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Language network dysfunction as a predictor of outcome in youth at clinical high-risk for psychosis

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Abstract

Objectives—Language processing abnormalities are a hallmark feature of schizophrenia. Yet, no study to date has investigated underlying neural networks associated with discourse processing in adolescents at clinical high risk (CHR) for developing psychosis.

Methods—Forty CHR youth and 24 demographically comparable healthy controls underwent functional magnetic resonance imaging while performing a naturalistic discourse processing paradigm. We assessed differences in blood oxygenation level-dependent (BOLD) activity between task conditions (Topic Maintenance vs. Reasoning) and between groups. Furthermore, we examined the association of regional brain activity with symptom severity and social outcome at follow-up, 6 to 24 months after the scan.

Results—Relative to controls, CHR participants showed increased neural activity in a network of language-associated brain regions, including the medial prefrontal cortex bilaterally, left inferior frontal (LIFG; BA44/45, 47) and middle temporal gyri, and the anterior cingulate (BA24&32). Further, increased activity in the superior temporal gyrus (STG), caudate, and LIFG distinguished those who subsequently developed psychosis. Within the CHR sample, severity of positive formal thought disorder at follow-up was positively correlated with signal change in the LIFG, superior frontal gyrus, and inferior/middle temporal gyri, whereas social outcome was inversely correlated with signal change in the LIFG and anterior cingulate.

Conclusions—These findings are consistent with a neural inefficiency hypothesis in those at greatest risk for psychosis, and additionally suggest that baseline activation differences may predict symptomatic and functional outcome. These results highlight the need to further investigate the neural

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Conflict of Interest

None of the authors report any biomedical financial interests or potential conflicts of interest.

Contributors

CEB designed and directed the study, and contributed to collaborative writing of the manuscript. FWS performed final modeling and analysis of the data and collaborative writing of the manuscript. TvE and MEH performed the experiment and provided initial quality assurance, scoring, and analysis of project data, as well as manuscript edits. MD and RC designed the task and edited the manuscript. TDC provided input into the study design and edited the manuscript.

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systems involved in conversion to psychosis, and how language disruption changes over time in at-risk adolescents.

Keywords

fMRI; schizophrenia; inferior frontal gyrus; psychosis prodrome; discourse; functional neuroimaging

1. INTRODUCTION

Investigating those who are at high-risk for developing psychosis is one way to examine potential markers for the onset, etiology, and progression of impairments in the early phases of psychosis, and offers the potential to identify those most likely to become ill (Whalley et al., 2006). By ascertaining individuals at risk for imminent onset of psychosis (i.e., clinical high-risk or prodromal patients) and following them over time (McGlashan, 1996; McGorry et al., 2003), we can improve understanding of the mechanisms of disease onset and progression.

Cannon et al. (2008) recently found that a prediction algorithm incorporating combinations of baseline clinical predictor variables (genetic risk for schizophrenia with recent functional decline, higher levels of unusual beliefs or suspiciousness, and greater social impairment) dramatically increased positive predictive power for determining subsequent conversion to psychosis. However, specificity of the model was low. Functional neuroimaging phenotypes may be able to improve our ability to identify those at greatest risk, as neural systems dysfunction may be closer to the underlying pathophysiology of the illness than behavioral phenotypes.

Very few studies, however, have examined functional neuroimaging phenotypes in youth at high-risk for psychosis, and existing studies are not well-powered to predict outcome over time (Morey et al., 2005; Seiferth et al., 2008; Whalley et al., 2006). For instance, using a sentence completion paradigm in subjects at genetic high risk, Whalley et al. (2006) found that those who subsequently developed schizophrenia (n=4) demonstrated increased parietal activity, decreased cingulate activity, and smaller increases in fMRI signal with increasing task difficulty in the right lingual gyrus and bilateral temporal regions. Applying a visual oddball task to clinical high-risk individuals, Morey and colleagues (2005) noted smaller differential activation in frontal regions between task-relevant and irrelevant stimuli in frontal regions; however, as only two of the ten putatively prodromal participants subsequently developed psychosis, this study was unable to examine baseline predictors of outcome..

