes in cortical volume may be an endophenotype indicative of psychosis risk. The proposed work is unique in that it focuses on children and young adults at a clinical high risk and may add to our understanding of when brain abnormalities occur in individuals at a putative state for psychosis. The relationship between grey matter volume and performance on social cognitive tasks as well as social functioning deficits in clinical high-risk children and adolescents has yet to be explored.

Research Questions

In this dissertation, I provide data to address the following questions:

Question 1: Do adolescents and young adults at clinical high risk for schizophrenia have deficits in social functioning relative to healthy comparison group? Do CHR individuals have structural deficits in regions that support social cognition and social behavior? Do these structural deficits, if they exist, predict social cognition and social functioning measures in this group of CHR individuals?

Paper #1: Lincoln, S.H., & Hooker, C.I. (2014). Neural structure and social dysfunction in individuals at clinical high risk for psychosis, *Psychiatry Research: Neuroimage,* 224, 152-158.

Paper #1 focuses on the relationship between neural structure and social functioning in adolescents and young adults at a clinical risk for schizophrenia. We look at whether grey matter volume in brain regions involved in social cognitive processing are also related to self-reported and interviewer-rated measures of social functioning, as well as grey matter volume in these regions and its relationship with social functioning outcomes in the high risk population.

Question #2: *Do children at clinical high risk for the development of schizophrenia have ToM deficits and social impairment? Do CHR children have deficits in neural structures that support ToM processing? Do deficits in these regions predict behavioral performance on ToM and social dysfunction?*

Paper #2: Lincoln, S.H., Kleeman, N., & Hooker, C.I. (in prep). Neural structure in children at clinical high risk for schizophrenia.

Paper #2 moves forward from the work in paper one, extending that research to a younger population. This paper focuses on children at clinical high risk for schizophrenia and a matched group of typically developing children. We investigate neural mechanisms that might indicate a specific vulnerability for psychosis, in particular grey matter volume in regions functionally related to social cognition.

Question #3: What neural regions are recruited in a novel ToM task in children ages 8-13? Is activation in these regions related to performance on behavioral measures of ToM? Is activation in these regions related to social functioning?

Paper #3: Lincoln, S.H., Kleeman, N., Dodell-Feder, D., Mukerji, C., & Hooker, C.I. (in prep). The neural basis of social cognition in typically developing children and the relationship to social functioning.

Paper three integrates the three factors of interest, neural function, social cognition, and social functioning, by identifying how neural activity during social cognitive processing relate to interview and self-report measures of social functioning.

Our research also looks at children at a clinical risk for schizophrenia, an understudied population in the literature, particularly when it comes to studies examining neurobiological abnormalities in this group. This work aims to expand research on the neurodevelopment of schizophrenia in novel ways, first by using a younger population (ages 8-13) and through the use of neuroimaging techniques to explore potential neurobiological abnormalities that may contribute to these dysfunctions in children at risk. We chose this age range carefully in order to remain consistent with previous literature and our knowledge of both critical periods in brain development and physical development. Additionally retrospective studies looking at data from large birth cohort studies have suggested that markers of the illness may be present in children as young as 7 or 8 years of age (Jones et al., 1994; Niendam et al., 2003). Identifying a relationship between the neurological processes underlying the social dysfunction evident before the onset of psychosis might allow us to gain an understanding of the progression of this disease. In particular, if we can demonstrate a relationship between structural and functional abnormalities and the impairment in social cognitive processes that may underlie the social dysfunction in this population, we may better understand a significant aspect of the neurodevelopmental pathway that leads to schizophrenia.

Paper #1: Neural structure and social dysfunction in individuals at clinical high risk for psychosis

Published in *Psychiatry Research: Neuroimage* (2014)

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Sarah Hope Lincoln and Christine I. Hooker

Abstract

Individuals at a clinical high risk for psychosis have grey matter volume abnormalities that are similar, though less severe, to individuals with schizophrenia. Less GMV in schizophrenia is related to worse social cognition and social functioning, however, the relationship between GMV and social functioning in CHR individuals has yet to be investigated. The aim of this study was to first, investigate differences in GMV between healthy controls (HC) and CHR individuals, and second, evaluate the relationship between GMV and social functioning in these two groups. Twenty-two CHR and twenty-one HC participants completed a structural magnetic resonance imaging (MRI) scan as well as self-reported and interviewer-rated measures of social functioning. Processing and analysis of structural images was completed using voxel based morphometry (VBM). Results showed that the CHR group had less GMV in the left post central gyrus, bilateral parahippocampal gyri, and left anterior cingulate cortex. Reduced GMV in the post central gyrus and the anterior cingulate was related to self-reported social impairment across the whole group. This study has implications for the neurobiological basis of social dysfunction present before the onset of psychosis.

Introduction

Abnormalities in neural structure, particularly reductions in grey matter volume (GMV), are well documented in schizophrenia-spectrum populations (Borgwardt et al., 2011; Jung et al., 2012). Individuals at clinical high risk (CHR) for psychosis are characterized by attenuated positive symptoms, brief psychotic episodes, which do not meet diagnostic criteria for schizophrenia, or a combination of genetic vulnerability and functional decline. These individuals have similar, though less severe, GMV reductions in regions consistent with those seen in individuals with schizophrenia (Fusar-Poli et al., 2012b). Importantly, among CHR individuals, those with more severe GMV reductions are more likely to develop schizophrenia or another psychotic disorder (for review see Pantelis et al., 2005; Smieskova et al., 2010). These findings have prompted the proposal that GMV deficits are a biomarker of schizophrenia and could facilitate early detection and intervention.

However, schizophrenia is a heterogeneous disorder characterized by psychological symptoms and behavioral problems in multiple domains (Harvey et al., 2007). Given that neural structures and functions map onto single behaviors more accurately than diagnostic categories, structural deficits in a single brain region are unlikely to predict the heterogeneous collection of symptoms associated with schizophrenia. An alternative and, potentially, more reliable approach for identifying biomarkers is to investigate the relationship between GMV and specific behaviors associated with schizophrenia (Cuthbert and Insel, 2010). This approach not only benefits from established basic research on brain-behavior relationships, but may also provide personally relevant clinical information since individuals at risk for or with the disorder have different symptom profiles.

Research with CHR individuals has examined GMV and its relationship to cognitive

deficits (Koutsouleris et al., 2012) and clinical symptoms (Cullen et al., 2012), but not the relationship between GMV and social functioning. Yet, social functioning may be an even more important factor to investigate in relation to GMV as it exists earlier than the onset of psychotic symptoms (Addington et al., 2008b; Cornblatt et al., 2012; Tarbox and Pogue-Geile, 2008), persists as a problem in individuals who do not transition (Cornblatt et al., 2012), and is a main cause of functional disability and poor outcome in individuals who transition to psychosis (Bellack et al., 1990; Hooley, 2010).

The current study looks at the relationship between GMV and social functioning in order to better understand the specific relationship between the neurobiological deficits underlying the disorder and functional impairment. Behavioral data indicate that CHR individuals have social cognitive deficits (Amminger et al., 2012; Bora and Pantelis, 2013), and poorer performance on social cognitive tasks is associated with transition to psychosis (Kim et al., 2011). Social cognitive processing and associated social behaviors are supported by a network of brain regions, including the medial prefrontal cortex (MPFC), anterior cingulate cortex (ACC), superior temporal cortex (including superior temporal sulcus (STS) and superior temporal gyrus (STG)), amygdala, and somatosensory related cortices (including postcentral gyrus, supramarginal gyrus, and anterior insula) (Adolphs, 2009).

Individuals with schizophrenia have GMV deficits in regions supporting social cognition and these abnormalities predict social functioning (Hooker et al., 2011; Tully et al., 2014). Previous research with CHR individuals shows abnormal neural structure in multiple brain regions, including regions related to social and emotional processing, such as the ACC, STG, ventral and dorsal MPFC, orbital frontal cortex (OFC), postcentral gyrus, supramarginal gyrus, and insula (Dazzan et al., 2012; Fusar-Poli et al., 2011; Meisenzahl et al., 2008b). CHR also have

structural abnormalities in medial temporal lobe regions associated with memory, cognitive-control, and other core cognitive functions; these regions include the superior, middle and inferior frontal gyri, parahippocampal gyri, and hippocampus (Meisenzahl et al., 2008b; Pantelis et al., 2003a; Witthaus et al., 2009). Longitudinal studies have shown that less volume in these regions (supporting both social cognition and cognition) is associated with greater risk of psychosis conversion (Borgwardt et al., 2007; Borgwardt et al., 2008; Takahashi et al., 2009b). Given the observed structural abnormalities in regions that process social and emotional information, such as the ACC, STG, MPFC, insula, postcentral gyrus, OFC, and supramarginal gyrus, it may be useful to investigate the relationship between GMV in these regions and social functioning, as abnormalities in these areas may be a specific biomarker for social dysfunction in psychotic disorders.

The aims of this study are twofold: (1) investigate differences in GMV between CHR and a matched healthy control group, and (2) identify the relationship between GMV and social functioning in these groups. We hypothesize that CHR individuals will have reduced GMV relative to HC in the following regions associated with social and emotional processing: STG, STS, ACC, MPFC, and somatosensory related cortices, including the postcentral gyrus and the supramarginal gyrus. To identify this relationship, we use self-report and interviewer-rated measures that assess daily functioning in social contexts, including interpersonal relationships as well as work and/or school. We expect to see a relationship between GMV and social functioning, such that greater volume in these regions will relate to better social outcomes. Although other regions, not part of the social cognitive network, may differ in volume between groups, we do not expect these non-social regions to relate to social functioning. Since structure and function of these social and emotional brain regions are known to correlate with social

behaviors in healthy adults (Adolphs, 2003a, b), we expect a continuous relationship between GMV and social functioning across all individuals.

Methods

Participants

CHR group. Participants include twenty-two individuals, 15-35 years of age, who met CHR status due to the presence of attenuated positive symptoms as defined by a score of 3 or greater on one of five positive symptom clusters (unusual thought content, paranoid ideation, grandiosity, perceptual aberrations, disorganized speech) assessed by the Structured Interview for Prodromal Syndromes (SIPS) (McGlashan, 2001). Participants' symptoms did not have to meet duration (within the last year) and frequency (4 times per month) for the prodromal syndrome to be included in the study. CHR participants were excluded for past or current Axis I psychotic disorder (including mood disorder with psychosis). However, CHR participants were not excluded for other Axis I or II disorders unless these disorders could explain their prodromal symptoms. Many CHR individuals have co-occurring disorders (Hui et al., 2013; Salokangas et al., 2012); thus, the goal of this recruitment strategy was to maintain external validity of our CHR sample. For example, a recent meta-analysis by Fusar-Poli and colleagues (2014) showed that the majority of CHR individuals have comorbid depressive and/or anxiety disorders, suggesting that symptoms of other Axis I disorders may be part of the prodromal state and not separate from the emerging psychotic process. Our final sample included one participant with current social anxiety disorder and history of panic disorder; and one participant who had Eating Disorder-Not Otherwise Specified (with mild severity). Only one CHR participant was excluded for co-occurring psychopathology; this participant had post-traumatic stress disorder (PTSD) and her prodromal paranoid symptoms only occurred within the context of PTSD symptoms.

Exclusion criteria for all participants (CHR and HC) included an IQ <70, history of neurological problems, head injury, loss of consciousness > 20 minutes, current or past substance dependence, or MRI incompatibility.

HC group. Twenty-one, healthy, age-matched controls were recruited. In addition to the exclusion criteria listed above, healthy participants were excluded for past or current Axis I/II disorder, or psychotic-like symptoms rated a 2 or higher on the positive symptom scales of the SIPS.

Clinical Measures

All participants were screened for psychopathology using the Structured Interview for Clinical Disorders (SCID) I (First, 1996) and II (First, 1997) . Full-scale IQ scores were obtained from the Wechsler Abbreviated Intelligence Scale (Wechsler, 1999). Social functioning was assessed by the Social Adjustment Scale (Sasaki et al.; Weissman et al., 1978) and the Global Functioning (GF): Social and Role scales (Cornblatt et al., 2007). These social functioning measures were chosen because of their good psychometric properties and validation for use with adolescents and young adults. The SAS is a self-report measure assessing multiple aspects of functioning. The Social and Leisure subscale of the SAS was our primary interest, as it specifically assesses the social aspects of day-to-day functioning, including social motivation and social activities. Standardized T scores are reported; higher scores indicate lower functioning. The Social and Leisure subscale was chosen because every participant completed this scale, whereas other subscales were not completed by all participants. The work subscale, for instance, failed to capture the role functioning of unemployed individuals. The GF: Social and GF: Role interviews were specifically created for the psychosis prodrome population. Scales are rated 1-to-10 (10=highest). GF: Social assesses social motivation/initiative and the number and quality of

interpersonal relationships. GF: Role assesses functioning in occupational, educational, and/or homemaker roles. Ratings for both scales incorporate environmental context (e.g. level of educational support) and developmental stage (e.g. age-appropriate interest in romantic relationships). The use of both self-report and interview-based measures is methodologically rigorous, as converging evidence from two different sources and types of measures for the same construct provides stronger support for the validity of the data.

Image Acquisition

Structural images were acquired on a 3.0 Tesla Siemens Tim Trio scanner using a 32-channel head coil. A three dimensional anatomical T1-weighted scan (MEMPRAGE) was acquired with the following parameters: 176 axial slices, 1x1x1 mm voxels, TE1(multi-echo): 1.64ms, TE2: 3.5ms, TE3:5.36ms, TE4:7.22ms; TR:2530ms; flip angle=7°; FOV=256mm x 256mm.

