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Subclinical delusional thinking predicts lateral temporal cortex responses during social reflection

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Neuroimaging studies have demonstrated associations between delusions in psychotic disorders and abnormalities of brain areas involved in social cognition, including medial prefrontal cortex (MPFC), posterior cingulate cortex, and lateral temporal cortex (LTC). General population studies have linked subclinical delusional thinking to impaired social cognition, raising the question of whether a specific pattern of brain activity during social perception is associated with delusional beliefs. Here, we tested the hypothesis that subclinical delusional thinking is associated with changes in neural function, while subjects made judgments about themselves or others ['social reflection' (SR)]. Neural responses during SR and non-social tasks, as well as resting-state activity, were measured using functional magnetic resonance imaging in 22 healthy subjects. Delusional thinking was measured using the Peters *et al*. Delusions Inventory. Delusional thinking was negatively correlated with responses of the left LTC during SR ($r = -0.61$, $P = 0.02$, Bonferroni corrected), and connectivity between the left LTC and left ventral MPFC, and was positively correlated with connectivity between the left LTC and the right middle frontal and inferior temporal cortices. Thus, delusional thinking in the general population may be associated with reduced activity and aberrant functional connectivity of cortical areas involved in SR.

Keywords: delusions; psychosis; fMRI; lateral temporal cortex; default mode network

INTRODUCTION

Delusions represent a defining symptom of psychotic disorders (Breier and Berg, 1999; McKay *et al*., 2007). Nevertheless, it has become increasingly clear that within the general population, ~5–6% of individuals without psychiatric disorders endorse beliefs similar to the delusions experienced by patients with psychotic illnesses (Freeman, 2006; van Os *et al*., 2009). Although the majority of people with subclinical psychotic symptoms are unlikely to develop full-blown psychosis (Dominguez *et al*., 2011), recent epidemiological studies suggest that delusion-like beliefs may be on an etiological continuum with delusions in psychotic disorders. For example, subclinical delusions share common risk factors with clinical delusions, such as urban living, social isolation, and depression (van Os *et al*., 2000). Also, a recent longitudinal study showed that childhood internalizing and externalizing problems are associated with a higher incidence in early adulthood of both (i) subclinical delusions and (ii) non-affective psychosis (Scott *et al*., 2009). In addition, one study found that delusion severity in patients with schizophrenia and bipolar disorder predicted greater levels of delusional thinking in the patients' non-ill, first-degree relatives (Schürhoff *et al*., 2003), suggesting that genetic vulnerability to delusions and clinical psychosis is expressed as aberrant beliefs in otherwise healthy individuals. These results support the possibility that some of the delusional thinking observed in non-clinical samples arises from the same pathophysiological mechanisms associated with delusions in psychotic disorders.

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Because delusions frequently involve misunderstandings of social situations (e.g. persecutory delusions) or of the person's position in the world relative to others (e.g. grandiose or religious delusions), it has been proposed that basic neurocognitive processes supporting the perception of the self and others [i.e. 'social reflection' (SR)] may be disrupted during the formation and maintenance of delusions (Bentall *et al*., 2001; Blackwood *et al*., 2001). Consistent with this theory, several studies have demonstrated associations between delusions in schizophrenia and impairments of the capacity for understanding the mental states of others ('theory of mind') (Frith and Corcoran, 1996; Langdon *et al*., 1997). Moreover, delusional thinking in the general population has been linked to a reduced ability to take an external perspective on one's own thinking (Warman and Martin, 2006) and a heightened self-focus when reasoning about social situations (Galbraith *et al*., 2008). However, the neural basis of these abnormalities is not yet understood.

Recently, investigating the neural correlates of deficits of SR in psychopathology has become more feasible because the neural systems mediating social perception have been characterized to some extent in healthy populations. Functional magnetic resonance imaging (fMRI) studies in healthy subjects have consistently shown that thinking about the self (Jenkins and Mitchell, 2011; Kelley *et al*., 2002; Schmitz *et al*., 2004) and other people (Gallagher *et al*., 2000; Frith and Frith, 2003; Saxe and Kanwisher, 2003) engages midline cortical structures [medial prefrontal cortex (MPFC) and posterior cingulate cortex (PCC)], and the lateral temporal cortex (LTC). The involvement of these areas in SR is typically manifested by increased activity of these brain regions during the performance of tasks involving the retrieval of information about the self and/or others, compared with tasks focusing on general semantic or physical features of the stimuli (Amodio and Frith, 2006). Also, interestingly, these same midline and lateral cortical regions show elevated activity (Gusnard *et al*., 2001; Gusnard and Raichle, 2001; Raichle *et al*., 2001) and increased functional coupling (Greicius *et al*., 2003; Greicius and Menon, 2004) during 'resting states' (i.e. when no task is performed). In studies of

schizophrenia, abnormalities in the magnitude or pattern of functional coupling among the regions of this 'default mode' network, including those showing aberrant activity during SR (Holt *et al.*, 2011a; Murphy *et al.*, 2010), have been reported (Bluhm *et al.*, 2007; Garrity *et al.*, 2007; Pomarol-Clotet *et al.*, 2008; Whitfield-Gabrieli *et al.*, 2009).

Consistent with the idea that abnormal neural function during SR may be associated with psychosis, dysfunction of default network regions, including the LTC (Brüne *et al.*, 2008; Murphy *et al.*, 2010; Wang *et al.*, 2011) and midline cortical structures (MPFC and PCC) (Brunet *et al.*, 2003; Holt *et al.*, 2011a; Russell *et al.*, 2000; Blackwood *et al.*, 2004), have been observed during reflection on the self and others in schizophrenia. Links between functional and structural abnormalities of regions of this network and the presence or severity of delusions have also been reported (Blackwood *et* al., 2004; Takahashi *et al.*, 2009; Rotarsk-Jagiela *et al.*, 2010; Menon *et al.*, 2011). Specifically, previous investigations of the neural correlates of delusions or psychotic symptoms have found evidence for both (i) state-related overactivity of limbic and default mode circuitry (Honey *et al.*, 2008; Rotarska-Jagiela *et al.*, 2010; Menon *et al.*, 2011), for example, delusional thoughts and associated neural activity may be elicited by ambiguous (Surguladze *et al.*, 2006; Holt *et al.*, 2011b) or threatening (Taylor *et al.*, 2007) information, as well as (ii) impaired recruitment of medial frontal (Blackwood *et al.*, 2004; Brüne *et al.*, 2008; Holt *et al.*, 2012) and temporal (Han *et al.*, 2007) cortex during social, emotional, or language processing. These previous studies suggest that in delusional states, disinhibition of circuits involved in socioemotional perception may interfere with their *task-dependent* functioning, perhaps particularly during emotional and social perception.

