Neural responses during social reflection in relatives of schizophrenia patients: Relationship to subclinical delusions

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1. Introduction

Disturbances in the capacity to reflect about the self and others (“social reflection” [SR]) are thought to make a contribution to the symptomatology (Bosia et al., 2012; Brent et al., 2014c) and social dysfunction (van Os et al., 2010) of schizophrenia. Several lines of evidence suggest that SR impairments contribute to the vulnerability to schizophrenia. First, SR disruptions (e.g., poor self-other boundary discrimination, or an altered sense of self) have been identified in children at genetic risk for schizophrenia (Keshavan et al., 2008) and are among the earliest reported symptoms in people later developing the illness (Poulton et al., 2000; Klosterkotter et al., 2001). Second, prospective studies have found deficits in the capacity to take the perspective of others (Schiffman et al., 2004) and impaired social function (Amminger et al., 1999; Tarbox and Pogue-Geile, 2008) in children and adolescents who develop schizophrenia. Third, a meta-analysis has shown that theory of mind [ToM] deficits are significantly greater in people at clinical high-risk for psychosis (i.e., “prodromal” individuals) and in unaffected relatives of schizophrenia patients (Bora and Pantelis, 2013). Furthermore, schizotypal traits (Pickup, 2006) and subclinical delusions (Galhaith et al., 2008) (e.g., mild delusional ideation that is thought in many cases to be on an etiological continuum with delusions in schizophrenia (Dominguez et al., 2011)) have been associated with SR impairments in otherwise healthy subjects. Based on these findings, one remaining question is whether SR impairment in schizophrenia is linked with a pattern of altered neural function that may represent an intermediate phenotype for the disorder.

Neuroimaging studies in healthy subjects have shown that SR tasks involving the retrieval of information about the self (Kelley et al., 2002; Schmitz et al., 2004; Jenkins and Mitchell, 2011) and/or others (Gallagher et al., 2000; Frith and Frith, 2003; Saxe and Kanwisher, 2003) consistently engage a network comprised of cortical midline structures ([CMS]; e.g., medial prefrontal cortex [MPFC] and posterior cingulate cortex [PCC]) and parts of the lateral temporal cortex ([LTC];
e.g., superior temporal gyrus [STG]). Also, these same brain areas show increased activity during resting-states (i.e., “default mode” activity (Buckner et al., 2008)).

Typically, brain areas underpinning SR show increased activation during tasks involving judgments about mental states (i.e., thoughts, feelings, intentions), or personality characteristics of the self or others, as opposed to judgments about their physical characteristics, or the semantic aspects of the stimuli (Amadio and Frith, 2006). According to simulation models of social perception, self-reflection may serve as a fundamental starting point for understanding other people (Gallese and Goldman, 1998). Consistent with this theory, a number of studies have shown considerable overlap between the pattern of neural activation observed during self-reflection and other-processing, including ToM (Happe, 2003; Lombardo et al., 2009; Tamir and Mitchell, 2010).

Several studies have reported aberrant activation in schizophrenia patients of MPFC and/or PCC (Blackwood et al., 2004; Holt et al., 2011a; Lee et al., 2011; Bedford et al., 2012; van der Meer et al., 2013) (CMS structures) and the LTC (Brune et al., 2008; Walter et al., 2009; Murphy et al., 2010; Pedersen et al., 2012) during SR tasks. A few studies have also linked altered CMS and LTC function during SR with subsyndromal psychotic symptoms (Brune et al., 2011; Modinos et al., 2011; Brent et al., 2014a). Additionally, several studies have provided evidence for similar alterations of CMS (Marjoram et al., 2006; de Achaaval et al., 2012) and LTC (Walter et al., 2011) during ToM in people at genetic risk for schizophrenia. Consistent with these task-based fMRI findings, abnormal resting-state functional connectivity of CMS in relatives of schizophrenia patients (Whitfield-Gabrieli et al., 2009; Jang et al., 2011; van Baaren et al., 2012) suggests that these regional abnormalities are linked to an overall change in the coordinated functioning of this network. Taken together, these results support the possibility that impaired functioning of the neural circuitry involved in SR in schizophrenia is genetically mediated in part and contributes to the emergence of psychotic symptoms.

