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## Deficit in a Neural Correlate of Reality Monitoring in Schizophrenia Patients

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**Patients who suffer from the devastating psychiatric illness schizophrenia are plagued by hallucinations, bizarre behavior, and delusional ideas, such as believing that they are controlled by malevolent outside forces. A fundamental human cognitive operation that may contribute to these hallmark symptoms is the ability to maintain accurate and coherent self-referential processing over time, such as occurs during reality monitoring (distinguishing self-generated from externally perceived information). However, the neural bases for a disturbance in this operation in schizophrenia have not been fully explored. Using functional magnetic resonance imaging, we asked clinically stable schizophrenia patients to remember whether or not they had generated a target word during an earlier sentence completion task. We found that, during accurate performance of this self-referential source memory task, the schizophrenia subjects manifest a deficit in rostral medial prefrontal cortex (mPFC) activity—a brain region critically implicated in both the instantiation and the retrieval of self-referential information in healthy subjects. Impairment in rostral mPFC function likely plays a key role in the profound subjective disturbances that characterize schizophrenia and that are the aspect of the disorder most troubling to patients and to society at large.**

**Keywords:** agency, cognition, fMRI, medial prefrontal cortex, self-referential processes, source memory

Patients who suffer from the devastating psychiatric illness schizophrenia are plagued by hallucinations (such as hearing harsh and critical voices coming out of nowhere), delusional ideas (such as believing that they are controlled by radio-waves), and the kinds of bizarre, disorganized thoughts, and behavior that have throughout history been classified as “madness.” Cataloguing these symptoms, mid-20th century psychoanalysts considered schizophrenia to be the quintessential disorder of the “self.” Indeed, behavioral research indicates that schizophrenia patients are unable to self-monitor multiple aspects of their inner and outer experiences. For instance, they are unable to distinguish between self-produced and externally produced tactile stimuli (Blakemore et al. 2000); they have trouble detecting and correcting their own action errors (Malenka et al. 1982; Turken et al. 2003); they do not show the normal enhanced memory performance for self-generated or self-referential items (Vinogradov et al. 1997); and they show reduced conscious awareness about their own knowledge base (Bacon et al. 2001). In functional neuroimaging experiments, schizophrenia subjects do not show normal modulation of activity in the right angular gyrus and the insula cortex in response to the degree of movement control of a virtual hand (Farrer et al. 2004); show a lack of normal error-related activity in the anterior cingulate cortex (Carter et al.

2001); and fail to activate brain areas involved in the monitoring of inner speech (McGuire et al. 1995; Shergill et al. 2003).

These important deficits do not fully account for the observed distortions in self-referential processing seen in schizophrenia, such as the lack of knowledge that one’s self has been the agent or author of prior mental events—what may in part be described as deficits in reality monitoring (the ability to distinguish between self-generated vs. externally perceived information) (Raye et al. 1980; Johnson et al. 1993). And yet, a fundamental human cognitive operation is our ability to maintain accurate and coherent self-referential processing over time. Without this, we would be incapable of understanding the source of our own thoughts, sensations, and actions; we would lack insight into our own attributes and mental contents; and we would not be able to construct a realistic or coherent personal narrative for our experiences (Bacon et al. 2001; Corcoran and Frith 2003; Riutort et al. 2003). We propose that a central feature of schizophrenia is an inability to retrieve in an efficient and accurate manner self-referential information, thus adversely affecting thinking patterns, autobiographical knowledge, and social behavior. Pursuant to this approach, we sought to answer the question: do patients with schizophrenia show abnormalities in the specific neural circuitry that is associated with the accurate recognition of self-referential information? (In this paper, we will employ the term “self-referential source memory performance” as a precise descriptor of our experimental task, which can be conceived of as one form of reality monitoring—distinguishing between internally generated and externally perceived information [Raye et al. 1980; Johnson et al. 1993].)

Neuroimaging studies of various forms of self-referential processing have demonstrated that medial prefrontal cortex (mPFC, corresponding to Brodmann’s area [BA] 10) is a key neural correlate when normal subjects engage in a number of introspective or internally generated mental processes in real time, such as daydreaming, making evaluative judgments about personal attributes or emotional content, and attributing mental states to others (Pardo et al. 1993; McGuire et al. 1996; Lane et al. 1997; Gusnard et al. 2001; Kelley et al. 2002; Zysset et al. 2002; Fossati et al. 2003). However, meta-analytic studies of imaging research relevant to BA 10 (Gilbert, Spengler, Simons, Frith, et al. 2006; Gilbert, Spengler, Simons, Steele, et al. 2006) reveal a great deal of functional specialization within this region along both the rostral-caudal and lateral-medial dimensions. For instance, medial and caudal subregions are engaged during “mentalizing” (thinking about the mental state of one’s self or others) specifically when there is emotional content (Gilbert, Spengler, Simons, Steele, et al. 2006); medial activations are also characteristic of low-demand externally oriented tasks where reaction times (RTs) are faster in the experimental condition

compared with the control condition (Gilbert, Spengler, Simons, Frith, et al. 2006). Such findings have led this research group to develop the “gateway hypothesis,” which posits that medial BA 10 influences the attentional balance between self-generated and perceptual information and contributes to the monitoring and verification of recollection (Simons, Gilbert, et al. 2005; Simons, Owen, et al. 2005; Burgess et al. 2007). As these are processes that are known to be impaired in schizophrenia, investigation of mPFC function in this illness is clearly warranted (see also Simons et al. 2006).