Given these findings and the associations previously found between delusions and SR deficits, one remaining question is whether delusional thinking is associated with a specific pattern of neural activity during social reflective processing. To examine this question, in this study, we measured the relationship between the severity of delusional thinking in healthy subjects and default network responses during SR. Taking a dimensional approach to studying neural correlates of delusional thinking in a non-clinical population allowed us to avoid the potential confounds of illness chronicity, medication effects, and institutionalization that commonly influence the study of delusions in patients with psychotic disorders (Claridge, 1987). In addition, we conducted a secondary analysis to determine whether region(s) showing associations between SR-related responses and delusions also exhibit changes in resting-state functional connectivity. Resting-state fluctuations in the blood oxygen level–dependent (BOLD) signal are thought to provide a measure of the default network's intrinsic (i.e. state and task independent) functional organization (Whitfield-Gabrieli and Ford, 2012). Because the degree of resting-state functional coupling among default network structures may reflect, at least in part, the strength of the anatomical connections between them (Buckner *et al.*, 2008; Greicius *et al.*, 2008; Andrews-Hanna *et al.*, 2010), abnormalities in resting-state coupling strength within the default network in delusional people would provide evidence for persistent alterations of those pathways in delusions.

We employed a well-validated fMRI paradigm used in a previous study of schizophrenia (Holt *et al.*, 2011a), in which subjects evaluate the degree to which trait adjectives describe themselves or a close other (Kelley *et al.*, 2002; Schmitz *et al.*, 2004; van der Meer *et al.*, 2010). Subclinical delusional thinking was measured using the Peters *et al.* Delusions Inventory (PDI) (Peters *et al.*, 1999). The PDI is a validated measure of delusional ideation in non-clinical subjects that shows strong correlations with standard measures of schizotypy (Peters *et al.*, 1999) and other subthreshold psychotic symptoms (e.g. hallucinatory experiences) (Larøi and van der Linden, 2005) and differentiates patients with psychotic disorders from healthy subjects (Schürhoff *et al.*, 2003; Scott *et al.*, 2009). On the basis of the evidence for abnormal function and connectivity of default network regions in schizophrenia (Whitfield-Gabrieli *et al.*, 2009; Murphy *et al.*, 2010; Holt *et al.*, 2011a) and clinical delusions (Blackwood *et al.*, 2004; Brüne *et al.*, 2008), we hypothesized that delusional thinking in non-clinical subjects would be associated with similar abnormalities of this network.

MATERIALS AND METHODS

Participants

Twenty-two right-handed, native English-speaking subjects (14 men and 8 women) without psychiatric disorders, as determined by the structured clinical interview for DSM-IV (Frist *et al.*, 2002), were recruited via advertisement and enrolled in the study. Subjects with neurological disorders, serious medical illnesses, substance abuse or dependence, and subjects with contraindications for MRI scanning (e.g. claustrophobia, metal implants) were excluded. Written informed consent was obtained from all subjects before enrollment in accordance with the guidelines of the Partners HealthCare Institutional Review Board and/or the Beth Israel Deaconess Medical Center's Committee on Clinical Investigations. Participants had a mean age of 37.4 (s.d. = 13.4) and a mean IQ measured with the North American Adult Reading Test (Uttl, 2002) of 111.8 (s.d. = 7.3). One subject did not have a full resting BOLD scan due to early scan termination and was excluded from the resting functional connectivity analysis. Behavioral response times were not recorded for one subject due to equipment failure. A different analysis of a portion of this dataset (16 of the 22 subjects) was included in a previous publication (Holt *et al.*, 2011a).

Clinical measures

The PDI is a 40-item measure of common delusional beliefs (e.g. Do you ever feel as if other people are talking about you behind your back?), rated on a 0 ('no') to 1 ('yes') point scale. Levels of anxiety and depression were measured using the Spielberger State-Trait Anxiety Inventory [STAI (Spielberger *et al.*, 1970)] and the Beck Depression Inventory [BDI (Beck and Steer, 1987)].

Stimulus presentation and task

The stimuli set of 144 words (trait adjectives, e.g. aimless, unenthusiastic, studious, mature) was divided into 4 lists of 36 words. The lists consisted of an equal number of positively and negatively valenced adjectives (Anderson, 1968), half of which were printed in upper case and half in lower case letters. The word lists were matched for mean word length, word frequency, and valence. During the functional runs, subjects were asked to make yes/no judgments about the words, presented one at a time, in four conditions: (i) 'does this word describe you?' [Self (S)]; (ii) 'does this word describe your mother?' [Other (O)]; (iii) 'is this a desirable trait?' [affect labeling (AL)], which involves judging and then labeling the affective valence (positive *vs* negative) of the word; and (iv) 'is this word printed in upper or lower case letters?' [Perceptual (P)]. For each subject, all 144 words were viewed during the experiment, and 1 of the 4 word lists was assigned to each of the 4 conditions. The pattern of assignment of word lists to particular conditions was counterbalanced across subjects. Each word was viewed for 3 s in 18-s blocks (six words per block; two blocks per condition) over three functional runs. Each block was preceded by an instruction screen viewed for 3 s, and each block was followed by a 21-s fixation period. Subjects registered their 'yes' or 'no' responses by pressing a button with the index finger of their right or left hand. The run order

and the use of the right or left hand for particular responses were counterbalanced across subjects.