Given the fundamental role of language processing abnormalities in schizophrenia, as both a key diagnostic sign (Caplan et al., 2000) and a vulnerability marker (Arboleda and Holzman 1985; Miklowitz et al., 1991), altered patterns of neural activation during language processing may be a valuable prognostic indicator. Formal thought disorder, a disruption in the flow of conscious thought inferred from disorganization of spoken language, reflects the most severe manifestation of disturbed language processing (Kuperberg et al., 2006). This disorganization may result from abnormalities in semantic processing networks, or may be tied to executive control functions involved in planning and monitoring speech (Kerns et al., 2004). In patients with established illness, these deficits are often associated with structural and functional brain abnormalities, in both prefrontal and temporal regions (Fletcher, 1998; Frith et al., 1995; Kircher et al., 2001; Shenton et al., 2001), which are putative neural correlates for executive (Carter et al., 1999; Glahn et al., 2008; Karlsgodt et al., 2007; Sabb et al., 2007) and semantic (Bookheimer, 2002; Chao et al., 1999; Mummery et al., 1999; Warrington and Shallice, 1984) processing, respectively. Several structural neuroimaging studies have also identified volumetric reduction in the left superior temporal gyrus (STG) in schizophrenia, the magnitude

of which is associated with the severity of formal thought disorder (Hirayasu et al., 1998; Petty et al., 1995; Rossi et al., 1994; Shenton et al., 1992).

Thought disorder has been shown to be a sensitive and specific predictor of schizophrenia and schizophrenia spectrum disorder in a variety of studies (Caplan, 1994; Caplan et al., 2000; Taylor and Amir, 1994). The severity of such abnormalities is also associated with long-term functional outcome (Racenstein et al., 2002; Racenstein et al., 1999; Richardson et al., 2002). Moreover, sub-clinical disturbances in the natural speech of healthy relatives of schizophrenic patients have been reported, supporting the notion that communication disturbances may be one manifestation of a genetic vulnerability to psychosis (Docherty and Gordinier, 1999). In addition, using a word/pseudo-word discrimination task, Li et al. (2007) found that – unlike healthy controls – schizophrenia patients and their non-ill siblings activated Brodmann's area 44 similarly for both language and non-language tasks, suggesting that fMRI measures of language processing may be valuable for use in the prediction of risk for developing psychosis. Similarly, in a cross sectional study of clinical high-risk individuals, patients with first episode psychosis and healthy volunteers, Broome et al. (2009) found that the at-risk group showed an intermediate pattern of activation in the inferior frontal cortex and anterior cingulate during an overt verbal fluency task. Yet, whether such abnormalities are predictive of illness onset remains unknown.

Thought disorder is typically measured behaviorally through clinical interviews, making it more challenging to evaluate during a functional imaging study. In order to passively challenge similar cognitive processes to those employed in natural speech, here we evaluated the neural correlates of language processing, using a naturalistic task that involves listening to question and answer sentence pairs, in individuals identified as putatively prodromal for psychosis. This study represents the largest functional neuroimaging study to date of clinical high-risk (CHR) individuals, and the first to examine baseline neural predictors of outcome. We hypothesized that CHR youth would show evidence of abnormality in brain regions critical for language function (i.e., inferior frontal and superior temporal regions), and that these alterations would be exacerbated in those who subsequently developed psychosis. We also examined the relationship between activity in these brain regions at baseline and severity of positive formal thought disorder and psychosocial outcome at follow-up.

2. MATERIALS AND METHODS

2.1 Subjects

Participants were 43 individuals at clinical high-risk for psychosis (CHR) and 26 demographically matched healthy controls (HC) from a longitudinal prospective study at the Center for the Assessment and Prevention of Prodromal States (CAPPS) at UCLA (see Table 1 for sample characteristics). The CHR and HC group did not differ in terms of age, IQ, sex, handedness, nor were there significant differences in baseline symptom severity or medication usage between the CHR subjects who subsequently converted to psychosis (CHR-P) and those who did not (CHR-NP). However, there was a trend for more males to convert to psychosis ($p=.07$); as such, region of interest (ROI) analyses of the CHR group included sex as a covariate.

Participants were screened with the Structured Interview for Prodromal Syndromes (SIPS, McGlashan et al., 2001) for the presence of one of three putative prodromal syndromes, based on attenuated subthreshold psychotic symptoms, transient psychotic symptoms, or a substantial drop in social/role functioning in conjunction with a diagnosis of schizotypal personality disorder or presence of a first-degree relative with a psychotic disorder. HC youth did not meet DSM-IV criteria for a psychiatric disorder as determined by the Structured Clinical Interview for *DSM-IV- Patient Version* (SCID-I/P; First and Pincus, 2002), did not have a first-degree family history of a psychotic disorder, or meet criteria for any of the three prodromal states

defined above. Additionally, we excluded participants with any neurological disorder, drug or alcohol abuse/dependence within the past 6 months, or Full Scale IQ below 70. Baseline DSM-IV diagnoses in the clinical high risk (CHR) group are as follows: Major Depressive Disorder (N=18), Social Phobia (N=3), Obsessive-compulsive Disorder (N=2), Alcohol Abuse, in full remission (N=2), Attention Deficit Hyperactivity Disorder (ADHD; N=1), Adjustment Disorder (N=1), Anxiety Disorder -Not Otherwise Specified (NOS; N=5), Depressive Disorder NOS (N=3), Pervasive Developmental Disorder NOS (N=2), Bipolar Disorder NOS (N=1), Psychosis NOS (N=1), and Eating Disorder NOS (N=1). All clinical interviews were conducted by Master's-level or Ph.D. mental health specialists, after being trained to rigorous standards of reliability (ICC>.85). Detailed information on recruitment, inclusion criteria, inter-rater reliability, and case consensus procedures are described in detail elsewhere (Meyer et al., 2005; Niendam et al., 2006). All participants completed informed consent approved by the UCLA Institutional Review Board.