Before proceeding with this line of inquiry in schizophrenia, however, one is first obliged to develop an experimental task that controls for the potential confounds observed in previous studies of mPFC and self-referential processing in healthy subjects, as suggested by the meta-analytic study of Gilbert, Spengler, Simons, Steele, et al. (2006). These potential confounds are as follows. 1) Mentalizing—Is mentalizing a required component or can mPFC activation occur with other forms of self-referential processing, such as recognizing the source of self-generated information? 2) Emotional content—Does mPFC activation only occur when the self-referential information is emotionally salient? 3) Task performance—How does one assess performance accuracy during mentalizing tasks or when asking subjects to imagine events or carry out other “internal” cognitive operations?

All 3 factors could be critical in interpreting results obtained in a study comparing schizophrenia patients to healthy subjects, as individuals with schizophrenia have difficulty with mentalizing, show abnormal behavioral responses and brain activation patterns in response to emotional stimuli, and almost always have lower performance on cognitive tasks (e.g., see Heinrichs and Zakzanis 1998; Poole et al. 2000; Taylor et al. 2005; Lee et al. 2006). Thus, we developed a self-referential task suitable for functional magnetic resonance imaging (fMRI) in which subjects make self-referential source memory decisions that do not require explicit mentalizing about one’s self or another person, that use stimuli with neutral emotional valence, and that permit assessment of performance accuracy so that functional imaging analyses in an event-related design can focus on accurate trials only. We asked subjects to generate target nouns during a sentence completion task (i.e., to engage in implicit encoding of self-referential information) and later, during fMRI, asked them to distinguish between the target nouns they generated and the target nouns the experimenter presented to them. In healthy subjects, we demonstrated that rostral mPFC plays a key role during this form of self-referential source memory (what we termed the accurate retrieval of cognitive agency) under these conditions of neutral emotional valence (Vinogradov et al. 2006). Given the known difficulties that individuals with schizophrenia have in monitoring their own cognitions and actions, we then asked: when schizophrenia subjects perform this same task and accurately identify themselves as the source of previously self-generated word items under emotionally neutral conditions, do they show the normal patterns of activation of rostral mPFC?

## Materials and Methods

### Subjects

Eight healthy comparison subjects (4 females) and 8 clinically stable outpatients with schizophrenia (3 females) were recruited and gave written informed consent according to the Committee on Human

Research guidelines at the University of California, San Francisco. Data from the healthy comparison subjects have been presented previously (Vinogradov et al. 2006). Schizophrenia subjects were diagnosed by *Diagnostic and Statistical Manual—4th Edition*—criteria (American Psychiatric Association Press), had been ill an average of 10 years (range of 5–15 years), and were being treated with a range of antipsychotic medications (mean chlorpromazine [CPZ] equivalents of 350 mg; one subject unmedicated). In order to avoid the confounds of clinical acuity and severe symptomatic or cognitive impairment on task performance, schizophrenia subjects were specifically recruited who were clinically stable, high functioning, able to meet the cognitive and psychological demands of the experiment, and matched to the comparison subjects on the background cognitive variables of intelligence quotient (IQ), parental socioeconomic status (as indicated by parental education), and current education/employment status. Although all subjects we recruited were from the young to mid-adult age range (25–50 years), this set of inclusion criteria resulted in a statistically significant difference in the age distribution between the 2 groups, due to the fact that early adulthood is the time of greatest clinical acuity and symptomatic instability in schizophrenia patients, and it is thus often difficult to recruit younger patients to participate in demanding experimental protocols. Healthy comparison subjects had a mean age of 28 years (range of 25–33 years), and schizophrenia subjects a mean age of 38 years (range of 25–51 years),  $t = 2.9$ ,  $P < 0.02$ .