MRI data acquisition

MRI data were acquired using a 3-Tesla Siemens TIM Trio magnetic resonance scanner (Siemens Medical Systems, Iselin, New Jersey). Functional imaging was preceded by the collection of a high-resolution, three-dimensional structural T1 magnetization prepared rapid acquisition gradient-echo scan [8 min 7 s, 129 sagittal slices, 1.33-mm thickness, repetition time (TR) = 2530 ms, echo time (TE) = 3.39 ms, flip angle = 7°, resolution = 1.3 × 1 × 1.3 mm). Then T2*-weighted echo-planar images were acquired (33 × 3-mm thick slices, 3 × 3 mm in-plane resolution) during three 6-min and 9-s functional runs, using a gradient-echo sequence (TR = 3000 m; TE = 30 m; flip angle = 90°). A 6-min and 20-s resting BOLD scan (TR = 5000 ms; TE = 30 ms; flip angle = 90°; 55 × 2-mm thick slices, 2 × 2 mm in-plane resolution) was also acquired. During the resting scan, subjects viewed a cross in the center of a gray screen and were instructed to fixate on the cross and to think about whatever they liked.

MRI data analysis

Preprocessing

Functional data were preprocessed and analyzed using the FreeSurfer Functional Analysis Stream (http://surfer.nmr.mgh.harvard.edu). Functional volumes were motion corrected using the Analysis of Functional NeuroImages algorithm, corrected for temporal drift, normalized for signal intensity, and then global intensity variations were removed. Normalized data were spatially smoothed (full width at half maximum = 6 mm) using a three-dimensional spatial filter. The individual cortical surface of each subject was morphed onto an average spherical surface representation to facilitate intersubject averaging of the functional data, which was carried out in a common spherical surface coordinate system using the General Linear Model with random effects.

Task-based fMRI analyses

For the primary contrast of interest, activation during SR [0.5(S) + 0.5(O)] was compared with activation during AL. Activation for the SR > AL contrast is considered to index neural activity during social processing because the SR task requires a greater level of detail and depth of explicit representation of social information (i.e. of the self or a close other), compared with the AL task. Moreover, similar to previous studies (Schmitz *et al.*, 2004; Moran *et al.*, 2006), we used AL as a baseline condition to control for the affective processing that occurs during the S and O tasks. In addition, to determine whether findings for the SR > AL contrast were driven primarily by activation during the S or O conditions, exploratory analyses were conducted using the contrasts S > AL and O > AL. Because the P task involved responding to questions with objectively correct answers, it served as an indicator of subjects' task engagement.

Because of previous findings of abnormal neural function in midline cortical structures during self-reflection (Holt *et al.*, 2011a) and aberrant LTC activation during other reflection (Murphy *et al.*, 2010) in schizophrenia, we planned to measure average percent signal change, compared with a baseline average signal intensity, in three a priori regions of interest (ROIs) within the default network: MPFC, PCC, and LTC (Figure 1A). These ROIs were defined using an automated parcellation method [FreeSurfer (Fischl *et al.*, 1999)], which determines boundaries between cortical regions on the basis of known sulcal and gyral landmarks in each subject's anatomical scan (Desikan *et al.*, 2006). Percent signal change within these ROIs [SR or AL *vs* a low-level baseline (i.e. the mean BOLD signal intensity across all functional runs)] was measured and compared between conditions using a 2 (task: SR, AL) × 3 (region: MPFC, PCC, LTC) × 2 (hemisphere: left, right) analysis of variance (ANOVA). Significant effects were followed up by planned paired *t*-tests.

In addition, a secondary cortical surface–based analysis (Fischl *et al.*, 1999) was carried out to localize significant effects found in the ROI analysis. A Monte Carlo simulation (10 000 iterations, height threshold of $P < 0.005$) was used to identify significant clusters of activated voxels (corrected cluster-wise $P < 0.05$). The locations of peaks of activation were identified using FreeSurfer and confirmed with the Talairach atlas (Talairach and Tournoux, 1988).

Task-based fMRI activation and symptom analyses

Means and s.d. for symptom data (total scores for the PDI, STAI, and BDI questionnaires) were calculated. Kolmogorov–Smirnov testing showed a normal distribution for PDI and STAI and percent signal change during SR, but not for BDI. Thus, correlations between fMRI data, PDI, and STAI were tested with Pearson's correlation coefficient (r), whereas correlations involving BDI scores were calculated with Spearman's rank correlation coefficient (r_s). To constrain the examination of our primary hypothesis to brain areas showing the most robust response during SR, we limited this analysis to regions showing significant effects in the ROI analysis and significant cortical surface activation for the SR > AL contrast. For these correlations, α was set at 0.05, after a Bonferroni correction was applied for the number of regions examined. Because all other correlations conducted were exploratory in nature, uncorrected P values are reported for those analyses.

Resting-state functional connectivity analysis

Conventional preprocessing techniques (Buckner *et al.*, 2009) involved realignment and normalization to Montreal Neurological Institute coordinates and temporal filtering to isolate low frequency (< 0.08 Hz) BOLD signal fluctuations. Images were corrected for spatial drift, temporal variance, and other potential causes of non-specific variance using nuisance regressors that included: the six parameters computed from the rigid-body motion correction, the averaged signal within a ventricular ROI, a region within the deep white matter, and the signal averaged over the whole brain. A seed-based analysis was performed by constructing a 4-mm radius sphere around the voxel showing the strongest relationship between SR-related activity and delusional thinking (see Results). Group averaging was performed on Fisher z transforms (Zar, 1996) using SPM5 (http://www.fil.ion.ucl.ac.uk/spm). Loci exhibiting positive or negative correlations with the seed were considered significant if they met a voxel-level height threshold of $P < 0.005$ and a whole brain cluster–corrected threshold of $P < 0.05$. In addition, exploratory whole brain analyses using PDI total score or percent signal change during SR as a regressor were conducted. These regression analyses were limited to regions showing significant ($P < 0.05$) positive functional connectivity with the seed (negative correlations were excluded). Correlations meeting a height threshold of $P < 0.01$ with an extent threshold of 25 voxels are reported.

