Exploring the Neural Correlates of Delusions of Reference

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Background: Referential delusions are the most common symptom of schizophrenia and offer an opportunity to examine the neural correlates of delusions because they occur in discrete episodes that can be studied in the scanner. The cortical midline structures (CMS) and subcortical regions, including the amygdala and striatum, are linked with self-reference in healthy adults. Less is known about the neural substrates of altered self-reference in schizophrenia.

Methods: In this study, patients with schizophrenia experiencing prominent referential delusions (n = 18) and healthy control subjects (n = 17) were presented with ambiguous sentences while in the magnetic resonance imaging scanner and asked to rate whether they felt the sentences had been written specifically about them. The sentences were either generic (nonpersonalized) or individually tailored personalized sentences, designed to induce referential ideation. We hypothesized that both groups would show activity in the CMS, limbic, and striatal regions and that induced referential ideation would be associated with greater activity in striatal areas in patients with schizophrenia.

Results: A robust main effect of endorsement (endorsed vs. nonendorsed) was observed in the CMS, as well as subcortical regions, including the nucleus accumbens/ventral striatum, amygdala, insula, and midbrain dopamine regions. A group-by-endorsement interaction was seen in the medial prefrontal cortex, insula and nucleus accumbens/ventral striatum. Activity in insula and ventral striatum also correlated with the strength of the delusions of reference.

Conclusions: Referential ideation in persons with delusions is associated with heightened CMS, limbic and striatal activity and reduced differentiation between self- and non-self-relevant information.

Key Words: Delusions of reference, fMRI, neuroimaging, schizophrenia, self-reference

Evidence linking delusions to the aberrant salience hypothesis comes primarily from self-reports of schizophrenia patients regarding delusional beliefs, rather than direct observation of the events and consequent appraisals from which these delusions originate. A major obstacle to examining this relationship is that the stimuli that trigger aberrant salience are inherently unpredictable and therefore difficult to examine in an experimental setting. One exception might be delusions of reference. Referential delusions were originally identified by Kraepelin (19) and are among the most common symptoms of schizophrenia, present in 67% of persons with the disorder (20). Patients experiencing these symptoms have the perception that stimuli, such as something in the newspaper, television, radio, or overheard statements of strangers walking by, somehow refers specifically to them. Alternatively, they have the spontaneous feeling that objects are specifically arranged or ordered so as to convey meaning or messages specifically to them (e.g., the series of license plates of cars parked on the streets) (21). In both cases, these instances of heightened self-relevance appear to be discrete moments during which people experience this sensation of aberrant salience, followed by a post hoc explanation of that experience in terms of one’s personal experience.

Although the neural correlates of delusions have not yet been examined in detail, an emerging body of literature has examined the neural correlates of self-reference in healthy individuals, in tasks in which people make trait attributions about themselves or others (22–27), or during subjective preference judgments (28). The brain regions collectively referred to as the cortical midline structures (CMS) have consistently been found to be involved in tasks requiring judgments of self-relevance, across various functional domains (verbal, spatial, motor, etc.). The CMS structures include the ventro-medial (vmPFC) and dorsomedial prefrontal cortex (dmPFC), the anterior cingulate cortex (ACC) and posterior cingulate cortex (PCC), and precuneus (29). These structures (medial PFC (mPFC), rostral ACC, and the precuneus) have strong connections with limbic and striatal dopamine regions (30).
A recent review by Schmitz and Johnson (31) (Figure S1 in Supplement 1) proposed the presence of two subsystems involved in appraisal of self-relevant stimuli: 1) a ventral “reflexive” self-referential system implicating a vmPFC-ACC–subcortical ventral pathway involved in the attribution of salience and 2) a dorsal “reflective” self-referential system involving a dmPFC–cortical–subcortical dorsal pathway that engages introspective processes (e.g., self-reflection, evaluation, recollection), which functions either in conjunction with, or independent of, the former system. Reward-processing tasks typically engage brain regions associated with the former system, whereas studies examining self-referential processing typically use tasks associated with the latter “reflective” system. These tasks have also been used to examine self-referential information processing in schizophrenia (32,33) but do not resemble the typical experience delusions of reference.