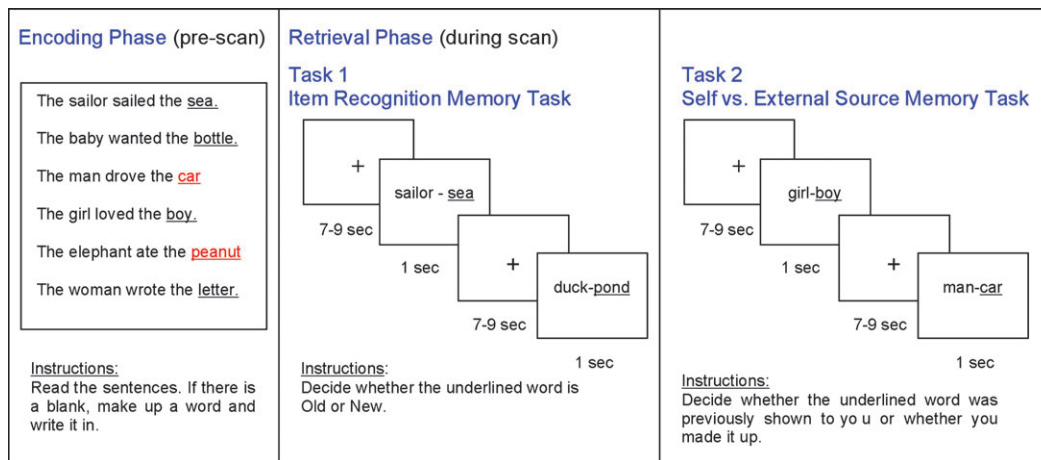
Mean IQ of the healthy comparison subjects was 112 (range of 105–125); mean parental education was 16 (range of 12–18); 2 of these subjects were enrolled in postcollege education, 3 were employed, and 3 were unemployed. In the schizophrenia sample, mean IQ was 108 (range of 102–119); mean parental education was 15 (range of 10–19); 2 subjects had completed 2 years of postcollege education, 4 were employed (2 full time and 2 part time), 3 were unemployed, and 1 was a student. There were no significant group differences on these background variables.

Schizophrenia subjects had a mean overall rating of 2.5 (range of 2.1–2.9) on the Positive and Negative Symptoms Scale (the scale has a range of 0–7; 2 indicates mild symptoms), with mean ratings of 2.8, 2.0, and 2.6 on positive, negative, and disorganized symptoms, respectively. None of the schizophrenia subjects had prominent negative symptoms.

### Cognitive Task

Each subject participated in an implicit encoding phase and a memory retrieval phase as adapted from Vinogradov et al. (1997, 2006) with the memory phase performed during MR imaging (Fig. 1). We employed an emotionally neutral sentence completion paradigm for the encoding phase and did not instruct subjects to focus on any aspect of their subjective experience; our goal was to ensure that the semantic and emotional associations for both self-generated and externally presented stimuli would be similarly constrained, with an implicit sense of agency as the only intervening variable.

In the encoding phase, subjects were told that they would participate in a reading and writing exercise and were presented with 180 sentence stimuli on paper. Each sentence had the structure noun-verb-noun with high semantic association and was emotionally neutral in content (*The sailor sailed the sea*). For two-thirds of the sentences, the subjects were asked to read the sentence to themselves, including the final underlined word; in these cases, the target noun was supplied by the experimenter. For one-third of the sentences, the final word was left blank (*The boy played with the \_\_\_\_*). Here, subjects were asked to make up and write down a final word and then read the sentence to themselves; in these cases, the target noun was generated by the subject. Both types of sentences were randomly interleaved throughout the study form. Although we did not directly assess the emotional or personal associations that subjects experienced during this encoding phase, the sentence completion paradigm was designed so that subjects would either generate or read target nouns under conditions of relative semantic constraint and low emotional valence. All subjects read over the entire set of sentence stimuli aloud in front of the experimenter at the end of the study phase but were given no further instructions. Subject-generated target nouns were immediately recorded and used during the retrieval phase as described below, which occurred in the scanner 45 min after the study phase.



**Figure 1.** Schematic of experimental design.

During the event-related fMRI session, subjects performed 2 cognitive tasks. In both conditions, stimuli were presented for 1 s, with a 7–9 s interstimulus interval during which subjects fixated on a central cross stimulus. No separate baseline “rest” period was included. In the first task, subjects performed item recognition. Subjects were asked to read word pairs that consisted of 2 nouns with the second noun underlined (e.g., *sailor-sea*). For each word pair, they were asked to decide whether the underlined target noun was a word they previously read in the study phase or whether it was new. Sixty experimenter-presented target nouns were randomly interleaved with 60 recognition foils (high-associate noun pairs not previously encountered) presented in 4 MR acquisition runs (ca. 5 min each, with 2 min of rest between runs). Next, subjects performed the self versus external source memory task. Sixty experimenter-presented target nouns from the study session (not presented in the item recognition task) and 60 self-generated target nouns were randomly interleaved and presented (in word pairs, as during item recognition) in 4 MR acquisition runs. For each word pair, subjects were asked “Did you make up the underlined word, or was it shown to you in one of the sentences you read?”—that is, they were asked to make a decision about the source of each target noun, whether it was previously supplied by the experimenter (externally presented) or whether it was self-generated. In both of the above tasks, subjects made a 2-finger forced choice button press response with the right hand. We used word pairs (the 2 nouns from the original study sentences) as our stimulus items in order to partially re-create the original context of the full sentence. The item recognition task was always presented prior to the source memory task in order to minimize introducing recollection of source for old items during item recognition.