RESULTS

Symptoms

Mean levels of delusional thinking (3.2 ± 3.4; range: 0–10), state anxiety (29.2 ± 6.6; range: 20–26), trait anxiety (31.1 ± 7.4; range: 22–26), and depression (1.9 ± 3.7; range: 0–14) (measured using the PDI, STAI, and BDI, respectively) were typical of those previously reported for healthy samples (Knight *et al.*, 1983; Beck *et al.*, 1988; Peters *et al.*, 1999). Consistent with prior evidence linking delusional thinking and

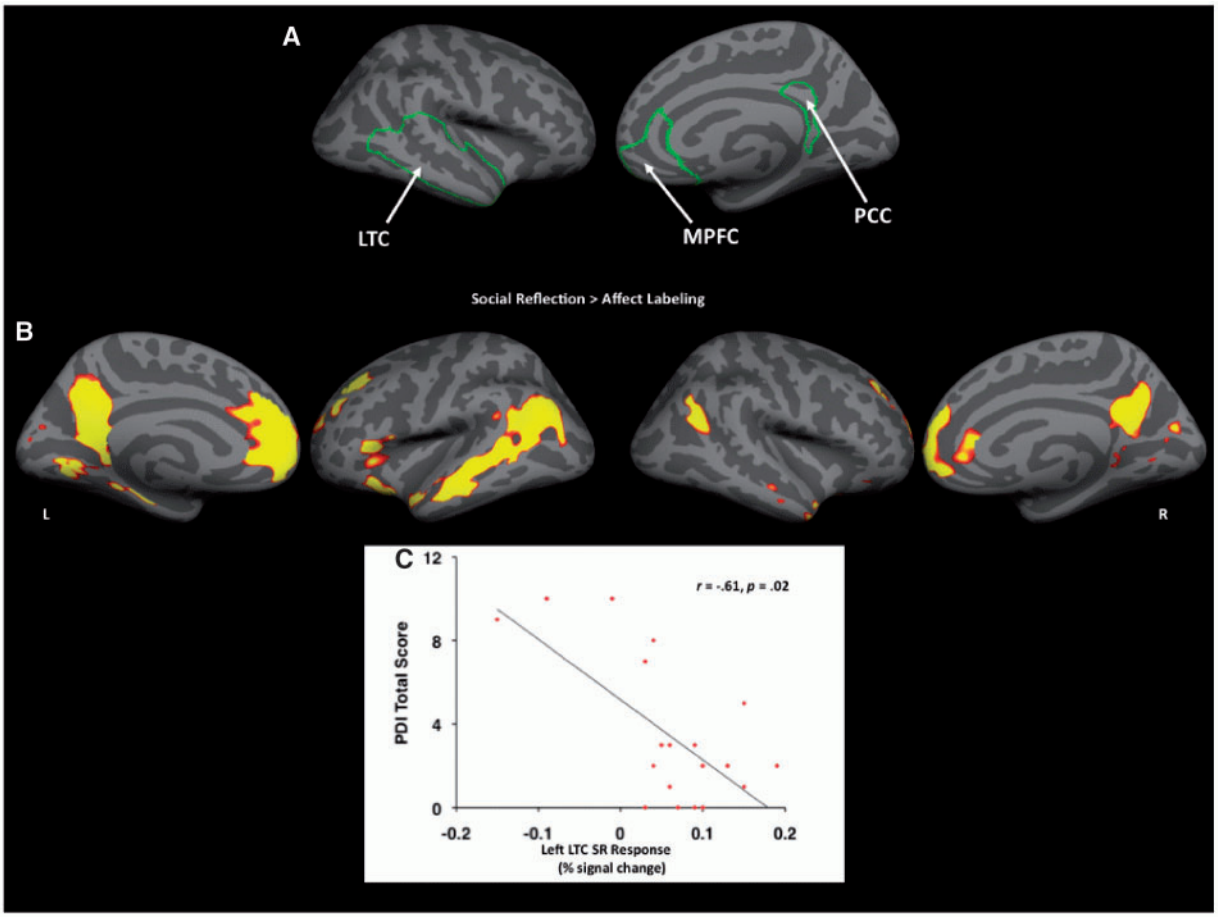

Fig. 1 The results of the cortical surface-based fMRI analyses. (**A**) The three anatomically defined ROIs [medial prefrontal cortex (MPFC), posterior cingulate cortex (PCC), and lateral temporal cortex (LTC)] are shown in these right medial and lateral views of a representative cortical surface. These ROIs were defined in each subject's anatomical magnetic resonance imaging scan, using an automated parcellation system (FreeSurfer; see Materials and Methods). (**B**) Cortical surface maps show activation patterns for the SR > AL contrast, $P < 0.005$. Vertices with significantly greater activation during SR compared with AL are labeled with warm (yellow–red) colors. (**C**) A scatter plot displays the negative correlation between levels of delusional thinking [measured as Peters *et al.* Delusions Inventory (PDI) total score] and responses of the left lateral temporal cortex (LTC) during social reflection (SR) measured as percentage signal change.

anxiety (Freeman, 2006), a significant correlation between levels of delusional thinking and trait anxiety was found ($r = 0.51$, $P = 0.02$).

Behavior

On average, 49.1% of the words seen during the S task were endorsed as 'like self'; 47.6% of the words seen during the O task were endorsed as 'like other'; and 48.1% of the words seen during the AL task were endorsed as 'desirable.' Subjects showed high levels of accuracy during the P task ($98.5 \pm 2\%$), indicating good attentional engagement. A repeated measures ANOVA revealed a main effect of condition for subjects' speed of responses $F(2,40) = 9.015$, $P = 0.001$. Post hoc paired *t*-tests with Bonferroni correction showed that response times during O (1.51 ± 0.23 s) were significantly greater than during S (1.42 ± 0.21 s; $t = -2.73$; $df = 20$; $P = 0.04$) and AL (1.37 ± 0.20 s; $t = 3.9$; $df = 20$; $P = 0.002$). There were no significant differences between response times during S and AL ($t = 1.6$; $df = 20$; $P = 0.39$).