Image Processing

Structural analysis was done using voxel based morphometry (VBM) with Statistical Parametric Mapping (SPM8; http://www.fil.ion.ucl.ac.uk/ spm/software/spm8). Structural images were preprocessed using the DARTEL SPM8 toolbox, which has been shown to improve normalization in the VBM process(Ashburner, 2007). After alignment to the DARTEL generated template, images were spatially normalized to MNI space and smoothed with an 8mm Gaussian kernel.

Statistical Analysis

For the whole brain analysis, an ANCOVA was performed to detect differences in GMV between the HC and CHR groups. Total intracranial volume (Mefford et al.) (sum of grey matter, white matter, and cerebrospinal fluid) was a covariate of no interest. Given the inherent

risk of missing true CHR abnormalities when using a conservative statistical threshold, we sought to balance the probability of Type I and Type II errors (Lieberman and Cunningham, 2009), by using a two-step statistical approach. First using a less stringent threshold (p<.001) for the whole brain analysis, and then correcting for multiple comparisons within regions of interest. First, we report between-group differences exceeding a statistical threshold of $p < .001$ (uncorrected for multiple comparisons) and cluster size (k) of 10 voxels. We then correct for multiple comparisons within hypothesized anatomical regions of interest using the Small Volume Correction (SVC) toolbox in SPM. Clusters that are significant at p<.05 with family-wise error (FWE) correction are designated with an asterisk (*). This two-step approach is recommended for new research areas, since whole-brain multiple test correction is a conservative threshold with high probability of Type II error. Thus, at this early stage of CHR research, Type II error (i.e. missing true CHR abnormalities) could impede progress by restricting the scope of future investigations. Marsbar toolbox (http://marsbar.sourceforge.net) was used to extract GMV from regions that were significantly different between the HC and CHR groups in the whole brain ANCOVA. These volumes were correlated with social and role functioning measures using Pearson product moment correlations, at $p < .05$ (two-tailed test).

Results

Clinical and demographic characteristics

The two groups did not differ in age, gender, or years of education, but the CHR group had lower average IQ than the HC group. As expected, the CHR group had higher psychotic-like symptom SIPS scores and worse social and role functioning (Table 1.1).

Table 1.1 Demographic and clinical details

	High Risk Subjects *n*=21	Control Subjects *n*=18	Differences Between Groups
Age: mean (SD)	22.05 (4.48)	22.22 (3.04)	$t(37)=.140$, $p=.89$
Education: mean (SD)	14.10 (2.40)	15.28 (1.32)	$t(30.09)=1.90$, $p=.07$
IQ: mean (SD)	108.10 (17.29)	118.11 (9.44)	$t(31.79)=2.29$, $p=.03$
SIPS Scale: mean (SD)			
Positive	12.38 (4.79)	.47 (1.01)	$t(22.16)= 11.10$, $p=.000$
Negative	6.57 (5.25)	.65 (1.22)	$t(22.64)= 5.01$, $p=.000$
Disorganized	2.76 (1.70)	.41 (0.62)	$t(26.20)= 5.87$, $p=.000$
General	4.43 (3.96)	.18 (.53)	$t(20.88)= 4.87$, $p=.000$
Global Functioning Scale (scale 1-10; higher scores reflect better functioning)			
Social	7.38 (1.63)	9.17 (0.99)	$t(33.55)=4.21$, $p=.000$
Role	6.81 (1.44)	9.00 (.686)	$t(29.60)=6.21$, $p=.000$
Social Adjustment Scale[a] (scale 1-100; lower score reflects better functioning)			
Social and Leisure	62.00 (9.88)	48.75 (5.92)	$t(31.77)=4.98$, $p=.000$

[a]Data reported are T scores which are standardized scores with X=50 and SD=10.

GMV Analysis

Regional differences in GMV: HC > CHR. CHR had less GMV than HC in the Left (L) ventral ACC, Right (R) postcentral gyrus, the midbrain, and bilateral parahippocampal gyri (PHG) (Figure 1.1, Table 1.2). Reduced GMV in CHR relative to HC in the ACC and postcentral gyrus are consistent with our hypotheses. Thus, small volume correction was conducted in the ACC and postcentral gyrus. The postcentral gyrus was significant after correction for multiple tests ($p<.05$, FWE). To ensure that the two CHR participants with a co-occurring Axis I disorder were not skewing results, the between-group ANCOVA was conducted again with these two participants removed from the sample. Results are similar to findings from the full sample (Supplemental Table 1.1).

Regional differences in GMV: CHR > HC. Compared to HC, CHR participants had more GMV in the L superior frontal gyrus, L middle frontal gyrus, and L rolandic operculum (Table 1.2).

Relationship between GMV and Social Functioning. GMV for each participant was extracted from the regions that were significant in the whole-brain group analysis of CHR<HC. We correlated social and role measures with each of these regions (Table 1.3).

As hypothesized, regions associated with social and emotional processing, the ACC and postcentral gyrus, correlated with measures of social and role functioning. Specifically, across the whole group, there was a significant relationship between ACC GMV and GF: Role as well as SAS: Social and Leisure subscale, such that greater volume in the ACC was related to better interview-rated role functioning and self-reported social functioning. Greater volume in postcentral gyrus regions was related to the Social and Leisure subscale of the SAS (Figure 1.2, Table 1.3).

Table 1.2. Between group differences in grey matter volume at threshold $p<.001$ (uncorrected) and cluster size $\geq$10 voxels. Coordinates are in MNI space.

Anatomical Region	**R/L**	**BA**	**Voxels**	**x**	**y**	**z**	***t-value***
HC > CHR							
Cerebellum	R	27	216	6	-39	-5	5.69
Parahippocampal gyrus	L	20	68	-30	-13	-21	4.08
Postcentral gyrus*	R	2,3	163	48	-25	46	3.98
Anterior cingulate gyrus	L	11	12	-12	30	-8	3.72
Parahippocampal gyrus	R	20	46	30	-13	-26	3.70
Postcentral gyrus	R	3,4	21	51	-16	33	3.54
CHR > HC							
Superior frontal gyrus	L	10	20	-19	51	24	3.70
Middle frontal gyrus	L	46	12	-31	51	27	3.63
Rolandic operculum	L	44	12	-43	6	15	3.63
Middle frontal gyrus	L	45, 46	12	-39	41	19	3.56

*significant with small volume correction at FWE, $p<.05$

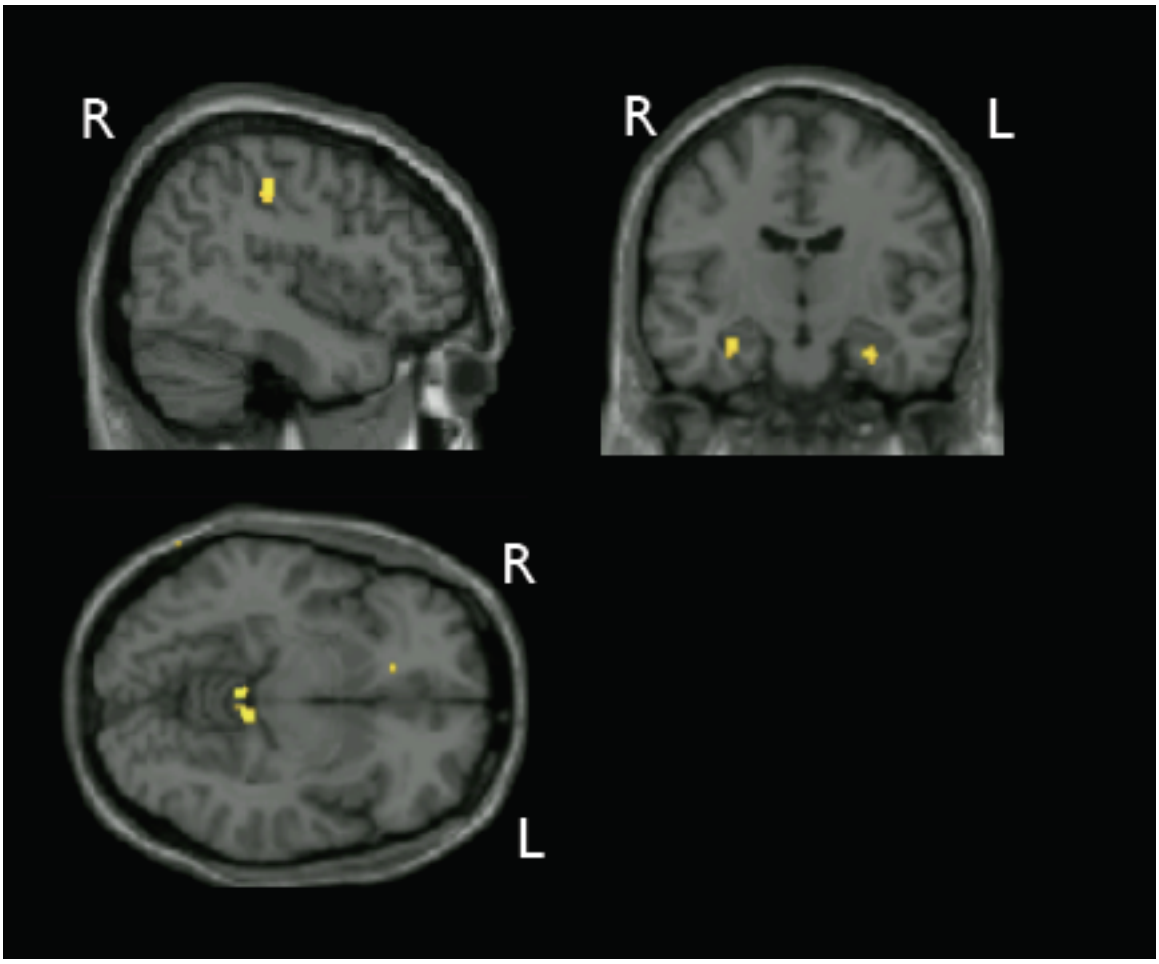

Figure 1.1 A whole brain ANCOVA for between group differences, controlling for TIV was conducted. These results demonstrate regions where GMV: HC > CHR, p<.001 (uncorrected), k=10.

Table 1.3. Correlations between grey matter volume and social functioning

	ACC	Left PHG	Postcentral gyrus (x=51)	Right PHG	Postcentral gyrus (x=48)	Cerebellum
Whole Group (*n*=39)						
GFS_Social	.18	.10	.12	.19	.13	.21
GFS_Role	.34*	.10	.21	.18	.25	.16
SAS_SocialLeisure (Higher scores equal greater impairment)	-.39*	-.06	-.45**	-.10	-.35*	-.32

*p<05, **p<.01

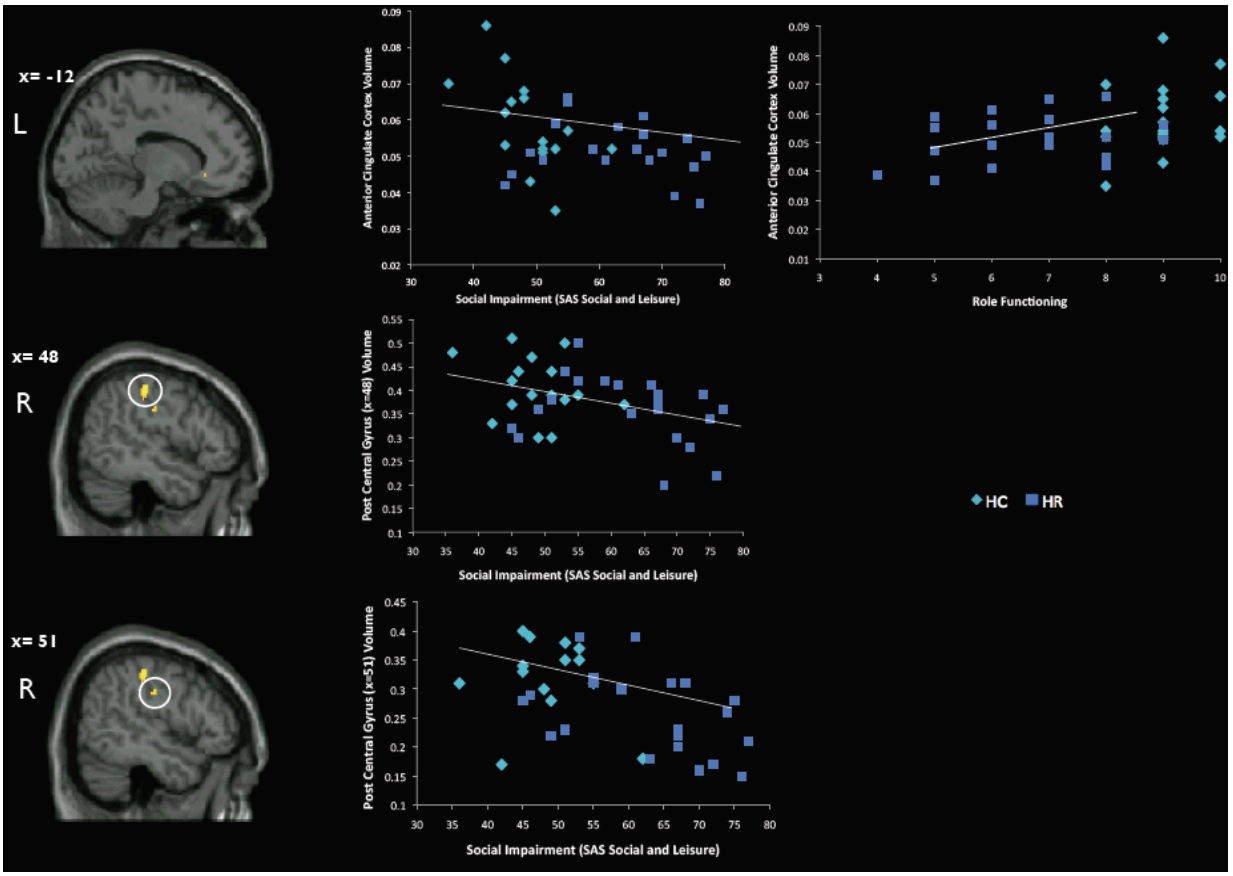

Figure 1.2. Volume from regions of interest identified in the whole brain ANCOVA HC > HR was correlated with social impairment and role functioning.