In this study, we were interested in capturing the neural activity associated with the sense of heightened personal self-relevances that characterizes delusions of reference—in which external stimuli appear to be directly and specifically about the individual. Hence, participants carried out a task in the magnetic resonance imaging (MRI) scanner in which they were presented with ambiguous statements written in the third person (e.g., “he likes to drink coffee”) and asked whether they had the feeling that the statement was written specifically about them (rather than simply a judgment of whether the statement was true of them). We created a set of “generic” nonpersonalized statements, as well as personalized subject-specific statements. These latter statements were actually “specifically about them” and were meant to induce referential ideation.

Because delusions of reference are characterized by the sensation of heightened self-reference to ambiguous (but not actually self-referent) stimuli, we hypothesized that 1) patients would endorse comparatively more non-self-relevant stimuli—that is, stimuli outside of their customized set—as being “specifically about them” relative to control subjects; 2) endorsement versus nonendorsement of statements as self-relevant would yield significant blood oxygen level–dependent (BOLD) response in the both the “reflective” dorsal and “reflexive” ventral cortico–subcortical appraisal pathways; and 3) patients would exhibit greater BOLD activation than control subjects in the dopaminergic components of the ventral cortico–subcortical appraisal pathway during stimulus endorsement because of abnormal hyperdopaminergic neuronal response in the striatum (5,6).

Methods and Materials

Participants

Eighteen participants with prominent delusions of reference, as measured by a “delusions of reference” item score > 3 on the Schedule for Assessment of Positive Symptoms (SAPS) were recruited from the Schizophrenia Program at the Centre for Addiction & Mental Health. These individuals were compared with 17 control patients from the Schizophrenia Program at the Centre for Addiction & Mental Health. These individuals were compared with 17 control patients from the Schizophrenia Program at the Centre for Addiction & Mental Health.

Inclusion criteria for patients were as follows: 1) aged 18 to 65 years, 2) English fluency, 3) DSM-IV diagnosis of schizophrenia or schizoaffective disorder, 4) voluntary status, 5) capable of consenting to study participation, and 6) able to undergo functional MRI (fMRI) of approximately 50 min duration. Exclusion criteria included 1) serious, unstable medical illness or any concomitant major medical or neurological illness; 2) acute suicidal or homicidal ideation; 3) DSM-IV substance dependence (except caffeine and nicotine) within 3 months; 4) current major depressive or manic episode; 5) metal implants, cardiac pacemaker, claustrophobia, or other limitations that would prevent carrying out the MRI component of the study; 6) illegal psychoactive drug use in the past 2 weeks; 7) severe head injury resulting in a loss of consciousness more than 30 min; and 8) SAPS formal thought disorder rating > 2. Criteria for control participants were similar to the patient group but included no present or previous psychiatric history, as measured by the Mini International Neuropsychiatric Interview (34). Patients and control subjects were matched on age, gender, and estimated premorbid IQ, measured using the Wide Range Achievement Test reading subtest (35). Capacity to consent was confirmed for all patient participants with the MacArthur Test of Competence (36), and after complete description of the study, written informed consent was obtained from all participants. The study was approved by the Research Ethics Board of the Centre for Addiction and Mental Health.

Task

The task was designed to evoke sensations similar to ideas or delusions of reference. During practice trials, participants were given the following instructions: “Sometimes people get a feeling that something they see or hear (like on TV or when people are walking past them) is actually about them. We want to know what causes that feeling.” They were then presented with ambiguous sentences describing personal characteristics (e.g., “He is lazy” or “She likes to drink coffee” with the pronoun matched to the gender of the subject). Subjects were then told, “As you see these statements, we want to know whether you feel that the statement was written specifically about you.” Participants used a two-button response box in their right hand and pressed “yes” or “no.” They carried out three practice trials, and it was clarified that they should not press “yes” merely if the sentence was self-descriptive or true of them, but rather only if they “had the feeling” that the statement had been written specifically about them, in a manner similar to what they may have experienced in the situations described earlier. It was clarified to all participants that this may be uncommon in the task. Following completion of the practice trials, participants were taken to the MRI scanner where they carried out two runs of the task. In each run, they carried out 60 trials (30 statements, each repeated twice). Thus, across both runs, participants saw 60 unique statements: 20 “neutral” (e.g., “He collects CDs,” “She has a driver’s license”); 20 “emotionally salient” (e.g., “He was in a horrible accident,” “Everybody hates her”); and 20 “personally salient” individually created subject-specific statements. These personalized subject-specific statements consisted of information about the individual’s current life circumstances, hobbies, interests, and symptomatology, all taken from the screening interview conducted a several weeks before the scanning session, which were meant to induce referential ideation.