#### Stimulus Presentation and Experiment Control

Visual stimuli were presented with PsyScope 1.2.5 on an Apple Macintosh PowerPC (MacOS9) and projected using an LCD video projector onto a back projection screen at the foot of the scanner table. Subjects viewed the screen using a mirror attached to the head coil and made finger-press responses on a fiber-optic 8-channel response pad (Lightwave Medical Industries Ltd., Vancouver, British Columbia). The response pad device collected scanner transistor-transistor logic (TTL) pulses generated at the onset of MR acquisition. Subject responses and scanner signals were recorded by the PsyScope presentation program. The PsyScope software generated a data file containing recorded event times for all stimulus presentation events, subject responses, and scanner TTL pulse events, allowing for precise retrospective temporal synchronization of stimulus events and image acquisition.

#### MR Methods

Imaging was performed on a 1.5-T General Electric Signa LX 8.3 scanner (General Electric, Milwaukee, WI). Anatomical imaging

consisted of a high-resolution T1-weighted radio frequency-spoiled GRASS sequence. Functional imaging consisted of blood oxygen level-dependent (BOLD) sensitive images acquired during performance of the experimental task, using a gradient-recalled echo-planar imaging sequence (time repetition = 3 s; time echo = 50 ms; flip angle = 60, matrix = 128 × 128, field of view = 26 × 26 cm, 19 slices, 5-mm thickness, 1-mm gap).

#### Data Analysis

Image analysis was performed on a Sun Ultra 10 workstation (Sun Microsystems, Santa Clara, CA) using MATLAB (Mathworks Inc., Natick, MA) and SPM2 software (www.fil.ion.ucl.ac.uk/spm). Prior to analysis, the functional images were converted to 3-dimensional Analyze format volumes. The first 4 volumes in each run were discarded. Images were realigned to the 5th volume within each run to correct for motion artifacts using a 6-parameter rigid body affine transformation. The resulting images were normalized to a standard stereotaxic space (Montreal Neurological Institute [MNI] template) using a 12-parameter affine/nonlinear transformation and spatially smoothed with an 8-mm full-width half-maximum isotropic Gaussian kernel. Data were submitted to a whole-brain general linear model analysis, fitting a reference hemodynamic response function to each event. Correct and incorrect trials were modeled separately. Image intensity was scaled to the mean global intensity of each time series.

In this study, we focused on the difference between schizophrenia subjects and healthy comparison subjects during the accurate retrieval of the memory of having generated the target word (sense of cognitive agency) in the source memory task. In order to determine whether our findings in schizophrenia subjects represented a specific deficit in self-referential source memory processing, or could be accounted for by general deficits in overall memory function, we examined the difference between schizophrenia subjects and healthy comparison subjects during accurate recognition in the item recognition task. To address whether our findings could reflect a general deficit in identifying the source of items, we compared the brain activity when subjects identified the source of externally presented items during the source memory task with activation obtained during accurate recognition of similar externally presented items as old items in the item recognition task.

Whole-brain contrasts of interest were performed on individual subject data from correct trials in both conditions. For each subject, we performed the following contrasts between conditions: self-generated items > externally presented items; old > new items; externally presented > old items. Second-level 1-sample *t*-tests were performed on the combined individual results to create random-effect group analyses for these contrasts for the healthy comparison subject group and for the schizophrenia group. Second-level 2-sample *t*-tests were performed on the combined individual results to create random-effect between-group analyses for these contrasts. For each contrast at the



group level, statistical parametric brain maps were generated that displayed the  $t$  value (in signal intensity) of each voxel that met a threshold of  $P < 0.001$  uncorrected for multiple comparisons. For the group-level results reported here, these images were overlaid onto SPM2's single-subject canonical T1 image in MNI space. Stereotaxic coordinates reported here were converted to approximate Talairach space from MNI coordinate space ([www.mrc-cbu.cam.ac.uk/Imaging/mnispac.html](http://www.mrc-cbu.cam.ac.uk/Imaging/mnispac.html)).

To test the a priori hypothesis that our main contrasts of interest would reveal differences in mPFC, we conducted a small volume correction (SVC) for multiple comparisons on the whole-brain group-level  $t$ -tests to test for significant differences within mPFC at a threshold of  $P < 0.05$  within and between groups, using the familywise error correction for multiple comparisons. Consistent with our previous study using this experimental design in healthy comparison subjects, and based on the work of Cabeza et al. (2004), we used a volume consisting of a 20 mm-radius sphere centered on Talairach coordinates:  $-4, 52, 8$ .

## Results

### Behavioral Data

Behavioral data for the 2 subject groups are summarized in Table 1. Data were sufficiently normally distributed to permit use of parametric statistical tests. Outlier analyses revealed one low outlier among both control and schizophrenia subjects for accuracy on externally presented items and one high outlier among controls for RT on externally presented and new items. The data were winsorized, and all analyses were carried out on both the winsorized and nonwinsorized data, with identical results in both sets of analyses.