Here, we investigated this possibility by comparing neural responses during SR in first-degree, non-psychotic relatives of schizophrenia patients and demographically-matched controls, using a well-validated fMRI SR paradigm (Kelley et al., 2002). Given the evidence for altered CMS and LTC activity during SR in schizophrenia, we predicted that, compared to controls, relatives would show aberrant CMS and the LTC activation during SR. Additionally, because of prior evidence linking impaired neural function during SR and subclinical delusions in healthy subjects (Brent et al., 2014a), we tested for a similar association in this cohort.

2. Materials and methods

2.1. Participants

Sixteen first-degree relatives (RELS) of DSM-IV diagnosed schizophrenia patients and 16 controls (CONS) were enrolled. Patients’ schizophrenia diagnoses were confirmed using the Structured Clinical Interview for DSM-IV Axis I Disorders ([SCID]; (Frist et al., 2002)). RELS had no history of taking psychotropic medications and no lifetime history of schizophrenia, Axis I psychotic disorders, major depression, bipolar disorder, or Axis I anxiety disorders based on SCID interviews. CONS were recruited via advertisement and had no first-degree relatives with schizophrenia or psychosis based on family psychiatric history screening interviews. CONS had no history of taking psychotropic medications, or of Axis I disorders as determined via the SCID. All subjects were right-handed and native English speakers. Subjects with neurological disorders, serious medical illnesses, substance abuse or dependence, or contraindications to MRI scanning (e.g., claustrophobia, metal implants) were excluded. Written informed consent was obtained from all subjects in accordance with the guidelines of Beth Israel Deaconess Medical Center’s Committee on Clinical Investigations and Partners HealthCare’s Institutional Review Board. There were no significant between-group differences in the demographic variables or across additional symptom and cognitive domains that were assessed (Table 1).

2.2. Stimulus presentation and task

During the experiment, participants were asked to make judgments (“yes” or “no”) about 144 trait adjectives, presented one at a time, in four conditions: 1) “does this word describe you?” [Self (S)]; 2) “does this word describe your mother?” [Other (O)]; 3) “is this a desirable trait?” [Affect Labeling (AL)]; 4) “is this word printed in upper, or lower case letters?” [Perceptual (P)]. Each word was viewed for 3 s in eight 18-second blocks (i.e., 6 words per block and 2 blocks per condition) during three (each 6 minute 9 second long) functional runs. Each block was preceded by an instruction screen viewed for 3 s and was followed by a 21 second fixation period. Subjects registered their responses via a button box, using the index finger of either the right or left hand. Additional details regarding the stimuli and task are included in the Supplementary Materials (see also Holt et al., 2011a and Brent et al., 2014a). Behavioral responses were not recorded for two CONS and one of the RELS due to equipment failure.

2.3. MRI data acquisition

Functional and structural MRI data were collected using a 3.0 Tesla TIM Trio magnetic resonance scanner at Massachusetts General Hospital (Siemens Medical Systems, Iselin, New Jersey) with echo-planar planar capability and a twelve-channel head coil. Acquisition parameters for the functional and anatomical scans, which were identical to those of our previous study (Brent et al., 2014a), are provided in the Supplementary materials.

2.4. fMRI analysis

Three mm isotropic functional data were analyzed using the FreeSurfer Functional Analysis Stream (http://surfer.nmr.mgh.harvard.edu/fswiki) using standard preprocessing methods. Images were spatially smoothed with a 6-mm (full-width-half maximum) 3-dimensional spatial filter. As done previously, we compared activation during SR [0.5(S) + 0.5(O)] with activation during AL (Brent et al., 2014a). Since the P task entailed responses with perfectly correct answers, it was used to assess subjects' task engagement. Prior fMRI work using the same SR paradigm employed here has shown alterations in CMS (MPFC and/or PCC) during self-reflection (Blackwood et al., 2004; Holt et al., 2011a; Bedford et al., 2012; van der Meer et al., 2013) and in the STG during other-reflection (Murphy et al., 2010) in schizophrenia. Thus, we hypothesized that we would observe differences between the two groups in SR-related activity within a priori, anatomically-defined regions of interest (ROIs): the MPFC, PCC, and STG. These ROIs were defined using an automated parcellation method (FreeSurfer (Fischl et al., 1999)) that uses sulcal and gyral landmarks of each subject's anatomical scan to delineate the boundaries between cortical areas (Desikan et al., 2006). To test our hypothesis, a regions-of-interest (ROI) analysis was conducted using responses averaged across each ROI during each condition, compared to a low-level baseline (Brent et al., 2014a). A 2 (task: SR, AL) × 3 (region: MPFC, PCC, STG) × 2 (hemisphere: right, left) × 2 (group: relatives, controls) analysis of variance was performed to test for group main effects or interactions. Significant effects were followed up by planned t-tests.