One healthy and two CHR subjects were excluded from analysis due to relatively stringent criteria for motion (≥ 2 mm of absolute movement, and/or 0.5 mm of relative movement between brain-volumes). Additionally, one healthy and one CHR subject were excluded due to technical difficulties during the scan; thus, 40 CHR youth and 24 controls were included in statistical analyses.

2.2 Clinical Follow-up

While we report only on baseline performance here, all participants also completed follow-up assessments approximately every 6 months, up to a maximum of 24 months, during which SCID and SIPS interviews were repeated, to determine changes in symptom status. In addition, the Schedule for Assessment of Positive and Negative Symptoms (SANS/SAPS) and measures of psychosocial functioning were rated by a PhD or Master's level clinician. Social functioning was assessed with the Social Attainment Survey (SAS; Goldstein, 1978), which contains seven 5-point items evaluating peer and romantic relationships and participation in activities. Scores on SAPS Thought Disorder items (Illogical Thinking and Global Formal Thought Disorder) and social functioning ratings from the final follow-up assessment point for each subject were used in correlational analyses to assess whether baseline functional imaging activity was predictive of subsequent symptom severity and social functioning.

Fifteen of our participants converted to psychosis during a follow-up assessment. Participants were considered 'converted to psychosis' at follow-up based on SIPS diagnosis of a Psychotic Syndrome. Diagnosis of a psychotic syndrome refers to psychotic symptoms of particular intensity (e.g., delusional conviction) and frequency or duration (one hour per day at an average frequency of 4 days per week during the past month) or of particular impact (seriously disorganizing or dangerous), designed to operationalize the threshold for a *DSM-IV* Axis I psychotic disorder diagnosis [i.e., schizophrenia-spectrum disorder, mood disorder with psychotic features, or psychosis not otherwise specified (NOS)]. *DSM-IV* diagnoses attained at the point of conversion were determined by direct SCID (First and Pincus, 2002) interview of the patient and their parent or guardian. During the course of follow-up, 15 (35%) of the CHR participants converted to a psychotic disorder: 5 (33%) were diagnosed with schizophrenia; 3 (20%) with schizoaffective disorder, depressive type; 1 (7%) with schizophreniform disorder; 1 (7%) with delusional disorder; 2 (13%) with Bipolar I Disorder with psychotic features; and 3 (20%) with Psychosis Not Otherwise Specified (NOS). Of the 40 CHR subjects included in data analyses, the majority (N=22; 55%) completed follow-up assessments up to 24 months, eight (20%) completed follow-up assessments up to 12 months and ten (25%) completed 6-month follow-up assessments.

2.3 Image acquisition

Scanning was performed on a Siemens 3-Tesla Allegra head-only magnet. Subjects were placed in the scanner and a second order shimming protocol was performed in order to minimize magnetic field inhomogeneities. We performed localizer scans from which we prescribed the functional slices. Prior to functional scanning, we acquired a full brain high-resolution matched-bandwidth spin-echo echo-planar scan for between subject registration (TR:4s, TE: 54ms, 128² matrix, 3mm/1skip, 30 oblique-axial [AC-PC aligned] slices). From this volume, 28 slices were chosen co-planar to the high-resolution structural scan to examine BOLD contrast across time using a Gradient Echo echo-planar sequence (TR:3s, TE:35ms, 64² matrix, 3mm/1skip, 70 timepoints).