They key general finding is that the schizophrenia subjects were slower and less accurate than the healthy subjects in recognizing the source of self-generated target words, a pattern of behavioral performance consistent with our early study examining a similar experimental paradigm (Vinogradov et al. 1997). However, as noted previously, there was a significant group difference in mean age, and age was correlated at a trend level with hit rate for self-generated items for the subject group as a whole (Pearson's  $r = -0.5$ ,  $P = 0.06$ )—though not with any other hit rates or false alarm rates (all  $P$ 's  $> 0.1$ ). We thus controlled for the effect of age in our analyses via use of multivariate analysis of covariance (MANCOVA), testing for group differences on hit rates for self-generated, externally presented, old, and new item types, with age entered as a covariate. The multivariate test was significant, indicating a significant effect of condition on source memory hit rate, independent of the effects of age,  $F_{4,10} = 8.5$ ,  $P = 0.003$ . Univariate analyses, with the effects of age controlled, revealed that the schizophrenia subject group had a significantly lower hit rate for self-generated items compared with the healthy control group,  $F_{1,13} = 32.4$ ,  $P < .001$ . The remaining univariate analyses revealed that, with the effect of age controlled, the groups did not differ significantly on hit rates for external items  $F_{1,13} = 0.58$ ,  $P = 0.46$ ; old items  $F_{1,13} = 0.71$ ,  $P = 0.41$ ; or new items  $F_{1,13} = 1.9$ ,  $P = 0.18$ . There were no interaction effects. These results indicate that the group differences in accurate recognition of self-generated items were neither related to the age difference between the 2 groups nor related to the poorer old versus new item recognition performance in the schizophrenia subjects.

Age was not correlated with RT on any of the item types for the subject group as a whole, though it showed significant correlations with both old and new items for the healthy

**Table 1**

Mean accuracy and RT data for item recognition (old, new) and source memory (self-generated, externally presented) for healthy comparison ( $n = 8$ ) and schizophrenia subjects ( $n = 8$ )

Items (60 trials each type)	Healthy comparison subjects		Schizophrenia subjects	
	Accuracy (SD)	RT (SD), ms	Accuracy (SD)	RT (SD), ms
Old	0.61 (0.19)	1661 (234)	0.42 (0.21)	2047 (497)
New	0.86 (0.09)	1741 (193)	0.76 (0.19)	1974 (493)
Self-generated	0.88 (0.04)	1615 (328)	0.64 (0.10)	2145 (427)
Externally presented	0.93 (0.05)	1733 (215)	0.88 (0.13)	1790 (282)

comparison subjects only ( $r = 0.8$  and  $0.9$ , respectively,  $P$ 's  $< 0.01$ ). MANCOVA was performed to test group differences on RTs for correct self-generated, experimenter presented, old, and new item types, with age entered as a covariate. The multivariate test was not significant  $F_{4,10} = 0.97$ ,  $P < 0.46$ , although univariate tests revealed trend level group differences: the schizophrenia subject group showed longer RTs, independent of the effects of age, on correct identification of self-generated items,  $F_{1,13} = 3.6$ ,  $P = 0.08$ , and old items  $F_{1,13} = 4.3$ ,  $P = 0.06$ , compared with the healthy control group. There were no interaction effects. This suggests the likelihood that self-generated and old trials were performed with less cognitive efficiency in schizophrenia subjects than in healthy comparison subjects.

Of note, both subject groups showed low hit rates on the old versus new item recognition task, with the schizophrenia subjects performing at floor. This finding indicates the difficult nature of this verbal memory task: first, during the encoding phase, subjects were not given any instructions about needing to memorize the target noun items for a later memory task; second, there were 180 target stimuli—semantically related, emotionally neutral noun pairs—that were later, in a “surprise” fashion, used to form the memory tasks; third, the recognition foils used in the old versus new item recognition task were also high-associate noun pairs, very similar to those from the original sentences and not at all easily distinguished from the “old” externally presented items. This task was difficult for the healthy subjects and was even harder for schizophrenia subjects (as is well established in the literature, deficits in verbal learning and memory are a hallmark feature of schizophrenia and are present even in subjects with a higher IQ or otherwise relatively intact cognition).

There was no correlation between medication status (CPZ equivalents) and the behavioral data (hit rates, RTs) for the schizophrenia subjects (all  $P$ 's  $> 0.1$ ). The restricted range on patients' symptom ratings precluded correlational analyses with behavioral or imaging data.

### Functional MRI Data

#### Self-generated Versus External Source Memory Task

Within-group analyses revealed, for healthy comparison subjects but not for schizophrenia subjects, significantly greater activity in bilateral rostral mPFC and adjacent anterior cingulate (BA 9, 10, 32) during accurate memory for the source of self-generated items as compared with externally presented items. Schizophrenia subjects showed significantly greater activation in basal ganglia and posterior cingulate (BA 31) (Fig. 2). Between-group analyses for the contrast of self-generated  $>$  externally presented items revealed that healthy comparison subjects had significantly greater activity than schizophrenia

subjects in right rostral mPFC (BA 9, 10) and in right superior frontal gyrus (BA 8) (Table 2). Schizophrenia subjects had significantly greater activity than healthy comparison subjects in scattered areas that included left supplementary motor area (BA 6), occipital cortex (BA 18), anterior cingulate (BA 32), and basal ganglia (Table 2). The SVC of mPFC performed on the group level revealed a significant cluster of 216 voxels for the healthy comparison subjects, with a corrected  $P < 0.001$ , and no significant clusters for the schizophrenia subjects. For the between-group contrast of healthy comparison subjects > schizophrenia subjects, the SVC revealed a significant cluster of 72 voxels with a corrected  $P < 0.001$  and no significant clusters for the schizophrenia subjects > healthy comparison subjects. These data indicate that, in healthy comparison subjects, but not schizophrenia subjects, activation of rostral mPFC was associated with the accurate retrieval of the memory of having generated a prior cognitive event.