2.5. Subclinical delusions and correlations with fMRI data

Subclinical delusions were measured using the Peters et al. Delusions Inventory [PDI] (Peters et al., 1999). The 40-item PDI is a validated self-report questionnaire (Peters et al., 1999) assessing delusions in the
non-clinical population. Each delusional idea is rated 0 (‘no’) or 1 (‘yes’), yielding a PDI-total score ranging from 0 to 40. Every endorsed belief is rate on three 5-point Likert subscales: Distress, Preoccupation, and Conviction. Because both subject groups were healthy and non-clinical, and to optimize our power to detect effects, our primary correlation analysis was conducted in the full cohort of subjects using Spearman’s rank correlation coefficient (r). The significance level was set at $p < .017$ (or $p < .05$ with Bonferroni correction for the number of ROIs (3) examined). Exploratory analyses in the two separate groups with PDI subscale scores were also conducted.

## 3. Results

### 3.1. Symptoms

Mean PDI-total scores (Table 1) both for the total sample and each group were consistent with prior studies in non-clinical populations (Peters et al., 1999; Brent et al., 2014a). There were no significant differences between RELS and CONS in levels of delusional thinking (mean PDI-total and delusional subscale scores) or any of the other clinical or cognitive characteristics measured.

## Table 1
Demographic and clinical characteristics of the participants.

<table>
<thead>
<tr>
<th></th>
<th>Total sample</th>
<th>Controls</th>
<th>Relatives</th>
<th>p value</th>
<th>Effect size</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>32, 19 female</td>
<td>16, 10 female</td>
<td>16, 9 female</td>
<td></td>
<td></td>
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<tr>
<td>Age (years)</td>
<td>43.8 ± 13.7</td>
<td>41.4 ± 14.2</td>
<td>46.1 ± 13.3</td>
<td>.25</td>
<td>.20</td>
</tr>
<tr>
<td>Education (years)</td>
<td>15.9 ± 2.5</td>
<td>16.2 ± 1.8</td>
<td>15.6 ± 3.0</td>
<td>.53</td>
<td>.08</td>
</tr>
<tr>
<td>MPE (years)</td>
<td>14.9 ± 2.7</td>
<td>14.1 ± 3.4</td>
<td>16.1 ± 3.5</td>
<td>.06</td>
<td>.58</td>
</tr>
<tr>
<td>Mean parental SES (a)</td>
<td>1.8 ± 1.0</td>
<td>2.1 ± 1.1</td>
<td>1.6 ± 1.0</td>
<td>.23</td>
<td>.47</td>
</tr>
<tr>
<td>Premorbid IQ (b)</td>
<td>109.9 ± 7.7</td>
<td>109.2 ± 8.6</td>
<td>110.7 ± 6.9</td>
<td>.59</td>
<td>.19</td>
</tr>
<tr>
<td>PDI* total (c)</td>
<td>3.4 ± 4.5</td>
<td>2.3 ± 2.3</td>
<td>4.5 ± 5.9</td>
<td>.15</td>
<td>.26</td>
</tr>
<tr>
<td>PDI* distress</td>
<td>8.0 ± 20.2</td>
<td>4.5 ± 6.4</td>
<td>11.6 ± 27.9</td>
<td>.28</td>
<td>.19</td>
</tr>
<tr>
<td>PDI* preoccupation</td>
<td>9.4 ± 19.7</td>
<td>5.5 ± 5.8</td>
<td>13.3 ± 27.1</td>
<td>.37</td>
<td>.16</td>
</tr>
<tr>
<td>PDI* conviction</td>
<td>10.9 ± 13.9</td>
<td>7.6 ± 7.6</td>
<td>14.2 ± 17.9</td>
<td>.19</td>
<td>.24</td>
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<tr>
<td>State anxiety (d)</td>
<td>31.1 ± 9.0</td>
<td>29.9 ± 7.4</td>
<td>32.3 ± 10.0</td>
<td>.44</td>
<td>.28</td>
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<tr>
<td>Trait anxiety (d)</td>
<td>33.7 ± 8.7</td>
<td>31.9 ± 8.3</td>
<td>35.6 ± 9.6</td>
<td>.26</td>
<td>.41</td>
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<tr>
<td>Depression (e)</td>
<td>4.0 ± 5.5</td>
<td>2.8 ± 4.9</td>
<td>5.3 ± 6.3</td>
<td>.18</td>
<td>.24</td>
</tr>
<tr>
<td>Physical anhedonia (d)</td>
<td>54.1 ± 4.4</td>
<td>55.3 ± 4.5</td>
<td>53.0 ± 4.2</td>
<td>.11</td>
<td>.29</td>
</tr>
<tr>
<td>Mood (f)</td>
<td>13.8 ± 1.9</td>
<td>13.9 ± 1.8</td>
<td>13.7 ± 2.1</td>
<td>.84</td>
<td>.04</td>
</tr>
<tr>
<td>ToM (phys. stories)</td>
<td>14.3 ± 2.3</td>
<td>13.6 ± 2.8</td>
<td>14.9 ± 1.4</td>
<td>.33</td>
<td>.19</td>
</tr>
<tr>
<td>WASI Vocabulary (g)</td>
<td>61.3 ± 8.4</td>
<td>60.2 ± 7.8</td>
<td>62.3 ± 9.0</td>
<td>.83</td>
<td>.48</td>
</tr>
<tr>
<td>WASI block design (h)</td>
<td>55.2 ± 10.1</td>
<td>54.8 ± 8.8</td>
<td>55.6 ± 11.4</td>
<td>.82</td>
<td>.08</td>
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<tr>
<td>Head motion (mm)</td>
<td>1.0 ± 0.7</td>
<td>1.0 ± 0.7</td>
<td>1.0 ± 0.8</td>
<td>.81</td>
<td>.05</td>
</tr>
</tbody>
</table>