2.4 Task Procedure

Given our aim to assess neural and clinical differences between youth who convert and do not convert to psychosis, we required a reliable biomarker that would activate brain regions involved in language processing in young subjects. We chose a blocked naturalistic language processing task previously validated in young subjects that assesses the ability to comprehend discourse (Caplan and Dapretto, 2001; Dapretto et al., 2005). Briefly, the task consisted of two condition blocks, '*Topic-Maintenance*' (TM) and '*Reasoning*' (R), with 24 seconds of rest preceding each block, and 18 seconds of rest after the second condition block. Each condition block consisted of a set of 12 question and answer pairs recorded by two female native-English speakers, presented at a rate of 6 seconds per pair (resulting in two 72 second blocks) over headphones (Magnetic Resonance Technologies) and controlled using E-prime software (Pittsburgh Software Tools) on a DELL-D810 computer. The order of the two conditions (TM or R) was counterbalanced across subjects. We instructed participants to respond as quickly as possible as to whether each question-answer pair made sense by pushing a 'yes' or a 'no' button on a button-box. In the TM block, we varied sentence features based on appraising whether the response to the question was 'on-topic', thus tapping executive components of language processing (context processing, monitoring, and working memory), while in the R block we varied features of the underlying semantic logic of the conversation, which putatively involve both anterior and posterior language systems [Sabb et al. (2007); Bookheimer, 2002; see Table 2]. The order of on/off topic and logical/illogical answers within each block was randomized, with no more than three answers of one kind occurring in a row. Participants' responses were later scored for accuracy and response times and compared using analysis of covariance (ANCOVA) with group (UHR-P, UHR-NP, HC) as the between-subject variable, covarying for sex..

2.5 Post-processing and Statistical Analysis

We processed the data using the FSL (v4) suite's FEAT tool (<http://www.fmrib.ox.ac.uk/fsl/>). Following correction for movement between brain volumes (MCFLIRT), the data were registered for group comparison in a two-step process using first the high-resolution matched-bandwidth scan and then a common reference brain (in MNI space) after undergoing skull stripping (BET).

We modeled single subject data with a high-pass filter of 144 seconds, a six-millimeter (FWHM) Gaussian smoothing kernel and pre-whitening (to account for the intrinsic temporal autocorrelation of the fMRI signal) with FMRIB's Improved Linear Model (FILM). Analyses used a mixed effects general linear model (GLM), in which task condition (Reasoning or Topic-Maintenance) was modeled as a within-subjects factor and diagnostic category was modeled as a between-subjects factor, using FSL's Local Analysis of Mixed Effects (FLAME, v5.91). After modeling individual subject data (i.e. FILM: level 1), second level analyses (between subjects) were run using FLAME-stage 1, providing z-maps of activity in each condition for each diagnostic group separately, and direct comparisons of conditions between groups. Group

contrasts were thresholded based on both the magnitude (minimum z-threshold of 2.0, except where noted) and extent (all analyses used a corrected cluster threshold of $p < 0.05$) of active voxels.

We additionally performed region of interest (ROI) analyses to explore relationships of neural activity to clinical outcome in brain regions that showed significant whole-brain group differences between CHR and control subjects. Anatomical ROIs were chosen from the Laboratory of Neuroimaging probabilistic atlas (Shattuck et al., 2008) for the left inferior frontal gyrus (LIFG), the left temporal lobe (middle and inferior gyri), bilateral representation of the anterior cingulate (ACC), the caudate, and superior frontal gyrus (SFG). Only voxels in these anatomical regions that had passed significant cluster thresholding in the general linear model (GLM) analysis of CHR vs. HC for either R-rest or R-TM were included. This was done to increase localization of our ROIs to distinct neuroanatomical regions, as our activated clusters frequently spanned multiple brain regions.

In order to perform an independent analysis of the relationship between brain activity and behavior (e.g., Kriekesgort et al., 2009), we extracted parameter estimates from the whole-brain GLM for each subject in the CHR group using the Featquery tool in FSL, which were then interrogated in SPSS (v. 16.0) using Pearson partial correlations (adjusting for sex) with Sidak's adjustment for multiple comparisons (Sankoh et al. 1997). Because the outcome variables we examined (clinical and social functioning scores within subjects) are not independent, we used a corrected p-value of .01 for these analyses, based on the mean correlation of the outcome variables ($r=.50$).

3. RESULTS

3.1 Behavioral Results

There were no significant differences in reaction time or accuracy between the three groups (CHR-P, CHR-NP, HC), for either the Topic-Maintenance or Reasoning conditions (see Table 1).

3.2 fMRI Whole Brain Analyses

Two whole brain GLM analyses were conducted, the first of which compared Topic Maintenance (TM) and Reasoning (R) conditions within and between the two groups (all CHR participants vs. HC; see Methods section above for model details). The second analysis examined only the CHR group, directly comparing fMRI data at baseline for CHR individuals who converted to psychosis at follow-up (CHR-P; $n=15$) with those who did not (CHR-NP; $n=25$). In each of these two whole-brain analyses, contrasts were set up to investigate group differences for each active task condition compared to rest (Reasoning – rest, Topic Maintenance – rest), as well as direct contrasts between task conditions (Reasoning – Topic Maintenance, and the reverse). Following these analyses, we performed ROI analyses to further interrogate neural activity in regions showing significant between-group differences.