Stimuli were presented using E-Prime software (Psychology Software Tools, Pittsburgh, Pennsylvania). Each statement was presented for 5 sec, with a variable interstimulus interval (ISI) of 1.5 to 3 sec during which participants saw a fixation cross. Participants could respond at any point before the presentation of the subsequent sentence.

After completing the task in the scanner, participants were presented with the stimuli once more and asked to provide specific ratings using visual analogue scales for the valence of the statement (rated from 0 = very negative to 10 = very positive), the self-descriptiveness of the statement (“How true is this statement of you?” from 0 not true at all to 10 very true), strength of endorsement (“How strong was the feeling that the statement was specifically about you?” from 0 = not very strong to 10 = very strong), and specificity of endorsement (“Could this be a statement about peo-
All contrasts, unless otherwise specified, were analyzed using a group, endorsement, and the group interaction. We carried out the analysis of the fMRI data using a T2*-sensitive spiral sequence (repetition time 200 ms). The first three volumes were discarded to allow for T1 equilibrium effects, and the data from the remaining 149 volumes were used in the analysis.

For localization purposes, inversion recovery-prepped three-dimensional fast spoiled gradient recalled T1-weighted anatomic images (120 contiguous axial 1.1 mm thick slices) were acquired (repetition time = 12 ms; echo time = 5.4 ms; flip angle 20°; matrix 256 × 256; field of view 200 × 200 mm).

Image Preprocessing

The data were preprocessed and analyzed using SPM5 (The Wellcome Department of Cognitive Neurology, London, United Kingdom; http://www.fil.ion.ucl.ac.uk/spm/software/spm5). All functional images were realigned to the first volume using a six-parameter rigid body transformation, and a mean image was created. Data from subjects who showed movement of greater than two voxels on any axis were discarded. The mean image generated was spatially normalized into standard stereotactic space, using the Montreal Neurological Institute echo planar imaging template. Computed transformation parameters were applied to all functional images, interpolated to isotropic voxels of 3 mm³, and the resulting images were smoothed using an 8-mm full-width half-maximum, isotropic Gaussian kernel.

Whole-Brain Data Analysis

We were interested in the difference between the statements participants endorsed as being specifically about them versus non-endorsed statements. We carried out the analysis of the fMRI data using a 2 group × 2 endorsement (endorsed vs. nonendorsed) repeated measures analysis of variance. We examined main effect of group, endorsement, and the group × endorsement interaction. All contrasts, unless otherwise specified, were analyzed using a whole-brain false discovery rate (FDR) corrected p value of < .05 and an extent threshold of 10 voxels.

Relationship with Symptomatology

To examine the relationship between psychotic symptomatology and the BOLD response during instances of referential ideation, we ran regressions in SPM at the second level, using BOLD response to endorsed trials as our contrast of interest and the SAPS referential delusions item as a covariate of interest. These results did not survive whole-brain FDR correction, and therefore a region-of-interest approach was used, specified using region-of-interest masks based on the Mawlawi et al. (37) criteria for striatal regions (bilateral masks of caudate, putamen, ventral striatum/nucleus accumbens) and Brodmann area masks for amygdala, insula, and mPFC.

Results

Data for four participants from the schizophrenia group and two participants from the control group could not be used because of excess head motion. The final sample consisted of 14 patients and 15 control subjects (see Table 1 for demographic information). All patients were on atypical antipsychotic medication (olanzapine = 5; risperidone = 2; quetiapine = 2; clozapine = 5; mean chlorpromazine equivalent dose = 412.9 mg) (38).

<table>
<thead>
<tr>
<th>Variable</th>
<th>Schizophrenia (n = 14/18)</th>
<th>Control Subjects (n = 15/17)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex (male/female)</td>
<td>10/4</td>
<td>10/6</td>
</tr>
<tr>
<td>Age (years)</td>
<td>40.57 (12.8)</td>
<td>35.87 (6.9)</td>
</tr>
<tr>
<td>School (years)</td>
<td>12.66 (2.48)</td>
<td>16.90 (2.1)</td>
</tr>
<tr>
<td>SAPS Delusions (Global)</td>
<td>3.8 (1.9)</td>
<td>—</td>
</tr>
<tr>
<td>SAPS Delusions of Reference</td>
<td>4.3 (.9)</td>
<td>—</td>
</tr>
<tr>
<td>SAPS Persecutory Delusions</td>
<td>2.1 (1.6)</td>
<td>—</td>
</tr>
<tr>
<td>SAPS Hallucinations (Global)</td>
<td>2.8 (1.9)</td>
<td>—</td>
</tr>
<tr>
<td>SAPS FTD (Global)</td>
<td>.4 (.6)</td>
<td>—</td>
</tr>
<tr>
<td>SANS Affective Flattening</td>
<td>1.2 (.7)</td>
<td>—</td>
</tr>
</tbody>
</table>