There were no significant differences between the relative and control groups in any of the demographic variables. Variables exhibiting a non-normal distribution are indicated with an asterisk (*). For non-parametric variables, differences between the two groups were assessed using the Wilcoxon-Mann-Whitney test. For normally distributed variables, differences between the two groups were assessed using an independent two-sample Student t-test.

### Table 2
Behavioral results.

<table>
<thead>
<tr>
<th></th>
<th>Self-refection</th>
<th>Other-refection</th>
<th>Affect Labeling</th>
<th>Perceptual*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean SD MDN IQR</td>
<td>Mean SD MDN IQR</td>
<td>Mean SD MDN IQR</td>
<td>Mean SD MDN IQR</td>
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<tr>
<td></td>
<td>p value</td>
<td>p value</td>
<td>p value</td>
<td>p value</td>
</tr>
<tr>
<td>Controls</td>
<td>1333 ± 224 1263 ± 300</td>
<td>0.65 ± 1467 261 ± 347</td>
<td>0.79 ± 1301 203 ± 347</td>
<td>0.27 ± 852 174 ± 278</td>
</tr>
<tr>
<td>Relatives</td>
<td>1369 ± 204 1398 ± 356</td>
<td>1.44 ± 242 1422 ± 327</td>
<td>1.37 ± 1378 165 ± 327</td>
<td>0.93 ± 903 203 ± 843</td>
</tr>
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</table>

<table>
<thead>
<tr>
<th></th>
<th>Self-refection (%)</th>
<th>Other-refection (%)</th>
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<tr>
<td></td>
<td>Mean SD MDN IQR</td>
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<tr>
<td></td>
<td>p value</td>
<td>p value</td>
<td>p value</td>
<td>p value</td>
</tr>
<tr>
<td>Controls</td>
<td>42.4 ± 13 45.7 ± 6.3</td>
<td>0.29 ± 440± 15</td>
<td>0.87 ± 490 ± 6.5</td>
<td>0.20 ± 960 ± 13.3</td>
</tr>
<tr>
<td>Relatives</td>
<td>48.1 ± 15 50.0 ± 9.7</td>
<td>0.28 ± 449± 14</td>
<td>0.92 ± 492 ± 2.9</td>
<td>0.20 ± 958 ± 13.3</td>
</tr>
</tbody>
</table>