Task-related BOLD responses

In the ROI analysis (Table 1), a significant Region by Task interaction ($F = 5.13$; $df = 2, 42$; $P = 0.01$) was found, but no Region by Task by Hemisphere interaction ($F = 1.27$; $df = 2, 42$; $P = 0.29$). Follow-up, planned comparisons showed a greater response during SR compared with AL in the MPFC ($t = 4.02$, $df = 21$, $P = 0.001$), PCC ($t = 4.11$, $df = 21$, $P = 0.001$), and LTC ($t = 4.6$, $df = 21$, $p = 0.0005$). Consistent with these results, the follow-up cortical surface-based analysis revealed clusters with greater responses during SR compared with AL in the MPFC and PCC bilaterally, and the left LTC (Figure 1B and Table 2A).

Correlational analyses

SR-related activation of the left LTC was negatively correlated with levels of delusional thinking ($r = -0.61$, $P = 0.02$, Bonferroni corrected: $P = 0.003/5$ regions) (Figure 1C). This association remained unchanged after controlling for trait anxiety. In contrast, there were no significant associations between left LTC responses during SR and state anxiety, trait anxiety, depression, or speed of responses during self-reflection or other reflection (all $rs < 0.28$, $ps > 0.30$). Although the responses of the right LTC during SR compared with AL did not reach cluster-wise significance, an exploratory analysis revealed that the right LTC SR response was also negatively correlated with delusional thinking ($r = -0.47$, $P = 0.03$, uncorrected). In contrast, there were no significant correlations between levels of delusional thinking and the magnitude of SR-related responses of the MPFC or PCC bilaterally, or significant associations between AL-related responses of any of the a priori ROIs and levels of delusional thinking.

Exploratory analyses of additional contrasts

For both the S > AL and O > AL contrasts, there was significantly greater activation of the MPFC and PCC bilaterally, and the left

Table 1 Results of the regions of interest analysis

	R MPFC	L MPFC	R PCC	L PCC	R LTC	L LTC
Social reflection (% signal change)	−0.02 (0.12)	−0.01 (0.11)	−0.05 (0.10)	−0.03 (0.08)	−0.01 (0.08)	0.06 (0.08)
Affect labeling (% signal change)	−0.09 (0.13)	−0.10 (0.11)	−0.10 (0.13)	−0.10 (0.11)	−0.02 (0.07)	0.01 (0.06)

Data are represented as means with standard deviations (s.d). Average percentage signal change during the social reflection (SR) and affect labeling (AL) tasks, relative to a mean blood oxygen level–dependent signal intensity baseline, was extracted from the three anatomical ROIs the medial prefrontal cortex (MPFC), posterior cingulate cortex (PCC), and lateral temporal cortex (LTC). An analysis of variance showed a significant region by task interaction (see Results). Significantly greater responses during SR compared to AL were found in all three anatomical ROIs ($n = 22$), $P < 0.05$).
L, left; R, right.

Table 2 Results of the cortical surface–based analyses

Region	BA	Area (mm^2)	Tal (*x*, *y*, *z*)	*Z* score	*P*
A. Clusters of significant activation for the SR *vs* AL contrast					
L medial frontal gyrus	11	2920	−8, 47, −10	4.89	5.0×10^{-7}
L middle frontal gyrus	9	304	−20, 35, 29	4.10	2.1×10^{-5}
L middle frontal gyrus	9	337	−25, 36, 27	3.72	1.0×10^{-4}
R medial and middle frontal gyri	9/10	1991	8, 50, 15	4.41	5.0×10^{-6}
L posterior cingulate gyrus	23/31	2688	−5, −58, 26	5.42	3.0×10^{-8}
R posterior cingulate gyrus	23/31	1088	8, −48, 25	4.61	2.0×10^{-6}
L angular and middle temporal gyri	21/39	5003	−40, −53, 24/−58, −14, −16	5.24	8.0×10^{-8}
R angular gyrus	39	617	45, −54, 25	4.61	2.0×10^{-6}
L inferior frontal gyrus	47	1371	−28, 17, −17	3.72	1.0×10^{-4}
B. Clusters of significant activation for the S *vs* AL contrast					
L medial and middle frontal gyri	9/10	2058	−9, 43, 20	4.75	1.0×10^{-6}
L middle frontal gyrus	9	365	−25, 37, 28	3.94	4.1×10^{-5}
R medial frontal gyrus	10	525	8, 52, 15	3.94	4.1×10^{-5}
L posterior cingulate gyrus	23/31	2108	−5, −59, 26	4.12	1.9×10^{-5}
R posterior cingulate gyrus	23/31	567	7, −57, 20	3.54	2.0×10^{-4}
L superior temporal gyrus	22	3218	−57, −49, 4	4.26	1.0×10^{-5}
C. Clusters of significant activation for the O *vs* AL contrast					
L medial and middle frontal gyri	11	2808	−9, 47, −12	4.75	1.0×10^{-6}
R medial frontal gyrus	10	2101	9, 61, −3	4.34	7.0×10^{-6}
L superior frontal gyrus	6	323	−19, 29, 35	4.11	2.0×10^{-5}
L posterior cingulate gyrus	23/31	1935	−6, −58, 30	5.27	6.8×10^{-8}
R posterior cingulate gyrus	23/31	1435	7, −54, 28	5.07	2.0×10^{-7}
L middle temporal gyrus	21	5417	−60, −17, −14	5.61	1.0×10^{-8}
R middle temporal gyrus	21	323	53, −19, −13	3.24	6.0×10^{-4}
R angular gyrus	39	1016	45, −54, 26	4.75	1.0×10^{-6}
L inferior frontal gyrus	47	2105	−29, 18, −17	4.11	2.0×10^{-5}
R inferior frontal gyrus	47	607	25, 15, −16	3.54	2.0×10^{-4}
L lingual gyrus	18	484	−14, −69, −2	3.78	7.8×10^{-5}

Location and size of clusters of vertices which showed significant SR > AL (A), S > AL (B), and O > AL (C) activation with Talairach (Tal) coordinates, *z* value, and *P* value for the local p minimum for each cluster. Clusters of activated vertices with a corrected cluster-wise *P* value < 0.05 were identified using a Monte Carlo simulation (see Materials and Methods). There were no loci that showed significantly greater activation for the AL condition, relative to SR, S, or O.
BA, Brodmann area; L, left; SR, social reflection; R, right; S, self reflection; O, other reflection. AL, affect labeling

LTC, similar to the pattern seen for the SR > AL contrast (Table 2A–C). Left LTC responses were also negatively correlated with delusional thinking for both the S ($r = -0.55$, $P = 0.008$) and O ($r = -0.62$, $P = 0.002$) conditions. There were no significant associations between MPFC or PCC responses during the S or O conditions and delusional thinking.