As expected, regions that are not primarily involved with supporting social and emotional processes, such as the parahippocampal gyri and cerebellum, did not correlate with measures of social functioning.

Discussion

This study found that, compared to healthy participants, CHR individuals had less GMV in the ventral ACC, PHG, postcentral gyrus, and midbrain. Correlational analyses revealed a significant relationship between GMV in the ACC and social and role functioning, as well as GMV in the postcentral gyrus and social functioning. Regions not involved in social and emotional processing, such as the cerebellum, that showed differential volume between groups, as expected, did not correlate with measures of social functioning. These findings suggest that structural abnormalities in social and emotional regions are related to social functioning deficits in CHR individuals.

The regions identified as having reduced GMV in CHR are consistent with prior studies in SZ and CHR. Differences in PHG structure (Job et al., 2005; Mechelli et al., 2011) are consistently reported in the literature for CHR relative to HC. Moreover, even greater reductions in GMV in the PHG have been found in CHR individuals who transition to a psychotic disorder relative to CHR individuals who do not transition (Mechelli et al., 2011).

A decrease in volume in the postcentral gyrus in CHR relative to HC is consistent with previous research (Meisenzahl et al., 2008b). Dazzan and colleagues (2012) found that CHR individuals who transitioned to a psychotic disorder had less GMV in the postcentral gyrus than those who did not transition, implicating this region as a risk marker for the disorder.

Previous research also shows reduced GMV of the ACC in CHR individuals (Job et al., 2005; Mechelli et al., 2011; Meisenzahl et al., 2008b). Our findings replicate these previous

studies. Additionally, work by Smieskova and colleagues (2010) shows that decreased GMV in the cingulate cortex is predictive of individuals at-risk who transition to psychosis versus at-risk individuals who did not transition.

In addition to GMV differences between groups, we found ACC volume was related to social and role functioning and postcentral gyrus volume correlated with social functioning. The ACC is known to play a role in emotion and social behaviors (Adolphs, 2001), is critical for social cognitive processes such as person perception, theory of mind, and thinking about the self (Amodio and Frith, 2006), and has been implicated in deficits in social cognition in patients with schizophrenia (Dodell-Feder et al., 2013; Hooker et al., 2011; Tully et al., 2014). Additionally, cortical thickness in the ACC in CHR individuals is negatively correlated with negative symptoms, indicating a relationship between this area and social engagement (Fornito et al., 2008). Building on this work, our results demonstrate that reduced ACC volume is related to poorer social functioning. Given that the ACC is a region involved in the integration of social and emotional processing, these structural abnormalities in CHR indicate that the ACC may be part of the neurobiological explanation for social dysfunction in CHR individuals.

Findings from this study also indicate that reduced postcentral gyrus volume relates to social dysfunction. Research shows that the postcentral gyrus and related somatosensory areas are important for social cognition, particularly emotion recognition (Adolphs et al., 2000) and affective mentalizing/theory of mind (Hooker et al., 2008). Given the importance of the somatosensory cortex and related areas in social and emotional processing, a reduction in GMV in the postcentral gyrus in CHR individuals may indicate a deficit in processes necessary for effective social cognition and social interactions.

Though we had no a priori hypotheses of greater GMV in CHR relative to HC, we found

significantly greater GMV in the lateral prefrontal cortex LPFC. While these findings should be interpreted cautiously, it is notable that abnormalities in LPFC, particularly dorsal (D)LPFC, structure and function are often observed in CHR and individuals in both early and chronic phases of schizophrenia. A study looking at GMV in MZ twins discordant for schizophrenia, found that SZ twins had less GMV in the DLPFC than the non-affected twins (Cannon et al., 2002). This finding has led some researchers to suggest that changes in cortical grey matter in the DLPFC may be a result of the progression and/or onset of the disease (Cannon et al., 2002; Sun et al., 2009). Given that our sample is early clinical risk and the majority of these individuals will not go on to develop a psychotic disorder (Fusar-Poli et al., 2012a), it may be that greater GMV in the DLPFC is a protective factor.

Several limitations are worth noting. First, the groups were not matched for IQ. We anticipated this difference, as a decline in IQ is part of the disorder (Woodberry et al., 2010). Additionally, we did not use whole-brain correction for multiple comparisons due to our concern regarding Type II error at conservative thresholds; while this is warranted for initial investigations, future research should verify these initial findings with larger samples and more stringent statistical thresholds (Lieberman and Cunningham, 2009). Though we limited our focus to social and role functioning, these are global constructs, and the scores on our functioning measures undoubtedly reflect the cumulative influence of many social and cultural variables that were not examined in the study. Thus, to fully understand social dysfunction in CHR, it will be important to investigate the relative contribution of GMV as well as other factors, such as socioeconomic status, that are known to influence functional outcome. Moreover, the influence of GMV on social functioning is, most likely, mediated by specific social cognitive processes, such as emotion recognition and theory of mind (Dodell-Feder et al., 2013; Gibson et al., 2010).

Previous research has found the relationship between clinical symptoms and social functioning in CHR groups (Corcoran et al., 2011) as well as neurocognition and social functioning (Niendam et al., 2007), and social cognition and social functioning outcomes (Pinkham and Penn, 2006). Next steps include looking at the relationship between GMV, social cognition and social functioning in CHR.

By focusing on a CHR group, we are able to study potential biomarkers of schizophrenia-spectrum characteristics, in individuals who experience, at a lesser severity, the clinical, social, occupational, and cognitive difficulties similar to patients with schizophrenia disorder. Our research demonstrates that structural abnormalities are present in adolescents/young adults with attenuated positive symptoms who may or may not develop psychosis, and these differences are related to social dysfunction, a symptom also evident before the onset of a psychotic disorder (Cornblatt et al., 2012). These findings suggest that structural abnormalities, particularly in neural regions involved in social and emotional processing, may underlie the social dysfunction seen in CHR individuals, and could be a potential biomarker of functional outcome.

Paper #2 Neural Structure in Children at Clinical High Risk for Schizophrenia

In preparation for publication.

Authors

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Abstract

Studies investigating risk factors for schizophrenia and other psychotic disorders indicate that a convergence of biological and environmental factors, including changes in neuroanatomy, may lead to susceptibility for this disease. Additionally, the literature suggests that deficits are present in social functioning before the onset of psychosis and these deficits continue to affect functioning after transition to full-blown psychosis. The current study aims to understand social functioning and its potential neuroanatomical correlates before the onset of psychosis. We measured the grey matter volume (GMV) in typically developing and clinical high risk (CHR) children, ages 8-13, as using structural magnetic resonance imaging (MRI) and voxel-based morphometry (VBM). We also assessed the social functioning in the two groups. Results showed that CHR children had worse social functioning and less grey matter volume in the right insula, right caudate, left fusiform gyrus, left anterior cingulate cortex, and left medial orbital gyrus. Additionally, we found correlations between performance on social cognitive tasks and GMV. This research suggests that reduced GMV in certain areas may be a marker for psychotic disorders and may also be related to social functioning deficits as typically seen in this population.

Introduction

The typical age of onset for schizophrenia is in late adolescence or early twenties (Kirkbride et al., 2012). However, research has shown that the pathogenesis of schizophrenia spectrum disorders may start much earlier. Research has identified several early developmental risk factors for schizophrenia spectrum disorders including maternal prenatal nutrition (Kirkbride et al., 2012) obstetric complications (Rosso et al., 2000) childhood adversities, including trauma, bullying, and discrimination (Varese et al., 2012), as well as a genetic risk with heritability estimates between .65-.70 (Wray and Gottesman, 2012). Studies investigating these risk factors have drawn the conclusion that a confluence of biological and social environmental influences during sensitive periods of development, affect susceptibility for schizophrenia spectrum disorders (Holtzman et al., 2013; Maki et al., 2005; Walder et al., 2014). Of particular interest has been how changes in neuroanatomical structure relate to the development of schizophrenia spectrum disorders, both as a progression of the disease-state (Gogtay et al., 2011) (Borgwardt et al., 2011; Sun et al., 2009) and a predictive biomarker (Koutsouleris et al., 2015; Koutsouleris et al., 2009).

Several studies have begun to highlight the role that abnormalities in brain maturation in early periods of development are related pathogenesis of psychiatric disorders (Cannon et al., 2003; Lenroot and Giedd, 2006; Paus et al., 2008). Atypical changes in neuroanatomy have been identified as a possible predictive factor for psychotic disorder. Reductions in grey matter volume (GMV) are consistent across multiple risk groups including clinical high risk (CHR) (Brent et al., 2013), familial risk (Bois et al., 2014), personality risk (DeRosse et al., 2015) as well as throughout stages of the disorder. Additionally, studies of typical brain development highlight early childhood through puberty as a critical period of brain maturation, and a period of

neuroanatomical development likely to be affected by insults to the brain (Toga et al., 2006). Elucidating abnormalities in GMV in children at risk for psychosis is important to understanding brain-behavior relationships related to psychotic symptoms and social dysfunction, as well as further clarifying the types and timing of structural changes in the progression of this disease.

Grey Matter Abnormalities in CHR

Meta-analyses of neuroanatomical studies of CHR young adults have demonstrated that these individuals have less GMV in temporal, limbic, and prefrontal regions relative to non-CHR comparison groups (Brent et al., 2013). Within these regions more specifically, studies have shown significant differences in GMV in areas of the brain related to social information processing, in limbic regions: including the insula (Borgwardt et al., 2007) (Fusar-Poli et al., 2011), anterior cingulate cortex (ACC) (Fusar-Poli et al., 2011) (Lincoln and Hooker, 2014) (Pantelis et al., 2003b), and temporal regions: superior temporal gyrus (Fusar-Poli et al., 2011; Takahashi et al., 2009a), temporo-parietal junction (TPJ), and regions of the prefrontal cortex: inferior frontal gyrus (Iwashiro et al., 2012), and medial prefrontal cortex (Cannon et al., 2015; Fusar-Poli et al., 2011; Sun et al., 2009). Overall these studies support the idea that individuals with a clinical high risk for schizophrenia have grey matter abnormalities that are similar, though generally less severe, to patients with schizophrenia (Borgwardt et al., 2011).

Additionally, research has shown that individuals who were recognized as prodromal and transitioned to a psychotic disorder had even greater reductions in grey matter versus those recognized as prodromal and did not transition (Borgwardt et al., 2011) (Smieskova et al., 2010). Specifically decreased GMV in the insula, prefrontal cortex, the cingulate cortex, and overall GMV in the cerebellum were predictive of those individuals at-risk who transitioned to psychosis versus the at-risk individuals who did not transition (Smieskova et al., 2010). Cannon

and colleagues (Cannon et al., 2015) found that CHR individuals who later transitioned to psychosis showed greater loss of grey matter, as measured by cortical thickness, in prefrontal regions than individuals who did not transition, of note these participants were not exposed to antipsychotics between the time of the first scan and the scan after the transition, suggesting that antipsychotics do not explain the progressive loss of grey matter in the transition to psychosis. These findings suggest that while some abnormalities in grey matter volume suggest an increased vulnerability for psychosis, other structural changes may be directly related to the process of transition to psychosis (Borgwardt et al., 2011).

While studies have advanced our knowledge of structural abnormalities in young adults and adolescents at risk for schizophrenia, to date there are no studies looking at structural abnormalities in school-aged children at clinical risk for psychosis. Children during this developmental period offer a particularly valuable snapshot in time on the development of a psychotic disorder. Theories regarding structural abnormalities have suggested that in concordance with other risk factors, abnormalities in brain development through puberty may partially explain the neurological abnormalities seen in adults with psychotic disorders. Research on adolescent brain development has demonstrated a decrease in grey matter volume throughout adolescence, which could be a result of several different factors including increased myelination, pruning of neural connections, and/or cell shrinkage (Sowell et al., 2003).

Previous research has suggested that structural abnormalities in psychotic disorders may be a result of over-pruning, or a yet identified disruption of this process, in adolescence (Keshavan et al., 1994) (Keshavan and Hogarty, 1999). A review of the structural changes in childhood onset schizophrenia, adolescents at clinical risk for psychosis, and typical patterns in children and adolescents, provides support for an accelerated progression of the maturational

process seen in typical development (Gogtay et al., 2011). Research suggests that there is less grey matter in specific regions in both the premorbid and prodromal phases of psychotic disorders, and that greater loss of GMV has been associated with the transition to psychosis. Additionally, research looking at behavioral markers suggests that social dysfunction, particularly the severity of dysfunction in adolescence is a significant predictor of the transition to psychosis. While research has focused on the relationship between structural changes and psychotic symptoms (Cannon et al., 2015), few studies examined the relationship between brain structure and social functioning. More specifically, no studies, to our knowledge, have looked at structural abnormalities and social functioning in school-aged children.