3.2.1 Clinical High Risk (CHR) vs. Healthy Controls (HC)—To assess reliability of the task, our first contrast compared *Reasoning* (R) vs. rest and *Topic Maintenance* (TM) vs. rest in CHR and HC subjects (see Figure 1). Consistent with previous studies (Caplan and Dapretto, 2001; Dapretto et al., 2005), this contrast revealed a bilateral network of brain regions involved in discourse processing across all CHR participants (Figure 1, left) and healthy controls (Figure 1, right). These regions were qualitatively similar between task conditions, and included the bilateral inferior temporal lobe, middle temporal gyrus, hippocampus, inferior frontal gyrus, and precentral gyrus.

Direct comparison of the groups (CHR, HC) and conditions (R, TM) revealed two contrasts in which the CHR group showed significantly more activity than HC (see Figure 2). First, the CHR group showed significantly more activity than HC in the Reasoning condition (versus rest) in the left inferior frontal gyrus, anterior cingulate, left inferior and middle temporal gyri, and occipital cortex (z voxel height threshold of > 1.7 , and corrected cluster threshold of $p < 0.05$). Similarly, we found an interaction in the direct contrast of Reasoning versus Topic-Maintenance between groups ($R > TM$ for $CHR > HC$); the CHR group showed more activity than HC in medial prefrontal regions, anterior cingulate, left inferior frontal gyrus, bilateral caudate, and posterior brain structures (lingual gyrus and occipital lobe; $z > 1.7$, $p < 0.05$).

3.2.2 CHR Intra-Group Comparison: Converters (CHR-P) vs. Nonconverters (CHR-NP)—Given the smaller sample size in this analysis, when examining interactions between group (CHR-P, CHR-NP) and condition (TM, R), we used a mask comprised of voxels that were previously active in the CHR-P group main effect contrast of all minus rest, in order to reduce noise from voxels that did not pass significance within group. In the Reasoning condition (minus rest), the CHR-P group showed significantly more activity than CHR-NP in a network of brain regions including bilateral temporal lobe, frontal operculum, left precentral gyrus, caudate, and other striatal regions (see Figure 3; voxel height threshold of $z > 1.7$, and corrected cluster threshold of $p < 0.05$). In contrast, there were no regions where the CHR-NP group demonstrated increased activity relative to the CHR-P group, and no other condition showed significant differences between the groups.

3.3 Neural Activity and Clinical Outcome

All regions of interest (ROIs) were determined from significantly active voxels in the (first) whole brain analysis that directly compared the entire CHR group and healthy controls (see Figure 2). Thus, only voxels that were significantly related to performance of the task (i.e. all-rest) were included in the ROI analysis. From these contrasts, we used functionally thresholded anatomical ROIs of the left inferior frontal gyrus (LIFG), left temporal lobe (middle and inferior gyri), bilateral representation of the anterior cingulate (ACC), caudate, and superior frontal gyrus (SFG), as described in the Methods section.

The relationship between percent signal change in these ROIs during task performance at baseline to clinical outcome (psychosocial functioning and severity of thought disorder) was then examined within the CHR group, with sex as a covariate. We found significant relationships – which survived multiple comparison adjustment – between signal change in the Reasoning minus Topic-Maintenance contrast for the LIFG, temporal lobe, and superior frontal gyrus and thought disorder scores, as assessed by the SAPS (Illogical Thinking and Global Formal Thought Disorder). In addition, signal change in the ACC and left IFG was inversely correlated with Social Attainment Survey scores at follow-up, indicating that greater activation in these regions during task performance predicted poorer social function at follow-up (Reasoning minus rest; see Table 3 and Figure 4).

4. DISCUSSION

This is the first study to our knowledge to demonstrate predictors of outcome in a clinically at-risk sample for psychosis using a baseline functional neuroimaging phenotype. Here we identified a network of brain regions that was differentially involved for those at risk for developing psychosis compared to healthy matched controls during performance on a naturalistic discourse processing task. Overall, the task elicited activity in the expected network of regions typically engaged in language tasks, including the inferior frontal gyrus (IFG), bilateral medial prefrontal regions, inferior and middle temporal gyri, as well as the anterior cingulate. However, clinical-high risk (CHR) participants showed increased neural activity

relative to healthy controls, in the medial prefrontal lobe bilaterally and anterior cingulate, as well as left IFG and left inferior and middle temporal gyri. Further, relative to CHR participants who did not develop psychosis, CHR subjects who subsequently developed psychosis showed a pattern of relative over-activation in language –associated brain regions, including the left inferior frontal gyrus and inferior temporal lobe, as well as bilateral striatum and thalamus, and the frontal operculum. Our findings of relative hyper-activation of language-related brain regions during discourse processing in youth at high risk for psychosis are consistent with a hypothesis of neural inefficiency in these vulnerable individuals (Karlsgodt et al., 2007; Potkin et al., 2009). These patterns are consistent with data from high-functioning patients with schizophrenia who show compensatory increases in brain activity during task performance (Karlsgodt et al., 2009).