Resting-state BOLD activity correlations

We followed up our main finding—a negative correlation between SR-related responses of the left LTC and delusional thinking—by testing whether this LTC region also showed aberrant functional coupling within the default network in association with delusional thinking. To examine this, a seed-based functional connectivity analysis was conducted, using a spherical seed centered on the coordinates of the activation peak for the SR > AL contrast within the left LTC (BA 21; [*x*, *y*, *z*]: −58, −14, −16). This seed (Figure 2A) demonstrated significant positive functional connectivity with several default network regions, including bilateral MPFC, PCC, and LTC (Figure 2B and C and Table 3A).

A whole brain analysis using PDI total score as a regressor revealed that delusional thinking was negatively correlated with the strength of functional connectivity between the left LTC and left MPFC ($z = 2.86$; $P = 0.002$) (Figure 3A and B and Table 3Bi) and also showed positive correlations with the connectivity between the left LTC and the right dorsal middle frontal gyrus ($z = 2.96$; $P = 0.001$) and right inferior temporal gyrus ($z = 3.90$; $P = 5 \times 10^{-5}$) (Table 3Bi).

A second whole brain analysis, using left LTC response during SR as a regressor, revealed that the magnitude of left LTC responses during SR was positively correlated with the strength of the connectivity between the left LTC and default network regions, including the left MPFC [$z = 4.01$; $P = 3.0 \times 10^{-5}$ (Figure 3C and D)], PCC, and inferior parietal cortex (Table 3Bii). Finally, there were negative correlations between left LTC responses during SR and the connectivity between the left LTC and right temporal cortices.

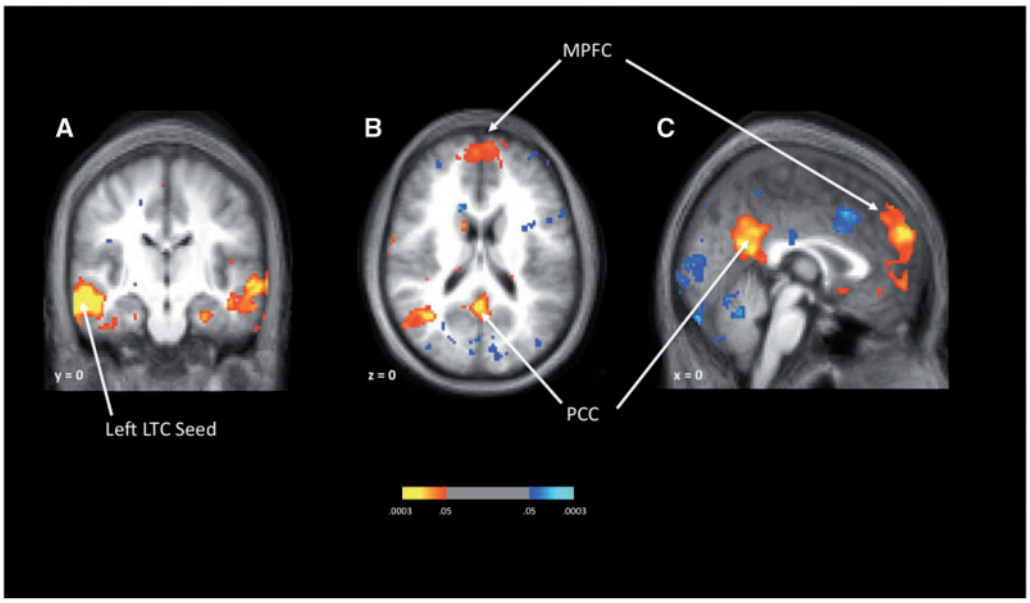

Fig. 2 Functional connectivity of the left lateral temporal cortex. Coronal (**A**), transverse (**B**), and sagittal (**C**) views of the T map of the connectivity of the left lateral temporal cortex (LTC) seed are displayed at a threshold of $P < 0.05$. The site of the seed and regions with high levels of functional connectivity with the seed (MPFC and PCC) are indicated with white arrows. Voxels with positive functional connectivity with the seed are indicated by warm colors (red and yellow); voxels with negative functional connectivity (anticorrelated) with the seed are indicated by cool colors (blue).