Previous research on the neuroanatomy of the at-risk state appears to involve specific GMV deficits in regions associated with social cognition. Extensive work has been done on a network of regions that are involved in different aspects of social cognitive processing. Studies have also found that these regions appear to be compromised in the progression of schizophrenia disorders. Processing social stimuli requires a group of regions, some focused on perception of social stimuli including the STS, which responds to biological motion, facial expression, and gaze (Adolphs, 2001). Other regions have been strongly tied to understanding the mental states of others including the TPJ, the STG, somatosensory and related cortices, precuneus, anterior cingulate cortex, inferior frontal gyrus, and the medial prefrontal cortex (Adolphs, 2001, 2009; Amodio and Frith, 2006; Saxe and Powell, 2006). Additional limbic/paralimbic regions including the insula, amygdala, and anterior cingulate cortex have been show to be related to the experience of empathy (Adolphs, 2010; Decety and Jackson, 2004).

Studies with young adult and adolescent at-risk individuals have found reduced grey matter volume prior to the onset of schizophrenia in these regions related to social cognitive

processing: STG (Borgwardt et al., 2007; Lincoln and Hooker, 2014; Takahashi et al., 2009b), somatosensory and related cortices (Lincoln and Hooker, 2014), precuneus (Borgwardt et al., 2007), ACC (Fornito et al., 2008; Lincoln and Hooker, 2014; Mechelli et al., 2011), inferior frontal gyrus (Chan et al., 2011), mPFC (Cannon et al., 2015), insula (Takahashi et al., 2009a) (Borgwardt et al., 2007), and amygdala (Chan et al., 2011; Job et al., 2003).

Knowing that these regions specifically relate to social cognition and social cognition affects social functioning, the relationship between GMV in these regions and social functioning may provide insight into an understudied brain-behavior relationship. Additionally, this paper focuses on GMV in these regions in a group of children, ages 8-13, at risk for a disease with the core characteristic of poor social functioning. The brain-behavior relationship may provide insight into onset, progression, and possible interventions for this disorder.

Social Functioning Deficits in CHR

Social functioning deficits are present before the onset of psychosis, in individuals at genetic risk for psychosis who fail to show overt positive symptoms, and in persist in at-risk individuals who never go one to develop a psychotic disorder (Cornblatt et al., 2012; Salokangas et al., 2013). These symptoms are not treatable by medication in patients, and are present when a patient is not acutely psychotic (Bond et al., 2004; Hamilton et al., 2000). Outcomes for non-converters suggest that this population remains socially impaired, with some improvement over time relative to individuals who convert to psychosis, but still demonstrating significantly lower social functioning relative to non-psychiatric individuals (Addington et al., 2011). Social impairment is a persistent problem for CHR individuals, even when positive and negative symptoms have remitted. Additionally, severity of social dysfunction in adolescents at risk for

psychosis is a significant predictor of transition to psychosis, above and beyond baseline measures of positive and negative symptoms (Tarbox et al., 2013).

Brain Structure and Social Functioning in Psychotic Disorders

Work across various stages of schizophrenia spectrum disorders, including schizophrenia (Hooker et al., 2011; Sasamoto et al., 2011), first-episode psychosis (Asami et al., 2012; Malla et al., 2011) and at-risk groups, CHR (Lincoln and Hooker, 2014), and genetic high risk (McIntosh et al., 2011), demonstrates that less GMV in regions associated with social cognitive processing is related to poorer social functioning.

One caveat to these studies is that their focus is later in the progression of development toward a psychotic disorder, and provides little information on what may be occurring at younger ages. Previous research suggests that there are progressive structural changes throughout the development of psychosis (Ziermans et al., 2012), yet the timing, course, and pathophysiological nature of these changes remains unclear. We do not know whether differences in GMV may be present in a younger population experiencing similar symptoms, or whether this is a progressive degeneration triggered by other biological changes associated with the onset of puberty.

Here, we aim to understand structural abnormalities before the onset of psychosis, by focusing on a younger age group than is typically studied in this research. The participants range in age from 8-13 (late childhood into early adolescence) with our target population presenting with psychotic like symptoms at a frequency and severity that puts them at risk for the development of a psychotic disorder. Looking at this age range provides a unique opportunity to add to the developmental picture of clinically at-risk youth and the processes related to psychotic symptoms.

Studies that have looked at theory of mind performance in CHR children and adolescents have reported mixed findings regarding social cognitive performance, with some reporting overactive or "hyper theory of mind" (Clemmensen et al., 2014) no impairments relative to typically developing peers (Stanford et al., 2011) and relative impairments in theory of mind between at-risk groups and controls (Healey et al., 2013). Despite the variability in findings, we predict that CHR children will show relative impairment to their TD peers on social cognitive tasks and self-report measures of social cognitive processing. Additionally, consistent with previous research on social functioning in at-risk individuals, we predict that CHR children will have lower social functioning as indicated by self and parent-report forms and interviewers with an examiner relative to their typically developing (TD) peers.

We expect that children at risk for psychosis will have abnormal grey matter volume in social cognitive regions relative to age-matched typically developing peers. Specifically, we predict that CHR children will have less GMV in the STS, STG, TPJ, MPFC, amygdala, and somatosensory related cortices, relative to a typically developing group of children. While the nature of the disruption of brain maturation in at-risk populations is unclear, we hypothesize that these particular regions will have less GMV given previous research in young adults indicating less GMV in these regions and previous research that suggests that less GMV is related to poorer social cognition and social functioning in patients with schizophrenia (Hooker et al., 2011) and at-risk individuals (Lincoln and Hooker, 2014). Additionally, when looking at the relationship between brain and behavior, we hypothesize that GMV in these regions will be positively related to social functioning and social cognitive ability across both groups.

Methods

Participants

Participants were 41 children aged 8-13 years. Participants were recruited in person from community centers, mental health clinics, and area hospitals, as well as via fliers and online advertisements. Harvard Internal Review Board (IRB) approved this study and consent was obtained by a legal guardian and assent obtained by the child for both the behavioral testing and the MRI. Exclusion criteria for both groups included: history of neurological problem (e.g. seizures, loss of consciousness >20 minutes), current substance use in the last 6 months, or an IQ <70, as measured by the Wechsler Intelligence Scale for Children, 3rd Edition (WISC-III) (Wechsler, 1991). Participants with any MRI contraindications as evidenced on the MR Screening Questionnaire were excluded from MRI studies.

CHR group (n=11). Eleven children between the ages of 8-13 who met criteria for clinical high risk (CHR) based on the Structured Interview for Prodromal Syndromes (SIPS) (McGlashan, 2001) took part in this study. Inclusion criteria included receiving a 3-5 score on the 5 positive symptoms subscales of the SIPS (unusual thought content, suspicion/paranoia, perceptual aberrations, grandiosity, and disorganized communication), occurring at a frequency of 3-4x a week, and whose symptoms had started or worsened in the last year. Participants were excluded if they had any of the following conditions: history of neurological impairment (including but not limited to history of loss of consciousness >30 minutes, seizures, stroke), or a history of comorbid psychiatric disorder that was not better accounted for by psychotic-like symptoms. Seven of the 11 children were currently taking antipsychotic medication.

Several participants were included who had comorbid Axis I disorders that were either related or risk factors for psychotic disorders or better explained by the prodromal state, including: Attention Deficit Hyperactivity Disorder, Post-traumatic Stress Disorder (PTSD),

Major Depressive Disorder, Panic disorder, Obsessive Compulsive Disorder (OCD), Generalized Anxiety Disorder, and a history of PTSD or MDD. A recent meta-analysis by (Fusar-Poli et al., 2014) showed that CHR individuals are characterized by high rates of comorbid depressive and anxiety disorders in addition to prodromal symptoms, and these symptoms exacerbate functional impairment (Fusar-Poli et al., 2014). This research suggests that the affective symptoms often present in the prodromal state, are a part the disease state and therefore a critical piece of the abnormalities that have been seen in the literature. Our conceptualization of these symptoms as characteristics of the prodromal state is consistent with previous researchers who have provided data that argue affective symptoms are part of the prodrome (Cornblatt et al., 2003)

TD group (n=30). A group of 30 typically developing, age, education, and IQ-matched children ages 8-13 was recruited for participation in this study. Inclusion criteria for typically developing children were: ages 8-13, English speaking, and at least one custodial parent available. Exclusion criteria specific to the TD group included: a current or past history of mental illness as measured by the K-SADS, or who scored a 2 or above on any question on the SIPS was be excluded from the study, or current use of psychotropic medication. Additionally, participants were excluded if they had first degree relative with a history of psychotic disorders, bipolar disorder, or autism spectrum disorder.

Clinical Assessments

Structured Interview for Prodromal Syndromes. The SIPS was originally developed to be used with children as young as 12 years of age. The SIPS is a structured interview assessing four areas of clinical symptoms that might indicate risk for the development of a psychotic disorder in children, adolescents, and young adults. The SIPS was originally developed to be used with children as young as 12 years of age. In order to use this measure with a younger

population in collaboration with colleagues at Children's Hospital Boston, we created a downward extension of this measure, changing the vocabulary to a 3rd grade reading level, without altering the content.

Social Cognition Assessments

The social cognition tasks in this study investigate different aspects of social cognition including emotion recognition, theory of mind, empathy, and emotion regulation.

Reading the Mind in the Eyes. The Reading the Mind in the Eyes Task (Baron-Cohen et al., 2001) requires the child to look at pictures of the eye area of faces and infer the emotional state of the individual. Participants were read a set of instructions and then presented with pictures of eyes. Each picture had four emotions listed and the participant was instructed to pick one of the four emotions. Each picture had only one right answer. The participant would verbally select which they thought was the correct emotion and the researcher would record the participants' responses. There were a total of 28 pictures presented.

Hinting Task. Originally developed for adults, but modified later by (Schenkel et al., 2008) for use with children and adolescents, the Hinting Task is a performance measure of theory of mind ability and empathy in children, in which children are asked to answer questions probing their ability to accurately interpret potentially awkward situations making mental inferences about the story character's cognitive and affective mental states. Participants were shown the printed stories while a researcher read the story aloud. The researcher then asked what a character in the story really meant by his/her statement. If the child answered this question correctly, they received a score of two. If the child answered this question incorrectly, they received another prompt and an additional question. Answering the second question correctly would earn a score of one. If they child did not answer either question correctly, they would receive a score of zero for that item. There were 10 stories with a maximum score of 20.

Social Functioning Assessments

Global Functioning Social Scale and Role Scale. Global Functioning Scales Social Scale (GFS: Social) and Global Functioning Scales Role Scale (GFS: Role)(Cornblatt et al., 2007) are interview-based measure that assesses friend and family relationships (social) and occupational, academic, or home-making performance (role). The scales yield social and role functioning scores between 0-10 with higher scores indicating higher levels of functioning. All children were assessed in regard to academics as role functioning.

Social Skills Improvement System-Rating Scale. A self-report measure for children, parents, and teachers, the SSIS (Gresham, 2008) rates three domains of functioning: social skills, problem behaviors, and academic competency. Of particular interest in this study were child and parent ratings of social skills, as well as child and parent ratings of problem behaviors, which included inherently social situations such as bullying, or behaviors that would affect social functioning included externalizing and internalizing behaviors. The SSIS has two separate forms, one for children ages 5-12 and another for children ages 8-13. To complete the forms, children and parents are asked to rate, separately, how true a statement is on a 4-point scale of *not true, a little true, somewhat true,* and, *very true.*

MR Image Acquisition and Processing

Image Acquisition. Structural images were acquired on a 3.0 Tesla Siemens Tim Trio scanner using a 32-channel head coil. A three-dimensional anatomical T1-weighted resolution scan (MEMPRAGE) was acquired with the following parameters: 40 slices per volume, TR=2.56s, TE=30ms, flip angle=85 degrees, with voxel size of 3x3x3.

Image Processing. Structural analysis was done using standard voxel based morphometry (VBM) with Statistical Parametric Mapping (SPM8) (Wellcome Department of

Cognitive Neurology, London, United Kingdom; http://www.!l.ion.ucl.ac.uk/spm/software/spm8). Based upon Statistical Parametric Mapping (SPM) techniques, voxel-based morphometry is an unbiased method of looking for specific structural differences in magnetic resonance images (MRI) between groups. VBM analyses evaluate the probability that each voxel of the MR image is grey matter, white matter, or cerebral spinal fluid (CSF). The images are spatially normalized to fit into the same space and then the density of these images is compared on a voxel by voxel basis (Ashburner and Friston, 2000; Honea et al., 2005; Williams, 2008). VBM analyses allow researchers to compare structural abnormalities between individuals with schizophrenia spectrum disorders and healthy controls as well as explore how these abnormalities are related to performance on specific social cognitive tasks.

Statistical Analysis

For the whole brain analysis, a between groups *t*-test was performed to detect differences in GMV between the TD and CHR groups. Total intracranial volume (TIV) was calculated by summing GM and WM and used as a covariate of no interest. Given known developmental differences in brain regions that can exist between children 8-13, age was also used as a covariate of no interest. Inferences were made using a statistical threshold of $p<.001$, k=20 uncorrected for multiple comparisons. Grey matter volume was extracted (for each participant) from regions that were significantly different between groups using the SPM8 MarsBar tool. These volumes were correlated with social cognitive and social functioning variables.