Our results also indicate that baseline neural activity during discourse processing was related to severity of positive formal thought disorder at follow-up, as well as social outcome. In particular, increased activity in the left ventral inferior frontal gyrus (during task performance in the Reasoning condition) was associated with increased severity of formal thought disorder at follow-up. Conversely, increased activity in the dorsal region of the inferior frontal gyrus was associated with poorer social outcome at follow-up, indicating that the observed patterns of relative hyper-activation in language-related brain regions have prognostic significance. Interestingly, cross-sectional associations between neural activity in these regions and concurrent clinical status (psychosocial functioning and severity of thought disorder) were not nearly as robust as were these predictive relationships. Specifically, there was only a significant inverse correlation (at the $p < .01$ level) between neural activity in the anterior cingulate and Social Attainment scores ($r = -.39$; $p < .008$). The significant associations between baseline neural activity in frontal and temporal ROIs and measures of thought disorder that were observed at follow-up did not reach this level of significance in the cross-sectional baseline comparisons. Because thought disorder scores tended to increase over the follow-up period in those who converted, the range of scores at baseline was restricted, which likely attenuated the findings. The results of our predictive analyses may help improve the accuracy of existing algorithms that attempt to predict those at greatest risk for psychosis based on clinical characteristics. Developing multivariate prediction algorithms for determining risk - that include functional and structural neuroimaging data- could provide additional information, as changes in neural activity could predate symptoms.

In this study, we found portions of both dorsal and ventral left inferior frontal gyrus were activated to a greater degree during semantic reasoning judgments in CHR individuals relative to healthy controls. Numerous fMRI studies have revealed the contributions of the left ventral aspects of IFG to language processing (Badre and Wagner, 2004; Dapretto and Bookheimer, 1999; Sabb et al., 2007), and specifically the evaluation of semantic incongruities in sentence processing. For example, Cardillo and colleagues (2004) used a sentence processing task with semantically congruent and incongruent endings (e.g., “the boy bounced the ball/wall”). They found that activity was greatest in the IFG during incongruent trials, which may reflect detection of an irregular or unexpected semantic ending. Dorsal regions of the left IFG have been linked to other components of language processing, including sequencing of information (Gelfand and Bookheimer, 2003), verbal working memory (Cabeza and Nyberg, 2000), and other executive processes including response planning (Derrfuss et al., 2004). Our data provide further support for the role of the left IFG in semantic processing through judgments of reasoning, and additionally suggest that these processes are over-active in CHR youth.

As expected, we also found group differences in temporal lobe language areas, including the inferior and middle temporal gyrus. Evidence from neuropsychological lesion studies (Warrington and Shallice 1984) as well as fMRI studies of semantic processing (Mummery et al., 1999; Rossell et al., 2001) highlight the importance of the temporal lobe in language

processing. There is also substantial evidence that this structure is perturbed in schizophrenia, and that the degree of temporal volume reduction is related to severity of formal thought disorder (Shenton et al., 2001). Semantic priming studies in schizophrenia patients find that automatic activation of lexico-semantic representations is normal and, in thought-disordered patients, even increased, suggesting a wider, possibly faster, automatic spread of activation (Kuperberg et al., 2008). In a review of this literature, Kircher (2008) hypothesizes that dysfunction of the semantic network, may be due to lateral temporal lobe abnormalities, and that temporal pathology is predominantly involved in the generation of positive formal thought disorder in schizophrenia. Our findings may extend this model by suggesting that lateral temporal dysfunction is present prior to the onset of illness in those at clinical high-risk.

Our discourse processing task also modulated activity in the anterior cingulate (ACC). While ACC activity is associated with a range of cognitive processes, converging evidence suggests that one specific role of this region is in error monitoring, or conflict detection of competing representations (Carter et al., 2001; Carter and van Veen 2007). Detecting and resolving conflicting/incongruent responses is a critical component of both conditions in our paradigm that require on-line context processing. Disruption of these cognitive processes – and corresponding ACC dysfunction – has been frequently demonstrated in patients with schizophrenia (Carter et al., 2001; Carter and van Veen, 2007), their relatives (MacDonald et al., 2005), as well as genetic high-risk samples (Whalley et al., 2006). Our results provide further evidence of abnormal ACC activity in an at-risk population, although further studies are needed to address the precise nature of this dysfunction.