FTD, Formal Thought Disorder; SANS, Schedule for Assessment of Negative Symptoms; SAPS, Schedule for Assessment of Positive Symptoms; WRAT, Wide Range Achievement Test.

*p < .01.

Table 1. Sociodemographic Characteristics of the Final Sample

<table>
<thead>
<tr>
<th>Variable</th>
<th>Schizophrenia (n = 14)</th>
<th>Controls (n = 15)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of Items Endorsed</td>
<td>26.64 (7.8)</td>
<td>18.93 (6.9)</td>
</tr>
<tr>
<td>Personalized Items Endorsed</td>
<td>17.50 (3.8)</td>
<td>16.60 (3.8)</td>
</tr>
<tr>
<td>Generic Items Endorsed</td>
<td>9.14 (4.9)</td>
<td>3.13 (1.9)</td>
</tr>
<tr>
<td>Neutral Generic Items Endorsed</td>
<td>5.08 (2.8)</td>
<td>2.20 (3.6)</td>
</tr>
<tr>
<td>Emotional Generic Items Endorsed</td>
<td>4.15 (3.55)</td>
<td>.87 (1.0)</td>
</tr>
<tr>
<td>Valence Rating (Endorsed Items)</td>
<td>4.76 (1.9)</td>
<td>6.33 (9)</td>
</tr>
<tr>
<td>Valence Rating (Nonendorsed Items)</td>
<td>3.93 (1.3)</td>
<td>3.64 (7.9)</td>
</tr>
<tr>
<td>Self-descriptiveness (Endorsed Items)</td>
<td>7.50 (1.7)</td>
<td>8.17 (1.4)</td>
</tr>
<tr>
<td>Self-descriptiveness (Nonendorsed Items)</td>
<td>1.62 (7.7)</td>
<td>2.62 (1.1)</td>
</tr>
<tr>
<td>Strength of Endorsement</td>
<td>7.50 (1.7)</td>
<td>8.17 (1.4)</td>
</tr>
<tr>
<td>Specificity of Statement</td>
<td>7.25 (1.6)</td>
<td>7.21 (1.1)</td>
</tr>
<tr>
<td>Reaction Time (Endorsed)</td>
<td>2.20 (3.3)</td>
<td>1.96 (3.3)</td>
</tr>
<tr>
<td>Reaction Time (Nonendorsed)</td>
<td>2.01 (3)</td>
<td>1.50 (1.3)</td>
</tr>
<tr>
<td>Reaction Time Difference (Endorsed – Nonendorsed)</td>
<td>.19 (.2)</td>
<td>.46 (.3)</td>
</tr>
</tbody>
</table>

*p < .01, independent samples t test (patients vs. control subjects).

*p < .001, independent samples t test (patients vs. control subjects).

*p < .05, paired samples t test (endorsed vs. nonendorsed).

*p < .001, paired samples t test (endorsed vs. nonendorsed).

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stimuli as did control subjects). There were between-group differences with patients endorsing more “generic” emotional items ($t_{26} = 3.28, p = .006$) and a trend toward more neutral items ($t_{26} = 2.39, p = .024$) than control subjects, reflecting the fact that patients endorsed significantly more generic stimuli overall.

When we examined the response latencies for endorsement decisions, we found main effect of group ($F_{25} = 16.27, p < .001$), endorsement ($F_{25} = 61.9, p < .001$), as well as a group × endorsement interaction ($F_{25} = 11.08, p = .003$), see Figure S2B in Supplement 1. Specifically, patients were significantly slower at eliciting nonendorsement responses than control subjects ($t_{27} = 5.75, p < .001$), again suggesting greater difficulty in classifying stimuli as being non-self-relevant.