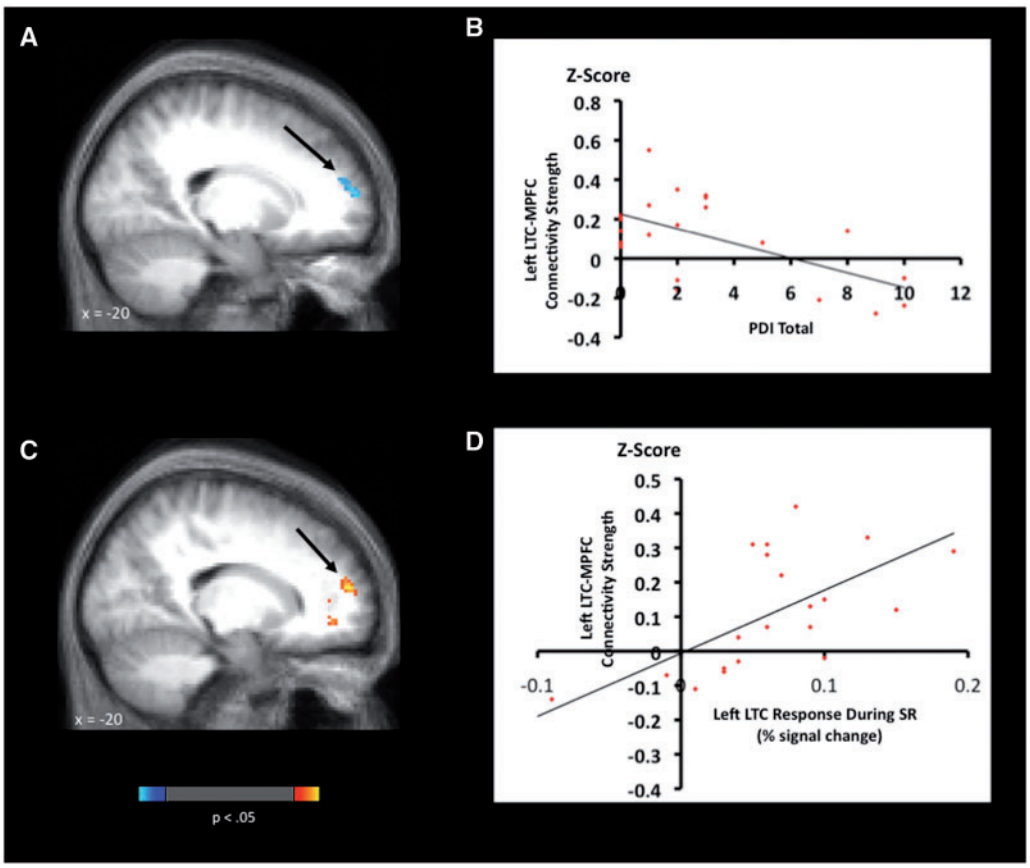

Fig. 3 Relationships between the strength of left LTC functional connectivity and (i) delusional thinking and (ii) its response during social reflection. (**A**) A sagittal view of the whole brain regression map revealing a significant negative correlation between delusional thinking and the strength of the connectivity between the left LTC and MPFC is displayed; the site with the highest correlation is indicated by an arrow. (**B**) A scatter plot {generated by extracting resting BOLD correlations between the left LTC and the MPFC site shown in the map in A (BA 10; [*x*, *y*, *z*]: −20, 56, 10)} further illustrates this relationship. (**C**) A sagittal view of the whole brain regression map of the relationship between left LTC functional connectivity and left LTC responses during social reflection (SR) is displayed. A significant correlation between SR-related left LTC activation and left LTC connectivity with default network regions, including the left MPFC (see arrow) was found; (**D**) A scatter plot {generated by extracting resting BOLD correlations between the left LTC and the MPFC site shown in the map in C (BA 10; [*x*, *y*, *z*]: −20, 53, 12)} illustrates the correlation between left LTC–MPFC connectivity strength and left LTC response during SR.

Table 3 Results of the functional connectivity analyses

Region	BA	*k*	Tal (*x*, *y*, *z*)	*Z* score	*P*
A. Regions showing positive or negative functional coupling with the left lateral temporal cortex					
Positive correlations					
L superior temporal gyrus	22	3103	−49, −20, −10	5.16	1.2×10^{-7}
R middle temporal gyrus	21	1885	60, −23, −2	4.82	7.2×10^{-7}
L dorsal posterior cingulate gyrus	30	796	−1, −50, 19	4.43	5.0×10^{-6}
L cuneus	19	660	−37, −58, 19	4.37	6.0×10^{-6}
L middle frontal gyrus	9	2161	0, 58, 28	4.36	7.0×10^{-6}
Negative correlations					
R supramarginal gyrus	40	894	61, −35, 36	5.13	1.4×10^{-7}
R precentral gyrus	9	409	33, 44, 28	4.67	2.0×10^{-6}
L parahippocampal gyrus	19	903	29, −62, 37	4.42	5.0×10^{-6}
L suprmarginal gyrus	40	767	−49, −38, 35	4.37	6.0×10^{-6}
R insula	13	516	34, 4, 15	3.92	4.4×10^{-5}
R cuneus	18	516	2, −94, 10	3.87	5.4×10^{-5}
L dorsal anterior cingulate gyrus	32	522	0, 17, 38	3.72	9.9×10^{-5}
B. Results of the whole brain regression analyses					
i. Correlations with delusional thinking					
Positive correlations					
R inferior temporal gyrus	20	35	59, −32, −14	3.90	4.8×10^{-5}
R middle frontal gyrus	8	36	15, 28, 47	2.96	1.5×10^{-3}
Negative correlations					
L medial frontal gyrus	10	32	−20, 56, 10	2.86	2.1×10^{-3}
ii. Correlations with left LTC response during SR					
Positive correlations					
L medial frontal gyrus	10	202	−14, 45, 1	4.25	1.1×10^{-5}
L medial frontal gyrus	10	36	−20, 53, 12	4.01	3.0×10^{-5}
L medial orbital frontal gyrus	11	39	0, 28, −26	3.52	2.4×10^{-4}
L dorsal posterior cingulate gyrus	30	232	−13, 48, 22	3.80	7.2×10^{-5}
L orbital frontal gyrus	47	115	−41, 23, −11	3.76	8.4×10^{-5}
L angular gyrus	39	48	−40, −62, 26	3.44	2.9×10^{-4}
Negative correlations					
R superior temporal gyrus	22	29	45, −17, −6	4.34	7.0×10^{-6}
R inferior temporal gyrus	20	27	54, −29, −23	2.91	1.8×10^{-3}

A. Location (BA and name of region) and size (*k*) of clusters showing significant positive and negative correlations with the left lateral temporal cortex (LTC) seed. B. Location (BA and name of region) and size (*k*) of clusters showing a significant association between their connectivity with the left LTC and (i) the magnitude of delusional thinking (PDI total score) or (ii) the left LTC response during social reflection. BA, Brodmann's area; Tal, Talairach; L, left; R, right; LTC, lateral temporal cortex; PDI, Peters *et al*. Delusions Inventory; SR, social reflection.