Certain limitations of this study should be noted. We used a naturalistic task that had previously been validated in adolescents, in order to maximize comprehension and accurate performance. While we found strong activation patterns in the Reasoning condition, results were less consistent in the Topic-Maintenance condition, with much more variability in fMRI signal between subjects. This could be due partially to the block design employed here. Although this design allowed maximum power to detect subtle differences in conditions between groups, we were unable to investigate the timecourse of processing of incongruous information. Future investigations using trial-based designs in CHR populations are clearly warranted to further characterize the contribution of the network of brain regions seen here that are putatively important for a complex phenotype such as discourse processing. In addition, as with all studies involving psychiatric populations, medication is a potential confound. In our study, several of the CHR participants were taking psychoactive medication although only a minority were taking atypical antipsychotics. However, baseline medications did not differ between those who later converted and those who did not, and therefore could not account for group differences in activation patterns. In addition, there was no relationship between antipsychotic medication use and activation in the brain regions that were differentially engaged across groups ($p > .20$). Nevertheless, we fully acknowledge that our study was not designed to examine differential effects of medications, and this could be better addressed in the context of a randomized clinical trial in which treatment is standardized.

4.1 Conclusions

Identifying predictors and mechanisms of conversion to psychosis among individuals ascertained in a clinical high risk or prodromal state are critical next steps along the pathway to prevention strategies. Our results suggest that neural activity during discourse processing has important predictive implications, as it is associated with subsequent thought disorder severity and social outcome. This is the first study, to our knowledge, to demonstrate functional differences in activity between those who convert to psychosis and those who do not, prior to illness onset. These findings may suggest strategies for the development of novel preventive treatments that can correct or compensate for the specific neurodevelopmental and

psychological changes associated with the formation of psychotic symptoms during late adolescence and early adulthood.

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Figure 1. Discourse processing activity for Reasoning and Maintenance conditions in each group
 Depicts four contrasts: Reasoning minus rest for clinical-high-risk (CHR) participants (top left) and healthy controls (HC; top right), and Topic-Maintenance minus rest for each group (bottom). Anatomical image is the FSL standard space template. Color bar shows z-statistical thresholds. Maps were thresholded with a z-statistic greater than 2.0 and a corrected cluster threshold of $p < 0.05$. Positive (+) Numbers show z-coordinate of FSL standard space template and are the same for each contrast. Images are in radiological convention (right is on the left).

Figure 2. Discourse processing – group x condition interaction

Statistical maps showing regions in which activity in the comparison of conditions differed between groups (healthy controls vs. CHR participants). Reasoning minus rest is presented on the left, and the direct comparison of the two task conditions (Reasoning minus Topic-Maintenance) is presented on the right. These maps determined regions that were further interrogated in ROI analyses. Anatomical image is the FSL standard space template. Both maps were thresholded with a z-statistic greater than 1.7 and a corrected cluster threshold of $p < 0.05$. Positive (+) Numbers show z-coordinate of FSL standard space template and are the same for each contrast. Images are in radiological convention (right is on the left).

Figure 3. Baseline neural activity associated with subsequent conversion to psychosis

Map shows differences in neural activity during task performance (Reasoning – rest) between those who converted to psychosis at follow-up (CHR-P) and those who did not (CHR-NP). Anatomical image is the FSL standard space template. Color bar shows z-statistical thresholds. Positive (+) Numbers show z-coordinate of FSL standard space template and are the same for each contrast. Images are in radiological convention (right is on the left).

Figure 4. Correlations between Clinical Characteristics and ROI activity in the LIFG

Brains depict neural activity for Reasoning vs. Rest comparison (yellow) and Reasoning vs. Maintenance (orange) for CHR > controls. Left panel displays left dorsal IFG activity for Reasoning vs. Rest, while Right panel displays left ventral IFG activity (Reasoning vs. Maintenance contrast). Graphs show correlation of percent signal change (x-axis) in these ROIs with scores on clinical measures at follow-up (y-axis). Top graph shows relationship of neural activity in dorsal IFG to follow-up Social Attainment Survey (SAS) scores, while bottom graph shows correlation of % signal change in ventral IFG with SAPS Thought Disorder Global Score at follow-up. As shown in Table 3, correlations were significant within the entire group of CHR participants. Those who subsequently converted to psychosis (CHR-P) and those who did not (CHR-NP) are shown separately here (blue=CHR-NP, red=CHR-P). Both maps were thresholded with a z-statistic greater than 1.7 and a corrected cluster threshold of $p < 0.05$. Images are in radiological convention, displayed on the FSL standard brain.