Results

Behavioral Performance

Group demographics are in Table 2.1. Behavioral performance on theory mind tasks as well as self-reported empathic and perspective taking abilities showed no differences between groups (Table 2.2). There was a trend for poorer performance on the Mind in the Eyes in CHR relative to TD (t=1.91, p=.07). As hypothesized, both CHR children and their parents reported poorer social functioning (t=2.10, p=.05; t=4.27, p=.00) and greater social problems (t=6.61, p=.00; t=7.77, p=.00) relative to typically developing children. Interviewer rated measures of social functioning also suggest poorer social skills in CHR children relative to TD children (t=6.76, p=.00) (Table 2.2).

Grey Matter Volume Analysis

Regional differences in GMV: CHR<TD. Compared to TD, CHR showed less GMV in the right insula, right caudate, left fusiform gyrus, left ACC, and the left medial orbital gyrus (Table 2.3).

Regional differences in GMV: CHR >TD. Compared to TD, CHR showed greater GMV in bilateral precentral gyrus and right supplementary motor area (Table 2.3).

GMV and Social Functioning Analysis

We extracted volume from three regions, the insula, caudate, and ACC. We chose to extract volume from regions with a voxel size greater than 20 (k>20) which included the insula and caudate. Additionally, we chose to extract volume from the ACC, despite not meeting the voxel threshold, because of previous literature that strongly supports differences in ACC volume in CHR individuals relative to healthy controls. We then correlated these volumes with our behavioral measures of social cognition and social functioning.

Whole Group Correlations. To investigate the brain-behavior relationship, we looked at GMV in relation to social cognition and social functioning. Across the whole group we performed a correlation analysis between GMV in the ROIs and social cognitive variables including the Reading the Mind in the Eyes and Hinting Task. We found a significant positive correlation between insula volume and performance on the Reading the Mind in the Eyes task (r=.421, p<.05) (Figure 2.1).

We then looked at the relationship between GMV and social functioning variables. We found a significant negative relationship between parents' reports of problem behaviors and volume in the ACC (r=-.584, p<.01), as well as a significant positive relationship between parents' reports of children's social skills and volume in the ACC (r=.349, p<.05) (Figure 2.1).

Table 2.1. Clinical and Demographics

		HC N=30	CHR N=11	Differences between groups
Gender:		12 male	6 male	U=141 p=.495
Age: mean (SD)		10.60 (1.83)	10.36 (1.91)	t(39)=0.362 p=0.72
Grade: mean (SD)		5.20 (2.00)	4.50 (1.90)	t(33)=0.948 p=0.35
IQ: mean (SD)		111.72 (17.39)	104.63 (14.89)	t(31)=1.04 p=0.31
SIPS Scale: mean (SD)				
	Positive	0.43 (0.74)	11.45 (3.39)	t(37)=-16.56 p=.000
	Negative	0.11 (0.32)	10.27 (4.20)	t(37)=-12.99 p=.000
	Disorganized	0.11 (0.42)	3.55 (2.16)	t(37)=-8.20 p=.000
	General	0.43 (0.92)	6.73 (3.20)	t(37)=-.963 p=.000

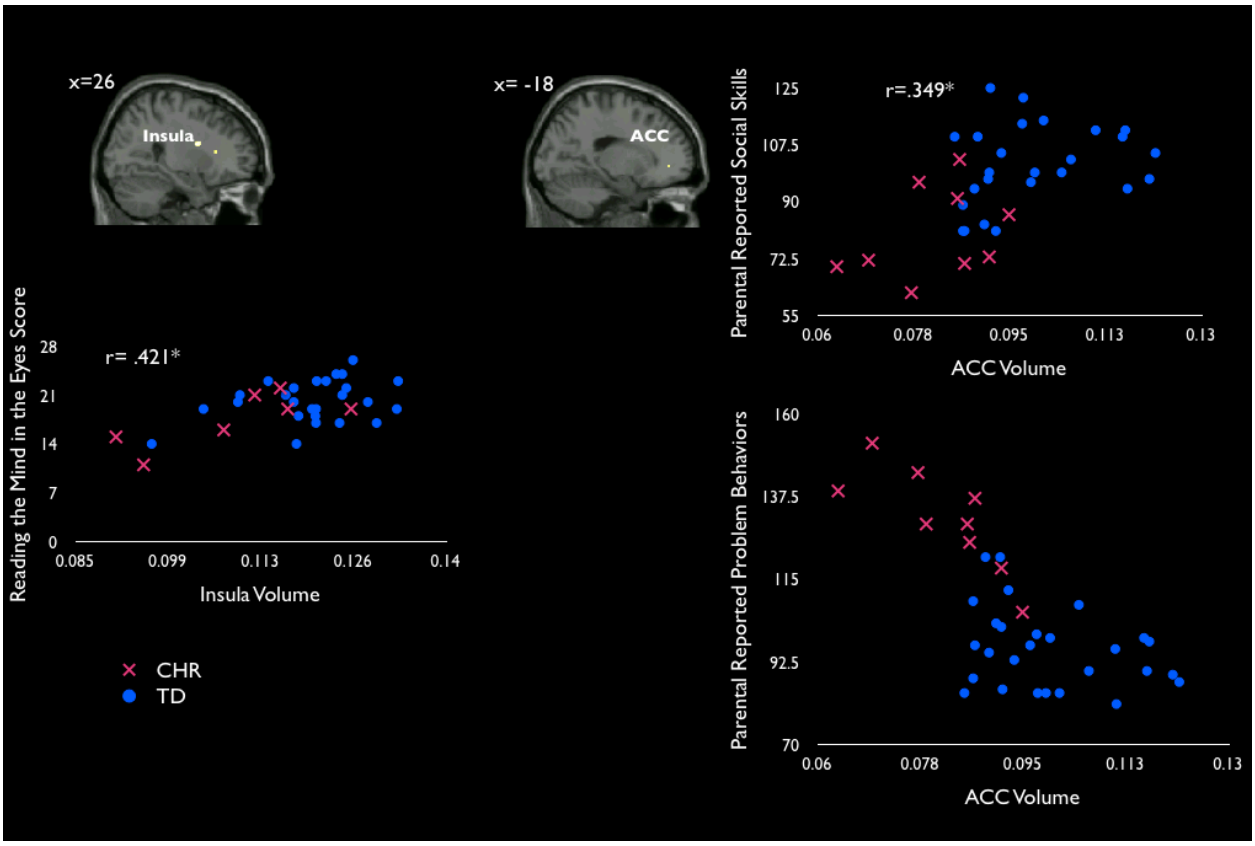

Figure 2.1. Volume from regions of interested identified in the whole brain analysis TD > CHR was correlated measures of social cognition and social functioning.

Table 2.2. Social cognition and social functioning variables

	HC N=30	CHR N=11	Differences Between Groups
Reading the Mind in the Eyes: mean (SD)	20.15 (3.00)	17.57 (3.82)	$t(31)=1.91$ $p=0.07$
Hinting Task: mean (SD)	17.00 (2.76)	15.60 (1.43)	$t(35)=1.52$ $p=0.14$
Social Skills Improvement Scale (SSIS): mean (SD)			
Self Report: Social Skills	102.39 (14.30)	90.25 (16.18)	$t(34)=2.10$ $p=0.05$
Self Report: Problem Behaviors	90.71 (8.73)	117.75 (14.57)	$t(34)=-6.61$ $p=0.000$
Parent Report: Social Skills	103.22 (13.81)	80.44 (13.96)	$t(34)=4.27$ $p=0.000$
Parent Report: Problem Behaviors	96.15 (10.99)	131.22 (13.88)	$t(34)=-7.77$ $p=0.000$
Global Functioning Scale: mean (SD)			
Role	8.35 (0.98)	8.46 (0.76)	$t(34)=5.55$ $p=.000$
Social	6.00 (1.49)	6.40 (0.97)	$t(34)=6.76$ $p=.000$

Tale 2.3. GMV differences between CHR and TD, controlling for TIV, and age, $p<.001$, k=20

Anatomical Regions	R/L	BA	Voxel (mm)	x	y	z	*t*
TD > CHR							
Insula	R	48	21 (567)	26	22	10	3.86
Caudate	R	48	58 (1566)	27	3	19	3.85
Anterior Cingulate Cortex	L	32	3 (81)	-18	42	2	3.49
TD < CHR							
Precentral gyrus	R	6	204 (5508)	30	-16	75	4.98
Precentral gyrus	L	4	59 (1593)	-38	-16	64	3.96
Supplemental Motor Area	R	6	33 (891)	4	20	61	3.76

Table 2.4: Correlations between GMV and social cognition and social functioning variables

	Insula	Caudate	Anterior Cingulate Cortex
Within Group (*n*=41)			
Social Cognition			
Hinting Task	.031	.302	.122
Reading the Mind in the Eyes	.421*	.134	.187
Social Functioning			
GFS: Role	.049	.134	.239
GFS: Social	-.08	.057	.170
SSIS Social Skills-Child	-.028	.042	.163
SSIS Social Skills-Parent	-.148	-.218	.349*
SSIS Problem Behavior-Child	-.044	-.267	.056
SSIS Problem Behavior-Parent	-.043	.077	-.584**

p<.05, p<.01***

Discussion

This study focused on brain structure and social functioning in an under-researched age group within the prodromal literature, children ages 8-13 at clinical risk for schizophrenia spectrum disorders. Using voxel based morphometry we looked at grey matter differences between CHR individuals and a matched group of typically developing children. Additionally, we looked at how differences in regions related to social cognitive processing may be related to performance on social cognitive tasks and measures of social functioning.

Our results that CHR children demonstrate poorer social functioning relative to TD peers, as assessed by both interview and self-report measures, are consistent with previous work with adolescents and young adults at clinical risk for psychotic disorders (Lincoln and Hooker, 2014) (Cornblatt et al., 2012) (Meyer et al., 2014). We saw a trend in social cognitive performance on the Eyes Task, with the CHR showing a sub-threshold poorer performance on this task relative to TD peers. While this finding is not inconsistent with previous work, it does not confirm whether behavioral differences on ToM tasks in school-aged children at risk for psychosis exist relative to their peers. However, given the small sample size of CHR children, we are hesitant to throw out this sub-threshold finding without further investigation with a larger group of CHR children.

Second, consistent with previous studies, we found reduced grey matter volume in limbic regions such as the anterior cingulate cortex and the insula. These results are consistent with previous work that focused on older adolescents and young adults, and suggest that GMV differences can be seen in school-aged children at risk for psychosis, even before the onset of puberty. We also saw reduced GMV in the caudate. While research has shown some association with social cognition and the caudate (Kemp et al., 2013), we had not hypothesized this region to be different in CHR children relative to TD children. While there is some research to support

abnormalities in the caudate in at-risk populations including genetic high risk (Nenadic et al., 2015) other research suggests that caudate volume does not differ between at-risk individuals and healthy controls prior to illness onset (Hannan et al., 2010).

Our third main finding is that of the aforementioned regions, GMV in the ACC and the insula, were related to performance on theory of mind tasks and measures of social functioning across the whole group. More specifically, there was a specific association between GMV in the insula and performance on a theory of mind task, with greater volume related to better performance. Additionally we found an association between volume in the ACC and parent reports of social skills and social problems.

Alterations in the ACC have been shown in psychotic disorders and in adolescents and young adults at clinical risk for psychotic disorder and these abnormalities differentiate between CHR individuals who do not transition versus those that do transition within a year's time (Fornito et al., 2008). Volume in the ACC has been shown to be related to social functioning in other populations. Fujiwara and colleagues (Fujiwara et al., 2007) found a relationship between abnormal structure in the ACC in patients with schizophrenia and impairment on an emotion attribution task. Additionally previous work in our lab with young adults at risk for schizophrenia demonstrates a relationship between ACC volume and social functioning. The current findings are in line with these studies, suggesting that differences in ACC volume can be seen in prodromal individuals, uniquely in this case, school-aged children, and that volume is related to measures of social functioning.

GMV in the insula was significantly positively related to performance on the Eyes task, and parent and child reports of social problems, and interviewer measures of social and role functioning. Previous research has shown that grey matter reduction in the insula may be related

to both a psychosis vulnerability, and, as evidenced by transition studies, a part of the progression toward a psychotic disorder (Takahashi et al., 2009a). Our study supports the idea that reduced GMV in the insula may be a vulnerability marker for psychosis, and that part of its role may be related to social cognitive and social functioning impairment.

When looking at greater GMV in CHR relative to TD, we found greater GMV in the precentral gyrus and supplementary motor area. We had no a priori hypotheses about increased grey matter volume in this group. Thinning or pruning of the cortex in healthy children typically begins in primary sensory and motor cortexes and then secondary sensory-motor cortices (Jernigan et al., 2011). Given that the typical brain maturation process is hypothesized to be disrupted in individuals who later develop psychosis, it is possible that the difference in volume in these regions is related to an abnormality in brain development. Another possibility is that alterations in the prefrontal cortex may be seen closer to the onset of a psychotic disorder and related to a specific symptom type. A study by Cannon and colleagues (Cannon et al., 2015) found that accelerated loss of GMV in the prefrontal cortex was specifically related to CHR individuals who had higher levels of unusual thought content at baseline.

Limitations

The primary limitation in this study concerns the lack of correction for multiple comparisons in our VBM statistics. These results should be interpreted cautiously because results do not survive correction. We attempted to balance type I and type II errors by using a less stringent threshold, which is an important consideration for a new field of study (Lieberman and Cunningham, 2009). These findings should be replicated with larger samples. Additionally, using regions identified as significantly different between groups for the correlational analysis, within the entire sample, may be biased and has the potential for inflated correlations. At the

same time, we have strong reason to believe that these findings are not erroneous, as previous research as indicated these regions are related to social functioning and social cognition in other populations (Hooker et al., 2011) (Lincoln and Hooker, 2014).