In order to determine whether these group differences in neural activation could be accounted for by the effects of age, we calculated the percent signal change in our a priori defined region of interest (used in the SVC analysis, Talairach coordinates 4, 52, 8), comparing the correct self-trials in the source memory task with the average “baseline” signal. We then examined the correlation of age with the percent signal change occurring in this region of rostral mPFC during accurate self-referential source memory performance across all subjects. We found no correlation between age and percent signal change in mPFC during the self-generated condition (Pearson’s  $r = 0.26$ , nonsignificant). This finding indicates that

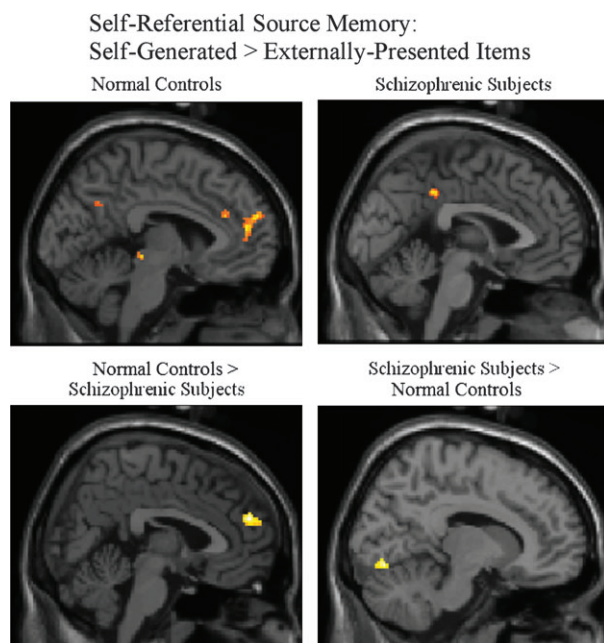
group differences occurring at the neural level in the BOLD signal in this task were not related to age differences between the 2 groups.

#### Old Versus New Item Memory Task

For the item recognition task (Table 3), within-group image analyses showed no significant differences in activation in healthy comparison subjects; schizophrenia subjects showed activation in left temporal cortex. Between-group analysis for item recognition showed greater activation in healthy comparison subjects than schizophrenia subjects in right parietal cortex and right insula, whereas schizophrenia subjects showed no regions of significantly greater activation than controls. This suggests that the disruption of mPFC activity we observed in schizophrenia subjects in the self versus external source memory task does not reflect a deficit in rostral mPFC function for memory tasks in general.

#### External Source Memory Versus Old Items

When we examined the neural correlates of accurately remembering the source of externally presented items as compared with simply recognizing similar externally presented items as old (the contrast of externally presented > old items, Table 4), healthy comparison subjects showed significant activation in bilateral subgenual cingulate cortex (BA 24, 32), left precentral gyrus (BA 6), and right temporal cortex (BA 21), whereas schizophrenia subjects showed activation in left subgenual cingulate (BA 32). Between-group analysis showed significantly greater activation in left precentral gyrus (BA 6) in healthy



**Figure 2.** Schizophrenia patients show a deficit in rostral medial prefrontal cortical activation during source memory for self-generated items. Upper panels: regions of greater fMRI activation following correct identification of the source of self-generated items compared with externally presented items in healthy comparison subjects ( $n = 8$ ) and in schizophrenia subjects ( $n = 8$ ) during a source memory task ( $P < 0.001$ , uncorrected for multiple comparisons). Lower panels: group differences between healthy comparison subjects ( $n = 8$ ) and schizophrenia subjects ( $n = 8$ ) in fMRI activation following correct identification of the source of self-generated items compared with externally presented items ( $P < 0.001$ , uncorrected for multiple comparisons).