Mean reaction times and percentage of response types with p values for the independent t-tests, or Wilcoxon–Mann–Whitney tests (for nonparametric data, indicated with asterisk [*]). Comparing the two groups means for the four experimental tasks. Both groups showed significantly greater response times during the Other condition compared to the Self or Affect Labeling conditions, but there was no significant difference in response times between the Self and Affect Labeling conditions. There were no between-group differences in response times for any experimental condition. Both groups showed comparable percentages of words rated as “like self,” “like mom,” or “positive” in the Self, Other, and Affect Labeling conditions, respectively. The percentage of correct trials in the Perceptual condition was similarly high in each group.
3.2. Behavior

ANOVA revealed no main effects of group, or group by condition interactions (all ps > .28) for reaction times, and no between-group differences in response types (see Table 2).

3.3. Functional MRI

A significant Region by Task by Group interaction (F = 4.20; df = 2, 30; p = .02, r^2_p = .12) was found, but no Region by Task by Group by Hemisphere interaction (F = .08; df = 2, 30; p = .92; r^2_p = .003). Follow-up, within-group analyses showed that CONS exhibited greater SR responses compared with AL (i.e., SR-AL activity) in the MPFC (t = 2.2; df = 15; p = .04; d = .57), PCC (t = 4.5; df = 15; p = .0005; d = 1.16), and STG (t = 2.4; df = 15; p = .03; d = .62). The RELS showed no significant SR-AL responses in any of the three a priori ROIs. Between-group comparisons revealed that, compared to RELS, CONS showed significantly greater SR-AL responses in the PCC (t = 2.3; df = 30; p = .03; d = .84) and STG (t = 2.3; df = 30; p = .03; d = .84), but not in the MPFC (t = −.05; df = 30; p = .96; d = −.02) (Fig. 1B).

3.4. Correlations

Total PDI score was negatively correlated with SR-AL responses (data for right and left hemispheres combined) of the PCC (r = −.42; df = 30; p = .01) and STG (r = −.49; df = 30; p = .004; [Fig. 2A, B]). These correlations between total PDI and the SR-AL responses of the PCC and STG remained significant when controlling for anxiety, depression, and anhedonia. A negative correlation between total PDI and the SR-AL responses of the MPFC, PCC, and STG, indicated a trend toward being significantly greater in RELS compared to CONS (z = −1.84, p = .07). There were no significant differences between any of the abnormal symptom and cognitive domains assessed and the SR-AL responses of the MPFC, PCC, or STG. Further, the results of the main ANOVA remained unchanged when total PDI scores were entered as a covariate.

4. Discussion

Here we found that first-degree relatives of schizophrenia patients showed significantly reduced SR-related activity in the PCC and STG, compared to demographically matched controls without genetic risk for schizophrenia or psychosis. These between-group differences were due to the presence of significant SR-related activity in all three a priori ROIs (MPFC, PCC, STG) in the controls, as expected, whereas relatives failed to show this activity in all three regions. Greater levels of delusional thinking also predicted reduced SR-related activity of these same brain regions across all subjects.

Altered PCC and/or STG function has been reported in prior studies of SR in schizophrenia (Blackwood et al., 2004; Lee et al., 2010; Holt et al., 2011a). The pattern of aberrant SR-related activation we observed in relatives differs from some prior neuroimaging findings in schizophre

nia (e.g., aberrant MPFC activity (for reviews see: Bosia et al., 2012; Brent et al., 2014c), or PCC hyperactivity (Blackwood et al., 2004; Holt et al., 2011a; Shad et al., 2012)). This is not inconsistent with the literature, as a risk phenotype may not entirely overlap with the pattern of disease-associated abnormalities (Kern et al., 2013). For example, medial temporal lobe hyperactivity is observed during memory tasks in mild cognitive impairment, whereas Alzheimer’s dementia is associated with reduced hippocampal and parahippocampal activation during memory task performance (Dickerson and Sperling, 2008).