Additionally, the majority of individuals in the CHR group were taking or had recently been taking antipsychotic medication, teasing out the effects of medication on brain development is not possible in this current study. At this time the effects of antipsychotics on brain development in school-aged children is unclear (Arango et al., 2012) (Ziermans et al., 2012) (Torres et al., 2013).

In summary, CHR children have report poorer social skills overall, and show a trend of poorer performance on a social cognitive tasks. Additionally, CHR children show less grey matter volume in regions related to social cognitive processing including the STG, insula, and ACC relative to typically developing children. Differences in social cognitive performance and social functioning are associated with differences in grey matter volume in these regions.

Paper # 3: The neural basis of social cognition in typically developing children and the relationship to social functioning

In preparation for submission

Authors

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Abstract

This study looks at differences in neural activity during a novel theory of mind task (ToM) in typically developing children, and the relationship between activity in these regions and social functioning. The movie-mentalizing task asks children to predict a character's mental state after a social interaction based on both verbal and non-verbal information. The task taps into affective theory of mind, or affective mentalizing, a critical skill for effective social interactions. We hypothesized that regions within the ToM network would be recruited for ToM processing. Additionally, we predicted that activation in these areas would be related to behavioral measures of social cognition and social functioning. The results support our first hypothesis; we found that typically developing children ages 8-13 recruit regions of the theory of mind network including the STS and TPJ for theory of mind processing. We did not find a relationship between neural activity for ToM and social cognition or social functioning.

Introduction

Theory of mind, or the ability think and reason about others' mental states, is critical for effective social interaction and communication. Given the significant relationship between theory of mind and social functioning, it is important to understand if the neurobiological response to thinking about the mental states of others is related to social functioning in children and adolescents. Deficits in theory of mind have been seen a variety of psychiatric disorders including autism spectrum disorders (Baron-Cohen, 1995; Happe and Frith, 1996), and psychotic disorders (Bora and Pantelis, 2013), and has been associated with social functioning impairment, characteristic of these disorders. Research investigating theory of mind tasks in healthy adults has demonstrated the recruitment of a network of regions that consistently responds to ToM tasks, including: the superior temporal sulcus (STS), temporoparietal junction (TPJ), and the medial prefrontal cortex (MPFC) (Saxe et al., 2004); therefore these regions are of primary interest in this study.

Additionally, behavioral research has extensively studied the development of theory of mind from infancy through adulthood, as well as the relationship between theory of mind and other aspects of social cognition to social functioning in children and adolescents. However, to our knowledge, no studies have bridged the gap from the neurobiology of theory of mind processing to social behavior in children. The following study tackles this gap in the literature by investigating the neural basis of theory of mind in school-aged children and the relationship among neural activity, theory of mind performance, and social functioning.

Development of Theory of Mind

Theory of mind develops during childhood after other cognitive building blocks such as language, joint attention, and other aspects of executive functioning develop (CITATION).

Behavioral research provides mixed information on the age at which children develop theory of mind with some studies suggesting 15-month old infants have the capacity to reason about mental states (Onishi and Baillargeon, 2005). Early in development, research suggests that infants and toddlers can make connections between physical cues such as gaze or facial expressions to behaviors related to perception or emotions (Saxe et al., 2004). Later in development, children appear to develop an ability to hold a mental representation of someone's mental state, and then use that mental representation to reason about beliefs, goals, desires, and emotions (Saxe et al., 2004).

More complex theory of mind abilities, such as those tapped by the false belief task, (e.g. Anne puts the ball in a box. Anne leaves the room. Mary moves the ball to the basket. Anne comes back. Where does Anne think the ball is?), appear to develop around the age of 4-5, with children as young as 3 typically failing these tasks, and 5 year olds successfully understanding that Anne will look where she last saw the ball, and not in the true location of the ball (Wimmer and Perner, 1983). This false belief paradigm is perhaps one of the most widely used tasks in ToM research. Research indicates that children ages 3 and younger, who fail the task, do not lack complete theory of mind, but rather that they lack a representational theory of mind (Saxe et al., 2004), which appears to develop in typically developing children between ages 4 and 5. Research looking at second-order false belief scenarios (e.g. Where does Anne think that Mary thinks the ball is?) finds that preschoolers on average fail this task, but by age 6 children can successfully complete second-order false belief tasks (Miller, 2009). Differences across early development for theory of mind ability have been linked to language, and executive functioning (de Villiers, 2014).

Neurobiology of Theory of Mind in Children.

Neuroimaging work has identified a network of brain regions that support theory of mind processing including posterior superior temporal sulcus (pSTS), superior bilateral temporoparietal junction (TPJ), and medial prefrontal cortex (MPFC) (Mar, 2011; Saxe and Powell, 2006; Van Overwalle, 2009). Importantly, recent work has shown that children and adults recruit the same regions during theory of mind tasks (Kobayashi et al., 2007; Saxe et al., 2009). Furthermore, there are important developmental changes in these regions; specifically the TPJ becomes more selective for mental state information relative to social information with age (Gweon et al., 2012; Saxe et al., 2009). More specifically, an adult TPJ will treat non-mental social and physical information generally the same by not responding to it, and appearing to care only about mental state information, whereas a child TPJ is initially responding to social information regardless of mental state content and over time becomes more selective for mental states. A study by Gweon and colleagues (2012) with children ages 5-11, found that within ages 5-11, the TPJ response became more specific for stories about mental states than physical appearance or relationships. Research also indicates changes in the MPFC neural activity with age. Moriguchi and colleagues (2007) found that activation in the dorsal MPFC increased with age during a ToM task. So while children at age 5 can reliably pass a false-belief task, we know that their theory of mind abilities are not as developed as adults; neurobiological studies showing differences in neural regions with age provide information as to why and how theory of mind abilities continue to develop throughout childhood and adolescence. Previous research looking at changes in theory of mind activity through puberty has come up with two competing theories to explain the changes in brain function in social cognitive regions during this time period. The first theory, neural efficiency, suggests the idea that in younger children these brain regions are

still in development and require more oxygen and energy, thus showing greater activation at younger ages and less activation or efficiency throughout adolescence (Burnett and Blakemore, 2009). The second theory suggests that younger children may be using a different strategy to understand complicated social interactions, and the pattern of the network of regions may differ as children age (Burnett and Blakemore, 2009).

Recent research has begun to look at this neural network and its relationship to aspects of social functioning in adults. For example, greater activity in ToM regions is related to better daily social functioning (Dodell-Feder et al., 2014) and less neural activity in the MPFC during a mentalizing task was related to social exclusion in healthy adults (Powers et al., 2013). Further research is necessary to elucidate the nature of this brain-behavior relationship, as well as to look at how it functions across the lifespan.

Social Cognition & Social Functioning in Children

Previous studies with typically developing children indicate that social cognition, specifically theory of mind, is related to a child's friendship formation and friendships. Fink and colleagues (2015) found that theory of mind ability at age 5 predicted children's development of friendships at age 5 and chronic friendlessness through age 7; with children with poorer theory of mind skills failing to make friends and remaining friendless throughout this development period.

Caputi and colleagues (2012) found that theory of mind was positively related to teacher's ratings of children's prosocial behavior over multiple time points. Additionally, individual differences in theory of mind ability were related to greater peer acceptance. Girls, ages 8-13, with better performance on theory of mind tasks, were less likely to report challenges making friends and feeling lonely (Devine and Hughes, 2013). Theory of mind performance at age five was predictive of being the victim of bullying, or a bully-victim (an individual first

victimized and then a bully) in adolescence, above and beyond factors such as IQ, gender, and childhood maltreatment (Shakoor et al., 2012).

Research has established a neural network for thinking about the mental states of others, such that these regions support theory of mind processing. Additionally, studies have found that behavioral measures of theory of mind are related to social functioning in day-to-day life. What remains less well understood is the brain-behavior connection between neural activity for ToM and social functioning, particularly in school-aged children. The following study aims to fill this gap by investigating the relationship among neural activity in a novel ToM task, behavioral measures of theory of mind, and social functioning.

The current study has three objectives 1) to look at the ToM network in school-aged children in response to an affective theory of mind task, versus the typical cognitive ToM task, 2) to test a novel, more ecological valid theory of mind task, as many tasks use a false belief paradigm which has come under scrutiny regarding the demands (e.g. attentional, linguistic, executive control) of this particular paradigm that may better account for differences in performance on this task (Bloom and German, 2000; Perner and Leekam, 2008), and 3) to understand how activation in brain regions involved in ToM processing relate to both social cognitive processing and social functioning.

In this study, we address these issues by scanning children using a novel theory of mind task. Our task, the movie-mentalizing task, gets closer to the recognition of theory of mind in social contexts that children might encounter, than a false-belief task such as the Sally-Anne task. Additionally false belief tasks use different stimuli in each condition, whereas this task controls for the use of stimuli by using each movie clip twice, once for predicting a character's response (ToM condition) and another time for counting the number of people (control

condition). In this way our task is tightly controlled for isolating affective mentalizing versus other social information. The movie mentalizing task uses the film "The Little Rascals" and five of its main characters to assess children's brain function as they watch movie clips and make decisions about what a character would do next (theory of mind condition) or how many people were in a scene (control condition). Saxe (2006) describes the importance of language or verbal communication in real life social conditions, indicating that theory of mind tasks that are most appropriate or best target the processes individuals use in day-to-day life will involve reasoning about third-person situations in which verbal communication is the primary modality. The movie-mentalizing task more accurately approximates how children might use social cognition in day-to-day life, asking them to reason about other children's mental states based on verbal and non-verbal communication between characters. In this task, children are asked to make prediction of a character's behavior/mental state (ToM condition) or perform a non-mentalizing counting task (control condition). Additionally, emotional reasoning, or affective mentalizing, is a key part of social functioning. Hooker and colleagues (2008) found that when reasoning about an emotional response, neural activity in emotion-related regions strongly correlated with participants' self-reported empathy. Therefore, this task should be a good predictor of social functioning and this has not been addressed the current theory of mind tasks.

We hypothesize that children will show increased activation in predicting a character's mental state (ToM condition) in regions in the theory of mind network including: the STS, TPJ, and MPFC, relative to a non-mentalizing, control condition.

Additionally, given that previous research has demonstrated a strong relationship between social cognition and social functioning, we hypothesize that a relationship between the neural bases of theory of mind will relate to theory of mind performance and social functioning.

More specifically, we hypothesize that the degree of activation in the theory of mind network during the ToM condition relative to the control condition will be positively related to our behavioral measures of theory of mind and social functioning.

Methods

Participants

Fifty-four typically developing (TD) children participated in the behavioral portion of the study. Twenty-eight of those children completed the movie-mentalizing task scan session. Seven subjects were excluded due to movement artifacts, resulting in a total of 21 participants. Participants (8M/13F) had a mean age of 11.4 years and mean education level of 5.83 years (Table 3.1). Of the 93 children that came into the lab to participate, 39 children were excluded from testing for one of the following reasons: IQ<70, elevated scores on Structured Interview for Prodromal Syndromes (SIPS) (McGlashan, 2001) family history of severe mental illness/autism, significant developmental delays from birth to age three, Axis I diagnosis on the Kiddie Schedule for Affective Disorders (K-SADS), or concern of coerciveness by guardian to participate.

Social Cognition Variables

Reading the Mind in the Eyes Task. The Reading the Mind in the Eyes Task (Eyes Task) (Baron-Cohen et al., 2001) requires participants to look at pictures of the eye area of faces and infer the emotional state of the individual. The Reading the Mind in the Eyes Task has been used with individuals with autism spectrum disorder, schizophrenia, personality disorders, and traumatic brain injury (Baron-Cohen et al., 2001; Bora et al., 2009; Fertuck et al., 2009) exhibits sensitive to normal variation and clinical impairment.

Hinting Task. The Hinting Task consists of 10 short scenarios describing a social interaction in which one of the characters hints at something to the other character. Children are asked to infer the meaning of the hint. If the child fails to accurately infer the hint, she/he is asked a follow-up question, which provides an additional clue. This task was originally created for an older age group, and was modified for children by Schenkel and colleagues (2008) to assess theory of mind in children and adolescents with bipolar disorder.

Social Functioning Variables

Social Skills Improvement System-Rating Scale. The SISS-RS (Gresham, 2008) can be used with multiple raters (child, parent, and teacher) to assess three major domains of children's development: social skills, problem behaviors, and academic competence. In this study we used the child and parent rated measures to assess social skills and problem behaviors. The social skills domain assesses the following aspects of children's social development: communication, cooperation, assertion, responsibility, empathy, engagement, and self-control. The problem behavior domain assesses: externalizing and internalizing behaviors, bullying, hyperactivity, and inattention. The SSIS-RS has been developed for use with children ages 3-18, with a specific test for 5-12 year olds and 13-18 year olds. Children and parents are asked to rate how true a statement is on a 4-point scale of *not true, a little true, a lot true,* and *very true.*

Global Functioning Social Scale. Global Functioning Scale Social Scale (GFS: Social) (Cornblatt et al., 2007) is an interview-based measure that assesses current friend and family relationships. The scale yields a total social functioning score, ranging from 0-10, with higher scores indicative of higher levels of social functioning.