**Table 2**

Source memory for self (contrasts for self-generated > externally presented word items) for 2 subject groups (healthy comparison,  $n = 8$ ; schizophrenia,  $n = 8$ ) and for between-group contrasts<sup>a</sup>

Anatomic region	Location	BA	z value	Number of voxels
Healthy comparison subjects				
Bilateral mPFC	-10, 48, 18		4.5	216 <sup>b</sup>
	-4, 57, 19	10	4.08	
	-4, 49, 12	10	3.87	
	2, 40, 20		3.74	
	8, 59, 19	10	3.63	
L precuneus	6, 52, 21	9	3.61	
	-8, -56, 36	7	4.3	39
Schizophrenia subjects				
R putamen	20, 11, -6		4.7	48
Posterior cingulate cortex	0, -37, 39	31	3.99	21
Healthy comparison > schizophrenia subjects				
R mPFC	6, 51, 20	9, 10	4.5	72 <sup>b</sup>
	6, 59, 17		3.71	
R superior frontal gyrus	18, 20, 47	8	3.98	30
Schizophrenia > healthy comparison subjects				
L supplementary motor area	-4, -14, 62	6	3.73	80
	-4, -11, 50	6	3.48	
	0, -21, 53		3.34	
R putamen	22, 9, -9		4.03	47
R occipital cortex	14, -74, -5	18	4.38	40
L dorsal anterior cingulate cortex	-2, 12, 36	32	3.86	40
L putamen	-16, 8, -2		3.89	31
L lateral globus pallidus	-14, -2, 4		3.42	

Note: L, left; R, right.

<sup>a</sup>Location ( $x, y, z$ ) corresponds to Talairach and Tournoux (1988); z values correspond to the maxima within activated clusters, with number of voxels indicated (a cluster threshold of 20 voxels was used).

<sup>b</sup>Indicates  $P < 0.001$  with SVC for multiple comparisons; all other values  $P < 0.001$  uncorrected.

**Table 3**

Item recognition memory (contrasts for old > new word items) for 2 subject groups (healthy comparison,  $n = 8$ ; schizophrenia,  $n = 8$ ) and for between-group contrasts<sup>a</sup>

Anatomic region	Location	BA	z value	Number of voxels
Healthy comparison subjects				
No significant activation				
Schizophrenia subjects				
L temporal cortex	-40, -72, 29	39	3.53	36
	-38, -63, 22		3.43	
	-44, -69, 24		3.28	
Healthy comparison > schizophrenia subjects				
R inferior parietal lobule	59, -24, 34	2	4.34	36
R insula	38, -25, 10	41	3.56	35
	40, -27, 7	13	3.36	
Schizophrenia > healthy comparison subjects				
No significant activation				

Note: L, left; R, right.

<sup>a</sup>Location (x, y, z) corresponds to Talairach and Tournoux (1988); z values correspond to the maxima within activated clusters, with number of voxels indicated (a cluster threshold of 20 voxels was used);  $P < 0.001$  uncorrected for multiple comparisons.

**Table 4**

Contrasts for externally presented (source memory task) > old word items (item recognition task) for 2 subject groups (healthy comparison,  $n = 8$ ; schizophrenia,  $n = 8$ ) and for between-group contrasts<sup>a</sup>

Anatomic region	Location	BA	z value	Number of voxels
Healthy comparison subjects				
Bilateral subgenual cingulate cortex	-6, 33, -5	32	3.96	28
	4, 31, -2	24/32	3.41	
L precentral gyrus	-57, 3, 29	6	4.09	23
	-51, 2, 35	6	3.64	
R temporal cortex	44, -22, -8	21	4.02	21
Schizophrenia subjects				
L subgenual cingulate cortex	-8, 43, 2	32	4.27	23
Healthy comparison > schizophrenia subjects				
L precentral gyrus	-51, -4, 30	6	3.56	20
Schizophrenia > healthy comparison subjects				
Basal ganglia	-2, 0, 6		3.98	45

Note: L, left; R, right.

<sup>a</sup>Location (x, y, z) corresponds to Talairach and Tournoux (1988); z values correspond to the maxima within activated clusters, with number of voxels indicated (a cluster threshold of 20 voxels was used);  $P < 0.001$  uncorrected for multiple comparisons.

comparison subjects than schizophrenia subjects, whereas schizophrenia subjects showed significantly greater differences in basal ganglia. These findings suggest that the lack of relative activation in mPFC shown by schizophrenia subjects in the contrast of self-generated > externally presented items during the source memory task was not due to a generalized neural deficit that occurs when they perform source memory operations.

## Discussion

We found that, compared with healthy comparison subjects, clinically stable schizophrenia patients carefully matched on general cognitive and psychosocial variables were slower and less accurate when remembering whether or not they generated a target word during an earlier sentence completion task (consistent with Vinogradov et al. 1997; Fisher M, McCoy K, Poole JH, Vinogradov S, unpublished data). This finding was

not due to simple response bias and was independent of age or poorer item recognition memory. More significantly, the functional imaging data revealed that, on accurate trials, relative activation of rostral mPFC (BA 10) was uniquely associated with this self-referential source memory operation in the healthy comparison subjects but not in the schizophrenia subjects.

This specific difference in neural processing was observed only when schizophrenia subjects had to remember that they were the source of previously generated information and was not observed when they were performing another difficult memory task (old vs. new item recognition) or when making a decision about the source of information not related to the self (external source memory vs. old item recognition for externally presented items). Indeed, schizophrenia subjects showed unique patterns of abnormal activity for each of the different comparisons, rather than a pattern of rostral mPFC dysfunction or generalized cortical hypoactivation across the various memory operations. Even if schizophrenia subjects were engaging in "lucky guessing" (rather than pure retrieval) for old items during the difficult item recognition task, when compared with the best control condition available to us (retrieval attempts for old items), accurate external source memory in schizophrenia showed no association with rostral mPFC activation. Taken together, our data suggest that a relative lack of activation in rostral mPFC in schizophrenia subjects is a specific abnormality that occurs when patients attempt to perform self-referential processing during memory operations for previously self-generated information.