Consistent with prior findings in schizophrenia and our results, evidence for aberrant activity of the left PCC (de Achaval et al., 2012) and left temporo-parietal junction (Walter et al., 2011) (including the STG) during ToM has been found in individuals at genetic risk for schizophrenia. In contrast, one study found no differences between relatives of schizophrenia patients and controls in the magnitude of neural responses during self-reflection (van Buuren et al., 2012). This may be related to a difference in power (our study collected data over three six minute-long functional runs, compared to the single four minute run collected in the earlier study (van Buuren et al., 2010)).

The relationship between abnormal neural function during SR and subclinical psychotic symptoms is incompletely understood. Models of delusions in schizophrenia suggest that impaired SR may play a role in the formation of delusional beliefs (Bentall et al., 2001; Salvatore et al., 2012b). Supporting this hypothesis, fMRI studies have demonstrated links between dysfunction of brain areas mediating SR, including the MPFC (Menon et al., 2011; Modinos et al., 2011), PCC (Holt et al., 2011b), and the STG (Backasch et al., 2013) and delusions in schizophrenia or schizotypy. Additionally, we previously found negative correlations between levels of delusional thinking in healthy individuals and 1) left LTC activation during SR and 2) left LTC-left MPFC resting-state connectivity (Brent et al., 2014a). Our current finding of a negative correlation between levels of subclinical delusions and STG and PCC SR-related activity replicates and extends this earlier work.

The association between subclinical delusions and SR-related activity may have a somewhat different pattern in people with genetic loading for schizophrenia, compared to those without this loading. Our within-group

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Fig. 1. Results of the fMRI analysis. (A) The three ROIs (medial prefrontal cortex (MPFC), posterior cingulate cortex (PCC), and superior temporal gyrus (STG)), defined a priori using FreeSurfer, are shown in these right medial and lateral views of a representative cortical surface. (B) Between-group comparisons showed that controls exhibited significantly greater SR-AL activation in the PCC and STG (* between-group difference, p < .05) compared to relatives, but not in the MPFC.
analyses showed that the relationship between subclinical delusions and SR-related activity in the PCC and STG was similar in relatives and controls. However, relatives showed a negative correlation between delusions and SR-related MPFC responses not observed in controls. Notably, relatives showed impaired SR-related PCC and STG responses compared to controls, whereas MPFC function was on average preserved in the relatives. One possible interpretation of these findings is that these regions are affected in a sequential manner in psychosis, with the STG and the PCC showing the earliest abnormalities (thus relatives showed the greatest changes in these regions, leading to significant between-group differences). The MPFC, on the other hand, may be affected later in the course of the illness, or only in those who have subclinical delusions. This model can be tested in future studies that longitudinally measure changes in SR-related functioning of this network and symptom severity in at-risk populations.

The interpretation of our study is limited by its sample size; replication of our findings in an additional, larger sample will be necessary. Also, future longitudinal studies can test if altered neural function during SR represents a stable, trait-like characteristic associated with genetic risk for schizophrenia, and whether worsening SR-related neural function is predictive of the transition to psychosis.

In summary, these results suggest that dysfunction of the neural circuitry mediating SR is related to the genetic liability to schizophrenia and the pathophysiology of delusional beliefs. Additionally, the breakdown of SR, combined with elevated stress, may lead to aberrant explanations of social experience and the emergence of psychosis (Brent et al., 2014b). Increasing evidence suggests that appropriately designed treatments (e.g., cognitive training (Eack et al., 2009; Subramaniam et al., 2012) and metacognitive psychotherapy (Lysaker et al., 2007; Salvatore et al., 2012a)) may ameliorate SR deficits in schizophrenia and improve real world functioning. Incorporating similar treatments into the care of people at risk for schizophrenia could preempt the deterioration of SR and potentially reduce the chances of transitioning to psychosis.

**Contributors**

Dr. Brent contributed to the study design, collected and analyzed the data, and wrote the first draft of the manuscript. Drs. Seidman and Keshavan contributed to the design of the study and data interpretation. Mr. Coombs assisted with data collection and contributed to data analysis. Dr. Moran contributed to data interpretation and design of the fMRI paradigm. Dr. Holt contributed to designing the study, data analysis/interpretation and the writing of the manuscript. All authors contributed to and have approved the final manuscript.

**Conflict of interest**

The authors have no conflicts of interest to declare.

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**Appendix A. Supplementary data**

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.schres.2014.05.033.

**References**