Movie Mentalizing fMRI Task

In the Movie Mentalizing Task, children watch video clips from the Little Rascals and are asked to respond either to a mentalizing question or a control question. This task is an event related design with two conditions: a theory of mind, or mentalizing, condition and a counting/control condition. The theory of mind condition starts with a screen and the face of a character and reads "Pay attention to" with the face below those instructions. The child is required to pay attention to that character throughout the film clip and then predict what that character might do next. The response screen read, "What would, 'picture,' do next?" with the picture being the same image they saw for the instructions. Below this question, children had 5 possible choices, which included *Cry, Say "Yuck," Smile, Yell, Cover Eyes,* repeated in that order for each trial. The control condition instructions read "Count how many people you see" The child was required pay attention to how many people he/she saw during the film clip. The response screen read "How many people did you see?" and below that on the same screen the child was presented with five possible choices: *1 Person, 2 People, 3 People, 4 People, 5 or more People*, repeated in that order for each trial. Each trial started with instructions to pay attention to a specific person (ToM condition) or counting the number of people in each scene (control condition) followed by the film clip for 10 seconds and then the response screen 8 seconds. A fixation cross, lasting 4, 6, or 8 seconds, followed the response screen (Figure 3.1).

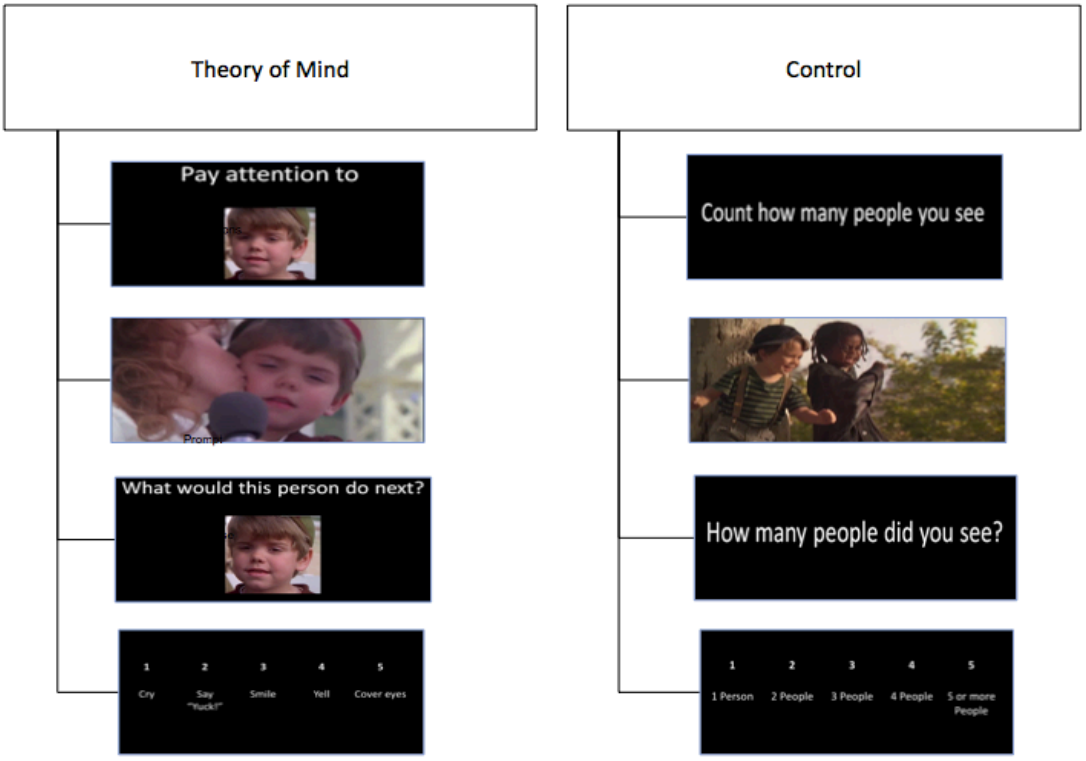

Figure 3.1. Movie mentalizing task.

Before going in the scanner, each child was introduced to the task on a laptop and given a practice run to make sure they understand how the task works. Additionally, children were oriented to each of the characters that they may encounter throughout the film. Given that this film came out in 1994, all but two children were unfamiliar with this film.

Children received a prize for each run that they completed (though they received all prizes at session completion regardless of completion of the scan), and an experimenter ("scan buddy") was present in the scan room with the child throughout the session. The scan buddy provided reassurance for participants who were nervous, and also served the role of informing the child, by squeezing his/her ankle, if he/she was moving too much.

Imaging Protocol

MRI Data Acquisition. Participants were scanned on a 3-Tesla Siemens scanner at the Center for Brain Science, Harvard University. Whole brain coverage was achieved by using 40 slices with a 3x3x3 mm voxel size and a .5 mm gap. Changes in blood oxygenation level-dependent (BOLD) MR signal were measured using a gradient echoplanar imaging sequence (TR=2.56s, TE=30ms, flip angle=85 degrees). Three time series with 236 volumes were obtained for each subject. We used prospective acquisition correction (PACE) on all functional runs. PACE applies an adjustment to slice acquisitions (up to 8 degrees and 2mm) during the functional scan in order to correct for head movement throughout the scan.

Images were processed with the use of SPM 8 (Statistical Parametric Mapping software; Wellcome Department of Cognitive Neurology, London, UK). Preprocessing occurred in the following steps: manual realignment of functional and structural images to match a standardized structural template, realignment to the mean functional image, co-registration of functional scans to the anatomical image, normalization to MNI space, and smoothing with an 8mm Gaussian

kernel. The artifact detection toolbox (ART), (http://www.nitrc.org/projects/artifact_detect), was used to identify outliers in movement (>3mm from the previous image) and global signal (+/- 3 SD from the global mean intensity signal) for each participant. Participants with more than 20% of volumes removed were excluded from analyses.

Statistical Analyses

We modeled the hemodynamic dynamic response for each condition. Hemodynamic response was modeled at the onset of each condition with a duration of 8s. Data was filtered at 128s. Seven events were modeled. (An instruction screen was presented for 10 seconds. This was modeled and regressed out). There were two primary conditions of interest: Response to ToM Question and Response to Control Question. We chose to analyze the response conditions only because this provides the cleanest contrast of mentalizing relative to social information. If we had analyzed brain activity while engaged in the task, it is possible that even in the counting condition children would attend to the story line of the movie at the same time, which provides mental-state information.

Whole brain analysis. We conducted a one-sample t-test of the contrast ToM response versus Control response. The whole brain random effects analysis was thresholded at $p<.001$ (uncorrected for multiple comparisons) with a cluster size of 50 voxels ($k=50$). Regions that survived at family-wise error have noted by an * in the table.

Whole Brain Region of Interest Analysis. Using the group analysis of ToM > Control, we focused on two regions of interest: right STS, and left TPJ. Using the MarsBar tool with SPM8, ROIs were defined as an 8mm sphere from the peak voxel identified at $p<.001$, $k=50$ from the group analysis in the a priori regions of interest. A contrast value was extracted for each participant's level of neural activity in the peak of each region.

Results

fMRI Results

Neural Activity for ToM > Control. Whole brain random effects analysis demonstrated greater activation in the theory of mind condition relative to control in our predicted regions of the theory of mind network including bilateral TPJ and the STS (Figure 3.2), as well as other regions related to social processing including the STG, precuneus, and bilateral temporal pole regions. These findings are consistent with prior studies of theory of mind in children and adolescents. Of note, in contrast to our hypothesis, we did not find significant activation in the MPFC in the ToM condition relative to the control condition.

Correlations between neural activity for ToM and social variables. We hypothesized that neural activity for ToM would be related behavioral measure of social cognition and social functioning. Activity in our regions of interest, STS and left TPJ did not show a significant correlation with measures of social cognition including Mind in the Eyes and Hinting Task, or measures of Social Functioning including GFS: Social, or SSIS Social Skills child and parent reports. Even when controlling for age and gender, due to possible differences in brain activity related to age/gender or theory of mind performance related to age/gender, we find no significant relationship.

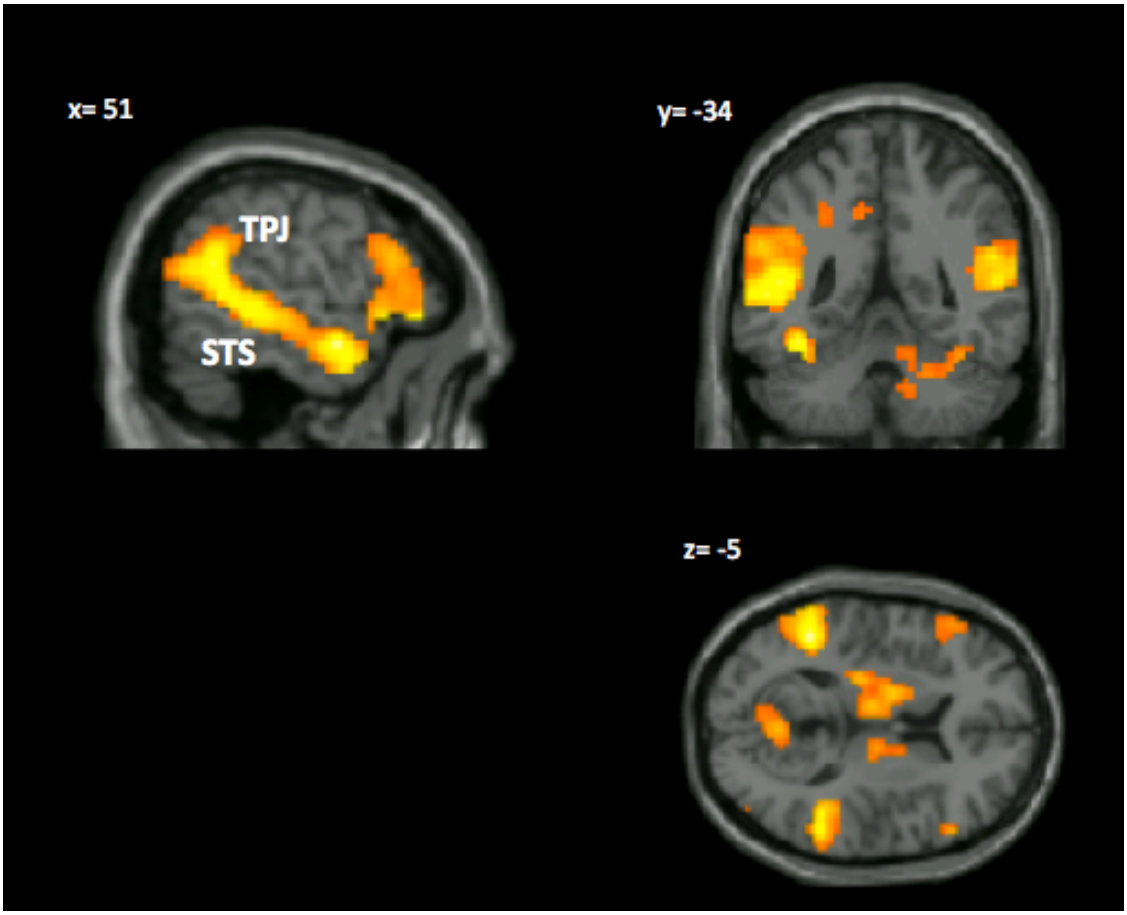

Figure 3.2. Brain activity theory of mind response > control condition response, $p<.001$, k=50

Discussion

This study uses a novel, ecologically valid theory of mind task to further evaluate the neurobiology of theory of mind in elementary and middle school-aged children, and its relationship to social ability. As predicted we replicated previous findings that children, ages 8-13, would show increased activation in the ToM network in response to thinking about mental states versus a control condition. Specifically, we found increased activity in both bilateral TPJ and the STS. Additionally these findings support the use of the novel, movie-mentalizing task, which gets around some of the concerns of false-belief paradigms, and provides both verbal and nonverbal information for children to rely upon to understand mental states. Finally, we begin to piece together the brain-behavior relationship between neural activity for ToM and social functioning.

A whole brain-analysis of neural activity for a ToM condition (predicting a character's mental state) versus a control condition (counting people) showed robust activity in several regions related to social cognitive processing, including two regions consistently recruited for ToM processing, left TPJ and right STS. Activation of the left TPJ when thinking about mental states is consistent with other research. Previous work by Saxe and colleagues (Saxe and Wexler, 2005) (Saxe and Kanwisher, 2003) has consistently demonstrated the role of bilateral TPJ in understanding the mental states of others. Saxe & Powell (Saxe and Powell, 2006) found that the TPJ responded selectively to tasks about people's thoughts versus stories about internal states (e.g. hunger) or social context. Recruitment of the STS was also expected. Previous research has identified the STS, particularly the posterior portion to be related to ToM processing. While frequently cited as a region that responds to biological motion as well as integrating the social context in which that biological motion occurs (Wyk et al., 2009), recent research has found that

the STS is also recruited for ToM processing (Mar, 2011; Van Overwalle, 2009). Our findings are consistent with this research, given that both the ToM condition and the control condition involved social information.