Table 1**Baseline Demographic Characteristics**

Characteristic	CHR Not Converted (N=25)	CHR Converted (N=15)	HC (N = 24)	F/Chi-square statistic, p-value
Demographic Characteristics				
Age at examination, mean ($\pm$ SD)	16.8 (3.1)	18.4 (4.2)	18.5 (3.2)	F=1.7, p=.17
% Female (N) ^a	40% (10)	13% (2)	50% (12)	$\chi^2=2.56$, p=.11
% Right Handed (N)	90% (22)	100% (15)	9 % (23)	$\chi^2=2.59$, p=.27
IQ ^b	107.0 + 17.2	109.1 + 14.5	110.9 + 14.5	F=1.7, p=.71
Task Performance				
Reasoning RT (ms)	4053 (487.0)	3985 (492.9)	4103 (257.8)	F=.37, p=.69
Reasoning % Correct	.80 (.18)	.79 (.16)	.84 (.08)	F=.75, p=.47
Topic-Maintenance RT (ms)	4386 (540.9)	4492 (365.9)	4587 (255.7)	F=1.5, p=.24
Topic-Maintenance % Correct	.85 (.11)	.83 (.17)	.86 (.14)	F=.26, p=.77
Clinical Characteristics				
SOPS Mean Positive Symptom Score ($\pm$ SD)	2.2 (.66)	2.6 (1.2)	N/A	F=2.0, p=.17
SOPS Mean Negative Symptom ($\pm$ SD)	1.9(.97)	2.5(1.4)	N/A	F=2.24, p=.14
GAF score, mean ($\pm$ SD) ^c	46.2 (12.5)	41.6 (16.3)	82.3 (10.2)	F=66.8, p<.001
Current Atypical Antipsychotic Use, n (%)	4 (16%)	3 (20%)	N/A	$\chi^2=1.16$, p=.28
Current Mood Stabilizer Use, n (%)	2 (8%)	3 (21%)	N/A	$\chi^2=1.45$, p=.23
Current SSRI Use, n (%)	7 (28%)	2 (14%)	N/A	$\chi^2=0.95$, p=.33
Current Benzodiazepine Use, n (%)	12%	14%	N/A	$\chi^2=.04$, p=.83

CHR subjects who did not develop psychosis (CHR-NP), CHR subjects who developed psychosis (CHR-P), and Healthy Controls (HC).

^aThere was a trend toward a gender difference between CHR-P and CHR-NP (p=.07).

^bIQ Estimate based on Wechsler Abbreviated Scale of Intelligence (WASI)

^cGAF scores did not differ significantly between CHR-P and CHR-NP (F=.98, p=.33).

Table 2

Example Stimuli of question-answer pairs for each condition, Topic Maintenance and Reasoning.

<u>Topic-Maintenance</u>	
<u>On topic</u>	
Q	How would you feel in an earthquake?
A	I run to my parents' room and I'm scared
Q	What are you doing today?
A	I am playing tennis
<u>Off topic</u>	
Q	How would you feel in an earthquake?
A	I go to Disneyland in the summer
Q	What are you doing today?
A	I call my mom sweetie
<u>Reasoning</u>	
<u>Congruent</u>	
Q	Do you like having fun?
A	Yeah, because it makes me happy
Q	Why are you wearing a raincoat?
A	So I won't get wet.
<u>Incongruent</u>	
Q	Do you like having fun?
A	No, because it makes me happy.
Q	Why are you wearing a raincoat?
A	So I won't get sad.

Table 3
Partial Correlations of Percent Signal Change in Regions of Interest with Clinical Outcome Measures at Follow-up

			Reasoning minus rest contrast					Reasoning minus Topic Maintenance contrast				
			ACC	LIFG	IT/MTG	SFG	ACC	Caudate	LIFG	IT/MTG	SFG	
SAPS Thought Disorder	R		-0.06	-0.10	0.03	-0.04	0.15	0.14	0.48	0.34	0.41	
Global Score	p* <		0.71	0.53	0.83	0.81	0.35	0.38	0.002	0.03	0.009	
	R		0.10	0.06	0.29	0.13	0.28	-0.11	0.52	0.47	0.48	
SAPS Illogical Thinking	p* <		0.54	0.70	0.07	0.42	0.08	0.52	0.001	0.002	0.002	
Social Attainment	R		-0.41	-0.43	-0.33	-0.35	-0.30	0.03	-0.26	-0.27	-0.29	
Survey Total Score	p* <		0.009	0.007	0.04	0.03	0.06	0.85	0.11	0.10	0.07	
Max-Z MNI coordinates	x,y,z		2,36, -14	-50, 14, 20	-36, -72, -8	2,38, -24	-12,26,20	10,6,-10	-42,32,32	-50, -80, -6	18,14, -26	
			ACC	LIFG	IT/MTG	SFG	ACC	Caudate	LIFG	IT/MTG	SFG	
*(2-tailed)												

Abbreviations: ACC – anterior cingulate cortex, LIFG – left inferior frontal gyrus, IT/MTG – inferior temporal/middle temporal gyrus, SFG – superior frontal gyrus, MNI – Montreal Neurological Institute Atlas. Maximum Z-value MNI coordinates are provided for each ROI; however, as ROIs tended to have multiple foci (i.e. local maxima) within the anatomically masked region, maximum Z-value coordinates do not reflect the full extent of neural activity.