On the postscan questionnaire, responses to the question, “How emotional is this statement?” indicated no differences between groups on mean valence ratings ($t_{24} = .78, p > .3$). Similarly, there were no differences between groups for the strength of endorsement (i.e., “How strong was the feeling that this statement was written specifically about you?”; $t_{24} = .35, p > .7$), specificity rating (“Do you think this statement is specifically about you?”; $t_{24} = .05, p > .9$), or on these measures when responses were divided into endorsed and nonendorsed items. For both groups, the endorsed responses were rated as being more positive and more self-descriptive than the nonendorsed items ($F_{24} = 368.48, p < .001$).

**fMRI Results.** The group × endorsement analysis of variance showed significant main effects of endorsement (endorsed vs. nonendorsed), a group × endorsement interaction, and no main effect of group.

The main effect of endorsement (endorsed vs. nonendorsed, see Figure 1, Table 3, and Table S1 in Supplement 1) showed significant activity across most of the brain at our a priori threshold, and therefore an even more conservative threshold of $p < .001$ (whole-brain FDR correction, 10-voxel extent threshold) was used for this analysis.

**Discussion**

Our behavioral results indicate that schizophrenia patients endorse more ambiguous stimuli as being specifically about them. Although both patients and control subjects show a similar level of endorsement to the personalized stimuli (which were actually specifically about them), patients endorsed many more generic, nonpersonalized stimuli as inducing a similar sensation of heightened self-reference. The reaction time data indicate that patients and control subjects take similar amounts of time to decide which stimuli are self-relevant but that patients are slower at judging stimuli deemed non-self-relevant.

In terms of neural activity, our results suggest that experiences of heightened self-reference of ambiguous stimuli are characterized by activity in the CMS, as well as subcortical regions associated with stimulus salience, such as the insula, VS, and midbrain dopaminergic regions; these findings are consistent with previous research on self-reference (29,30,39). Although participants showed greater BOLD response to stimuli evaluated as self-referential (compared with stimuli evaluated as non-self-referential), the magni-
tude of the difference appears to be smaller in parts of the mPFC, VS/NA, and the insula in patients. The BOLD response in the insula and VS was also positively correlated with the intensity of referential delusions experienced by the patients.

The behavioral and imaging data thus provide converging evidence that in patients, there appears to be reduced differentiation between the stimuli considered self-referential and non-self-referential, making it more difficult for them to correctly reject the information as non-self-relevant. This mirrors findings from reward-learning paradigms that find patients show elevated striatal activity in response to nonreinforced, “neutral” (or nonsalient) stimuli (12,15), consistent with the “aberrant salience” hypothesis. These findings are also consistent with Schmitz and Johnson’s two-process model of self-referential processing, which suggests that the activity in VS-limbic-vmPFC pathway is associated with the attribution of salience, and “reflexive” self-reference, which might be heightened in patients. Over time, numerous instances of such experiences of heightened self-relevance might increase anxiety or negative affect and further prime the system in the direction of increasing vigilance. The sensations of anxiety and heightened self-reference, in turn, contribute to paranoia. The resulting self-generated explanations, based on the individual’s life history and psychodynamic processes, are the delusions with which the patients present.

The finding of systematic hyperactivity in regions involved in self-reference are also consistent with a growing body of research looking at activity in the “default mode network” and its link to self-reflection and internally oriented processing (40–43). The default mode network has been found to show abnormal connectivity (44) and reduced task-related suppression (45,46) in schizophrenia. We also found activity in regions, such as the superior temporal gyrus (see Tables S2 and S3 in Supplement 1), that have been implicated in sensations of heightened self-reference associated with mutual eye gaze, in which the patient feels that averted gaze is direct, causing the sensation of “people are looking at me” when they might not be (47–50).

Neurobiological theories of self, such as the somatic marker hypothesis (51), propose that the sense of self lies along a continuum of awareness, ranging from highly aware explicit (or “reflective”) modes of self-evaluation to more implicit “reflexive” modes of self-referential processing, such as that associated with a “gut feeling” in motivational disposition. The latter end of this self-awareness continuum has received comparatively less attention in neuroimaging research; however, reflexive self-referential processes guide much of our daily decision-making behaviors. The paradigm used in this study aimed to address this issue. Unlike other studies, which looked at the neural correlates of “reflective” self-referential processes by asking people to judge whether a presented statement was “true of them,” this study asked subjects to endorse the statement only if they felt it had been written specifically about them, irrespective of whether they thought it was self-descriptive, thus engaging both reflective and reflexive processes. Interestingly, a number of patients following the scanning session reported that the experience was similar to the sensation evoked during delusional ideation, necessitating debriefing after the scanning session to reassure participants that the statements were taken from their prior screening interview.