Contrary to our hypotheses we did not see significant activation in the MPFC for the ToM condition. The MPFC is one of the most consistently replicated findings in ToM research. Mitchell and colleagues (Mitchell et al., 2005) demonstrated that the MPFC is involved in both self-referential thinking as well as mentalizing about others. The ventral MPFC plays an important role in empathy (Hooker et al., 2008) and perspective taking whereas the dorsal MPFC is important for shared attention and goals, as well as the ability to monitor one's self and other's responses to social interactions (Saxe and Powell, 2006). However, recent developmental work suggests that the MPFC, particularly in middle childhood, does not differentiate between thinking about other people's states of mind versus thinking about people. Saxe and colleagues (Saxe et al., 2009) increased specialization of the right TPJ from ages 6-11, when children responded specifically to questions about mental states versus social questions about people. Work by Gweon and colleagues (Gweon et al., 2012) found that while TPJ activity became increasingly selective with age, MPFC activity did not differ between children and adults. These findings, and our findings, support the idea that the MPFC may respond equally to information about mental states and information about people in children, as in adults. Given that our control condition was matched to control specifically for mental states and not the presence or absence of people, it is possible that the MPFC was responding equally to both conditions which resulted in a lack of differential activity in ToM versus Control.

We did not find a significant relationship between activity in regions of the ToM network and performance on social cognitive tasks and measures of social functioning. Given the

relatively small sample size, this study should be repeated with a larger sample size and continuum of social functioning. Establishing the relationship between neural processing of theory of mind, social cognitive performance, social functioning in typically developing children is critical to our understanding of what may underscore the impairments in social functioning, particularly for individuals with psychiatric disorders such as autism and schizophrenia spectrum disorders.

Table 3.1: Demographics & Clinical Details

	Participants N=21
Gender (F/M)	13F/8M
Age: mean (SD), [range]	11.24 (1.67), [8-13]
Education: mean (SD), [range]	5.83 (1.76), [2-8]
IQ: mean (SD), [range]	111.44 (15.04), [79-135]
Global Functioning Scale	
Social	8.42 (.692), [7-9]
Social Skills Improvement System – Rating Scale	
Social Skills Child Report	103.71 (14.88), [80-127]
Problem Behavior Child Report	90.53 (7.96), [78-108]
Social Skills Parent Report	103.06 (12.08), [81-128]
Problem Behavior Parent Report	95.65 (10.65), [81-121]
Hinting Task	17.68 (2.03), [13-20]
Reading the Mind in the Eyes	20.67 (3.13), [14-26]

Table 3.2. Within group one sample t-test ToM > control (N=21)

Anatomical Regions	R/L	BA	Voxel (mm)	x	y	z	t
ToM > Control							
Temporal pole	L	11	2319	-51	-1	-17	9.33*
Inferior frontal gyrus	L	38		-45	17	-8	8.99*
Superior temporal gyrus	L	21		-48	-52	16	8.04*
Temporoparietal junction	L	41		-42	-46	28	4.79
Fusiform gyrus	L	37	240	-42	-52	-20	8.87*
Superior temporal sulcus	R	21	786	51	-34	-5	7.98*
Middle temporal gyrus	R	22		54	-43	7	7.04
Fusiform gyrus	R	19	619	36	-73	-20	6.99*
Precuneus	L	7	712	-27	-55	52	6.76*
Midbrain	L		718	-6	-19	-8	6.17
Precentral gyrus	R	6	89	36	-1	49	6.07

*Region survives at p<.05 FWE

Table 3.3: Correlations between neural activity for ToM and social cognition and social functioning

Controlling: Age and Gender	Superior Temporal Sulcus (R)	Temporoparietal Juncture (R)
GFS: Social	.299	.321
SSIS: Social Skills Child Report	.040	-.064
SSIS: Problem Behavior Child Report	.259	.164
SSIS: Social Skills Parent Report	.012	-.071
SSIS: Problem Behavior Parent Report	.136	.329
Hinting Task	-.094	-.245
Reading the Mind in the Eyes	.224	-.021
IRI: Perspective Taking	-.092	.009
IRI: Empathic Concern	.035	.284

Discussion and Conclusion

Summary of Findings

This dissertation presents a systematic investigation into the neural mechanisms of social cognitive processing and social functioning and how disruptions in neural systems may explain social impairment in CHR individuals.

Paper #1 demonstrated that GMV in the ACC and postcentral gyrus, regions associated with social cognitive processing, is reduced in adolescents and young adults at clinical risk for psychosis relative to a healthy control group. Reduced GMV in these regions is consistent with other studies of at-risk individuals (Fornito et al., 2008). The relationship between structure and function of these regions and social cognitive processing is well established (Adolphs, 2009). Thus, we looked at how reduced GMV in these regions might explain social impairment in CHR individuals. Greater volume in these regions predicted better social functioning across the whole sample. Social functioning impairments are present before the onset of psychosis, predictive of severity and transition status, and non-responsive to psychopharmacological treatments (Addington et al., 2008b; Cornblatt et al., 2012; Hamilton et al., 2000). By understanding the connection between brain abnormalities and impaired behavior in this group, we may be able to provide more targeted treatments.

Paper #2 extends the findings of Paper #1 to an understudied population, children ages 8-13, demonstrating early psychotic-like symptoms that meet criteria for a prodromal or clinical high risk status. Knowing that social deficits are one of the earliest predictors for of future onset of psychosis (Addington et al., 2008b), understanding how these deficits relate to the neurobiological progression of schizophrenia, is a critical step in understanding the pathophysiology of the disorder. Eleven CHR children and 30 TD children participated in

behavioral testing and an MRI. Behavioral differences show that CHR children have poorer social functioning and self-report poorer perspective taking ability. Structural differences were found between the two groups, with the CHR children showing reduced GMV relative to the TD children in the insula and ACC. Additionally, GMV in these regions was positively related to theory of mind processing and social skills. The results of this study confirm that neuroanatomical differences exist in a younger CHR population, and that differences in regions associated with social cognitive processing are related to performance on theory of mind tasks and overall social functioning across the whole group and within the CHR group.

Paper #3 looks specifically at typically developing children ages 8-13 and neural activity in response to a novel theory of mind task. Paper #3 sets the stage for future work looking at neural activity and its relationship to social impairment in children at risk for psychosis. To our knowledge previous developmental work has not looked at the relationship between neural activity for theory of mind and its relationship to social cognition and social functioning in typically developing children. In order to understand how this process might go awry in children with psychiatric symptoms, we need to clarify this relationship in a typically developing population first. The first goal of this study is to replicate previous findings of the ToM network in children, which has previously been found to consist of the MPFC, bilateral TPJ, and the STS (Dodell-Feder et al., 2013; Saxe et al., 2004). Previous literature has highlighted a variety of concerns regarding widely used theory of mind tasks (Bloom and German, 2000; Perner and Leekam, 2008), and suggested that research move away from the traditional false belief as well as move away from relying solely on verbal information. The task presented in paper #3 as children to predict behaviors based on the mental state of a character in a movie clip, straying from a false-belief paradigm, providing a more ecologically valid scenario, and using both verbal

and nonverbal modalities. We found greater activity in bilateral TPJ and the STS in response to ToM condition versus a control condition, but did not see differences between conditions in the MPFC. The second goal of this study was to understand if neural activity in a theory of mind task would correlate with performance on theory of mind tasks, as well as social functioning. This finding makes sense in light of recent research that demonstrates that the MPFC responds equally to thinking about the mental states of others and to social information (Gweon et al., 2012). Our control condition contained social information, and therefore it is likely that the lack of activity in the MPFC is explained by an equal response to each condition. Additionally, we did not see a significant relationship between neural activity and theory of mind performance or social functioning.

Implications

The ability to interact effectively with other people is crucial for children to be successful as children and adults. Several mental health issues in adolescents and adults, particularly illnesses like schizophrenia, may be related to and potentially even predicted by social problems that start in early childhood. All three papers focus on increasing the field's ability to identify neurodevelopmental abnormalities that predate and predict illness onset. Given the right conditions and opportunities, brain development could be modified to overcome genetic influence or environmental stressors in early childhood that may lead to the development of psychotic disorders later in life.

The findings in papers #1 and #2 are consistent with the proposal that structural abnormalities exist in at-risk individuals before the onset of psychosis, and that deficits in regions primarily involved in social and emotional processing are associated with early predictive deficits in social functioning. In this model, structural abnormalities are a biomarker

for schizophrenia, evidence of a disruption in typical brain development, and contribute to the social dysfunction seen in individuals at-risk for schizophrenia spectrum disorders. Consistent with previous research in at-risk populations, papers #1 and #2 found structural abnormalities in regions associated with social cognitive processing in both young adults and children at clinical high risk for psychosis. Moreover these studies find that less grey matter volume in these regions is related to deficits in social cognition and social functioning, suggesting that structural abnormalities may set the stage for these impairments, which are both risk factors and symptoms of schizophrenia spectrum disorders.

Paper #3 focuses on functional activity for theory of mind processing and its relationship to social cognition and social functioning in typically developing children. While this paper does not look at brain function in an at-risk population, it does inform future research with this population. Neurodevelopmental changes, particularly as they relate to social cognition, between childhood and adolescence are relevant and necessary to understand in typically developing children in order to fully understand and identify abnormalities in CHR children.

Additionally, this paper validates the use of a novel theory of mind paradigm that focus more specifically on affective mentalizing. Affective mentalizing is more closely related to aspects of social functioning (Hooker et al., 2008) and therefore may be a particularly important process to understand in relation to the neurobiology supporting social cognition and social functioning. In this paper we demonstrate that as children think about the mental states of others, they recruit regions in the theory of mind network including the TPJ and STS. The strengths of this task include its use of both verbal and non-verbal information, the use of the same stimuli in theory of mind and control conditions, and its potential to be a more engaging task for children due to the use of stimuli from a children's movie and scenarios that involve other children The

movie mentalizing task presented in paper #3 offers a valid paradigm for studying theory of mind in children.

More broadly, the findings of this dissertation have implications for understanding the neurobiological progression of schizophrenia. We chose to focus on social dysfunction, as it is a unique variable, identified as both a risk factor and symptom of schizophrenia spectrum disorders. Social functioning is both a predictor and symptom of schizophrenia spectrum disorders. Research suggests that social isolation creates stress, which increases an individual's risk for a psychotic disorder (Hoffman, 2007; Selten et al., 2013). Additionally social dysfunction is a core symptom of schizophrenia spectrum disorders. Its duality as both a predictor and a symptom makes social functioning a particular interesting and important variable of study. These papers contribute to a growing body of literature investigating the neurobiological mechanisms of social cognition and social functioning in individuals at risk for psychosis.

Critically, by elucidating the neurodevelopmental course of the illness, clinicians and researchers will be in a better position to employ early intervention measures and may additionally suggest a locus for intervention via neural plasticity-based intervention programs. Though in its infancy, studies of cognitive remediation have begun to look at the benefits of this intervention for individuals at-risk for schizophrenia. Hooker and colleagues (2012) found that patients with schizophrenia who engaged in cognitive and social cognitive training showed changes in brain activity in regions associated with social cognitive processing from pre to post training scans. Moreover, brain activity in these regions predicted improvement on social cognitive measures at time 2. Additionally, a pilot study with individuals at clinical high risk found that targeted cognitive training improved role or occupational functioning in these

individuals, indicating both a feasibility of this type of intervention as well as the effectiveness of the intervention (Hooker et al., 2014). There is some evidence that cognitive remediation and other interventions designed to help brain development are effective in several different groups of children, suggesting that remunerative processes or mechanisms may be harnessed to help overcome neurobiological deficits (Bryck and Fisher, 2012). The possibility of affecting change in brain development in early childhood to prevent or lessen the severity of schizophrenia and related disorders is an exciting new challenge. The research presented in this dissertation suggests that both brain abnormalities and social functioning are evident before the onset of psychosis. As a result, targeting these areas of development in children and adolescents at-risk for psychotic disorders is a critical and promising next step.

Limitations

While these studies provide a snapshot in time of brain structure and function in individuals at-risk for psychosis, longitudinal studies to assess change over time would help disentangling the cause and effect of social functioning as a risk factor and as a symptom. Moreover, following the CHR children through adolescence would provide additional information on the specific hypothesis that brain abnormalities in schizophrenia arise from an exaggeration of the typical brain maturation process (Keshavan and Hogarty, 1999). Additionally, all three papers, though paper #2 in particular, are underpowered in regard to sample size. Though our findings are consistent with previous research, future research should be done to repeat these studies, with a larger sample, to support our findings. Finally, our study does not address the temporal development of social functioning and social cognitive deficits, and brain abnormalities. The directionality of interactions among brain-behavior, and the social environment remains unclear. It is possible that CHR individuals have deficits in social

reciprocity, joint attention, following eye gaze, and other fundamental aspects of learning social interactions, from an early age, and in turn these lost experiences affect brain structure (Blakemore, 2010). On the other hand, atypical brain development may start in prenatal phases, such that these individuals are already at risk, due to structural and functional abnormalities, to struggle with social interactions. Longitudinal studies, looking at social interactions in an even younger sample, and a better understanding of the typical neurobiological mechanisms that support social cognitive processes and social functioning will help address these questions.

Conclusions

This dissertation presents an investigation of the neurobiological mechanisms that support social cognition and social functioning in typically developing children and young adults, and in children at clinical high risk for psychotic disorders. Findings show that (1) structural abnormalities exist in CHR individuals, predating the onset of psychosis, and these structural abnormalities in CHR individuals include regions that support social and emotional processing, (2) less grey matter volume in these regions is related to poorer social cognition and poorer social functioning, and (3) affective mentalizing, in a novel task, robustly recruits theory of mind regions in typically developing children. These findings have implications for our understanding of social cognitive and social functioning impairments in individuals at risk for psychotic disorders, and highlight brain abnormalities in regions related to social cognitive processing as possible biomarkers for psychosis.

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