DISCUSSION

Summary of findings

Here such as, we found that in a sample of healthy subjects, a greater level of delusional thinking was associated with lower responses of the left LTC during reflection on the self and others ('SR'). Although anxiety and delusional thinking were correlated with one another, anxiety did not show the same relationship to neural responses during SR. Further, our main finding was unaltered after controlling for anxiety, suggesting that this pattern of neural activity may be specifically linked to delusional thinking. Several associations between delusional thinking and the functional connectivity of the left LTC were also observed, with negative correlations between delusional thinking and left LTC-MPFC connectivity and positive correlations between the connectivity of the left LTC and right dorsal frontal and inferior temporal cortices. Because we also found that the magnitude of the left LTC response during SR predicted the strength of the functional coupling between the left LTC and left-sided default network regions, including the MPFC, these results suggest that reduced LTC responsivity and reduced functional coupling between the LTC and MPFC may be linked in delusion-prone individuals. Thus, poor functional coupling between frontal and temporal cortices in delusional states may lead to impaired responses of regions of this network (such as the left LTC) during SR. Because portions of the LTC have been shown to play a key role in mental operations involving inferring the mental states or intentions of others (Goel *et al.*, 1995; Brunet *et al.*, 2000; Saxe and Kanwisher, 2003), our results suggest that reduced input to this region from frontal cortical areas could lead to errors in the attribution of intentions during social interactions, which could give rise to delusions. Increased coupling between the left LTC and right dorsal frontal and inferior temporal cortices in delusional thinking may, in turn, represent a compensatory response to reductions in LTC activity and LTC-MPFC connectivity. Overall, these results suggest that attenuated activity and aberrant connectivity of a lateral temporal-medial frontal network are associated with delusional thinking in non-clinical subjects.

Relationship to previous findings

Previous studies have found links between abnormalities in the function or size of temporal lobe structures and the presence or severity of delusions or symptoms of psychosis in general (Liddle *et al.*, 1992; Kaplan *et al.*, 1993; Silbersweig *et al.*, 1995; Takahashi *et al.*, 2009; Rotarsk-Jagiela *et al.*, 2010). For example, Takahashi *et al.* (2009) showed that progressive gray matter volume reduction of the left superior temporal sulcus was associated with greater severity of delusions during first episode psychosis and with greater risk of transitioning to psychosis in individuals at risk for developing psychotic disorders. Other studies have linked delusions in schizophrenia or schizotypy and abnormalities in the function of other default network regions, including the MPFC (Modinos *et al.*, 2010, 2011; Menon *et al.*, 2011) and PCC (Holt *et al.*, 2011b). Overall, this prior work and this study are consistent with the possibility that default network function is disrupted in individuals prone to or actively experiencing delusions.

Moreover, the evidence linking aberrant default network responses with delusions in schizophrenia, and our findings of reduced activity in the same network in association with delusional beliefs in healthy subjects, support the hypothesis that delusional thinking in the general population is on a neurobiological continuum with clinical delusions.

However, the interpretation of our findings is limited by the fact that we measured delusions via self-report. Thus, it is possible that delusional thinking was underreported among our participants. Although conducting semistructured interviews may have enhanced our assessment of delusional thinking, the PDI has reliably distinguished patients with psychotic disorders from healthy subjects (Schürhoff *et al.*, 2003; Scott *et al.*, 2009), suggesting that it is a valid measure of delusion-like beliefs. Future studies measuring delusional thinking using several different methods, including interviews, are needed to confirm these initial findings.

The role of the lateral temporal cortex in social cognition

In healthy subjects, neuroimaging studies have shown that the LTC is reliably recruited during a wide range of social cognitive processes, such as theory of mind (Goel *et al.*, 1995; Russel *et al.*, 2000; Calder *et al.*, 2002; Perner *et al.*, 2006; Brüne *et al.*, 2008), empathy (Völlm *et al.*, 2006), face recognition (Kircher *et al.*, 2001; Platek *et al.*, 2006), and self and other processing (Saxe *et al.*, 2006; Svoboda *et al.*, 2006). Although previous studies frequently report MPFC activity during tasks requiring self-awareness and self-referential processing (Northoff and Bermpohl, 2004; Heatherton, 2011; Frith and Frith, 2012), activity within the LTC has been most commonly seen during tasks requiring subjects to judge mental states and attributes of others (Lou *et al.*, 2004; Hein and Knight, 2008). However, the existence of networks specific to self or other processing is a subject of ongoing debate (Happé, 2003; Lou *et al.*, 2004; Denny *et al.*, 2012). According to simulation models of social perception, self-reflection may serve as the basis for inferring attributes and intentions of others. Thus, the networks mediating these seemingly distinct mental processes may be overlapping (Tamir and Mitchell, 2010). We found that LTC responses during self and other-reflection were both negatively correlated with levels of delusional thinking. Follow-up studies employing an event-related design (with behavioral measurements indicating the degree of self or other relevance of stimuli) will be needed to test whether delusional thinking is more closely related to disrupted processing of self or other-relevant information or whether both are affected.

Other models of delusions

Studies of the cognitive basis of delusions have found abnormalities in associative learning and memory processes in delusional patients (Corlett *et al.*, 2007; Romaniuk *et al.*, 2010; Holt *et al.*, 2012). These abnormalities may give rise to delusions via inappropriate 'prediction error' signaling (i.e. signaling that there is an environmental stimulus that violates one's expectations) (Corlett *et al.*, 2006, 2007) or an inability to retrieve a 'safety signal' (a fear extinction memory) in a context-appropriate manner (Holt *et al.*, 2012). These data suggest that people with deficits in associative memory processes supporting emotional/salience processing may be more vulnerable to delusions. However, these data do not account for a key phenomenological feature of many delusional beliefs – that they tend to involve social themes, rather than random events. One possibility is that associative memory abnormalities in delusions may be particularly disruptive of social cognitive processes. Future studies examining associative memory processes and social perception in the same subjects will shed further light on this issue.

Clinical implications and future directions

These findings have several clinical implications. First, if abnormalities of the neural circuitry supporting SR contribute to delusional beliefs, psychosocial interventions fostering improved self and other understanding may provide a valuable adjunct to antipsychotic medications in the treatment of strongly held delusions and could promote recovery of social functioning (Lysaker *et al.*, 2011). Second, the patterns of brain activity associated with delusional thinking could serve as quantitative biomarkers to facilitate the early detection and treatment of psychosis. To establish the predictive validity of such a biomarker, follow-up studies must confirm that the delusion-associated patterns of LTC activity and connectivity reported here are also found in the prodromal stages of clinical psychosis. Future longitudinal studies can ultimately determine the degree of overlap between the pattern of neural responses during SR seen in people with attenuated delusional beliefs and those who develop clinically impairing delusions.

Conflict of Interest

None declared.

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