All participants were on medication, which might have had some effect on neural activity. Despite this, all patients showed delusions of reference and had elevated striatal activity, as hypothesized a priori. We would therefore predict effects of a larger magnitude in never-medicated patients with delusions of reference. Ambiguous statements may be less naturalistic than videotaped scenes as used by Park et al. (52); however, our method allowed us to tailor the ambiguous stimuli for each participant. Thus, we were able to create experiences akin to ideas of reference as noted by 

Table 3. Main Effect of Condition and Group × Condition Interaction in A Priori Regions of Interest

<table>
<thead>
<tr>
<th>Region</th>
<th>MNI Coordinates of Peak Voxel</th>
<th>F Value</th>
<th>Z Value</th>
<th>Cluster Size (Voxels)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ventral striatum/nucleus accumbens</td>
<td>10, 10, 4</td>
<td>29.82</td>
<td>4.71</td>
<td>29</td>
</tr>
<tr>
<td>Caudate</td>
<td>−10, 12, 2</td>
<td>27.06</td>
<td>4.52</td>
<td>34</td>
</tr>
<tr>
<td>Medial prefrontal cortex</td>
<td>−6, 56, 18</td>
<td>38.89</td>
<td>5.26</td>
<td>1687</td>
</tr>
<tr>
<td>Anterior cingulate</td>
<td>4, 32, 40</td>
<td>37.92</td>
<td>5.21</td>
<td>21</td>
</tr>
<tr>
<td>Anterior cingulate/precuneus</td>
<td>−6, −66, 36</td>
<td>59.04</td>
<td>6.18</td>
<td>422</td>
</tr>
<tr>
<td>Substantia nigra/VTA</td>
<td>−8, −22, −10</td>
<td>41.82</td>
<td>5.42</td>
<td>402</td>
</tr>
<tr>
<td>Insula</td>
<td>−28, 20, −4</td>
<td>36.20</td>
<td>5.11</td>
<td>63</td>
</tr>
<tr>
<td>Hippocampus</td>
<td>−26, −28, −10</td>
<td>37.33</td>
<td>5.18</td>
<td>50</td>
</tr>
<tr>
<td>Amygdala</td>
<td>−12, −6, −16</td>
<td>29.21</td>
<td>4.67</td>
<td>21</td>
</tr>
</tbody>
</table>

FDR, false discovery rate; MNI, Montreal Neurological Institute; VTA, ventral tegmental area.

All regions significant at a whole-brain FDR corrected threshold of p < .001 with a 10-voxel extent threshold, except the amygdala, which was significant at a lower threshold of p < .05 whole-brain FDR corrected and a 10-voxel extent threshold.

All regions significant at a whole-brain FDR corrected threshold of p < .05 with a 10 voxel extent threshold.
participants themselves. Follow-up studies are required to examine the specificity of the pattern of deficits seen here with the use of a clinical control group (patients without delusions of reference), as well as to examine the relationship between these instances of aberrant salience and other abnormalities in social cognition. Longitudinal studies would be beneficial to determine whether the patterns of activity change as delusions fluctuate.

Our results demonstrate for the first time that sensations of heightened self-relevance to ambiguous stimuli (a process thought to reflect the underpinnings of delusions of reference) are associated with increased BOLD response in a distributed network, likely involving numerous neurotransmitters, in parts of the mPFC as well as subcortical limbic and midbrain dopaminergic regions. Although it is worth stressing that these changes in BOLD response may also reflect downstream consequences of misattribution or other psychological mechanisms not reflected in BOLD activity, we speculate that the differential patterns of activity in the dmPFC, insula and striatal regions may underlie the phenomenological differences experienced between patients and control subjects and suggest that the decisions of self-reference and specificity of ambiguous stimuli might be the result of differential inputs from the “reflexive” and “reflective” networks in patients versus control subjects.

Following a continuum model approach, these same processes may, to varying degrees, also underlie the sensation of heightened self-consciousness experienced as part of “normal” experience in moments of heightened affect and play a role in other psychiatric conditions, including social anxiety and body dysmorphic disorder. A better understanding of cognitive and neural processes involved in delusions may also allow us to develop treatment options, such as transcranial magnetic stimulation or attentional bias modification, for symptom amelioration in treatment-refractory patients.

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