As previously reported by us (Vinogradov et al. 2006), and similar to the findings of Kelley et al. (2002), we found increased activity in rostral mPFC in the healthy comparison subjects only when we performed the direct contrast between retrieval of the source of self-generated > externally presented items. In contrast, Gilbert et al. (2005) demonstrated sustained rostral mPFC activity associated with tasks that involved externally oriented versus self-generated processing, and this group has also found mPFC activation during low-demand externally oriented tasks (Gilbert, Simons, et al. 2006). In our experiment, during accurate memory of the source of self-generated items, subjects had to both process externally presented stimuli (word pairs) and then to "switch" their attention to internally generated processes in order to retrieve, monitor, and verify the self-referential memory of having created the target word. The "gateway model" referred to earlier (Burgess et al. 2005; Burgess et al. 2007) proposes that medial BA 10 influences the attentional balance between self-generated and perceptual information, rather than being exclusively involved in processing self-generated information; in this manner, it contributes to the monitoring and verification of recollected information. However, this region also shows activation in direct contrasts of social stimuli versus baseline conditions (Iacoboni et al. 2004) and social versus nonsocial stimuli (Harvey et al. 2007), raising intriguing questions about the relationship between self-referential and social processes (Fisher M, Thangavel A, Subramaniam K, Poole JH, Vinogradov S, unpublished data). As Gilbert, Spengler, Simons, Steele, et al. (2006) and Gilbert, Spengler, Simons, Frith, et al. (2006) point out, there is a considerable amount of functional segregation within medial BA 10, warranting the design of future studies that directly focus on the activation patterns obtained in subregions of mPFC in response to specific task requirements.



Overall, our findings indicate that clinically stable outpatients with schizophrenia—even when they are able to accurately retrieve the memory of having created a target word—do so without the normal pattern of relative activation of rostral mPFC seen in various other types of self-referential tasks in healthy subjects (Pardo et al. 1993; McGuire et al. 1996; Lane et al. 1997; Gusnard et al. 2001; Raichle et al. 2001; Kelley et al. 2002; Zysset et al. 2002; Fossati et al. 2003; Vinogradov et al. 2006). Instead, they show greater-than-normal activation in visual cortex, motor cortex, cingulate gyrus, and basal ganglia, possibly reflecting an attempt to retrieve visual and motor cues associated with the original implicit encoding episode. This appears to index a less efficient (slower, less accurate) alternate retrieval mechanism for the recognition of self-generated information, consistent with multiple other reports of inefficient neural operations in schizophrenia subjects (e.g., Hazlett et al. 2000; Carter et al. 2001; Callicott et al. 2003; MacDonald et al. 2005). (Of note, less efficient neural processing has also been demonstrated in patients who have never been medicated [MacDonald et al. 2005], suggesting that our findings are not likely due solely to medication status.)

What might be the behavioral consequence of impairment in these critical neural correlates? In healthy comparison subjects, relative activation of rostral mPFC during encoding of stimuli attributed to the self predicts subsequent memory performance (Craik et al. 1999; Kelley et al. 2002; Macrae et al. 2004), whereas activation of this neural correlate during memory operations occurs when subjects remember that they were the originator of a prior mental event (Cabeza et al. 2004; Vinogradov et al. 2006). In contrast, schizophrenia subjects do not use this neural process during self-referential source memory operations and instead appear to search through associated visual, orthographic, and motor memories of their experience. We suggest that such a strategy, which behaviorally results in less efficient and less accurate performance, contributes to distortions in a patient's subjective experience over time. Recent functional neuroimaging experiments have also revealed that schizophrenia patients demonstrate abnormal brain activation patterns when required to monitor their own motor actions (McGuire et al., 1995; Carter et al. 2001; Farrer et al. 2004) and when imagining another person's mental state (Lee et al. 2006). Exploration of the relationship of these deficits to the disturbance in memory for self-generated information is of interest for future studies.

In summary, we propose that impairment in the specific neural processes that support self-referential source memory contributes to the unique and profound ongoing subjective disturbances that characterize schizophrenia and that are most troubling to patients, their families, and society. In a large behavioral study, we have recently shown that deficits in this meta-memory function are uniquely related to basic social cognition abilities in patients (such as facial memory, facial emotion recognition, and vocal prosody identification) (Fisher M, McCoy K, Poole JH, Vinogradov S, unpublished data). Understanding and addressing the deficits in neural operations that support self-referential processing and its relation to social cognition will be important areas for future remediation efforts in schizophrenia—as important, if not more important, than the commonly recognized impairments in attention and memory, in terms of interpersonal functioning and quality of life for our patients.

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