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Impairment of Working Memory Maintenance and Response in Schizophrenia: Functional Magnetic Resonance Imaging Evidence

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Abstract

Background—Comparing prefrontal cortical activity during particular phases of working memory in healthy subjects and individuals diagnosed with schizophrenia may help to define the phase-specific deficits in cortical function that contribute to cognitive impairments associated with schizophrenia. This study featured a spatial working memory task, similar to that used in non-human

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†deceased

*This manuscript is dedicated to the memory of our friend, colleague and collaborator, Patricia Goldman-Rakic, Ph.D. May your work, your dedication and your inquiring mind ever serve as an inspiration to us!

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primates, that was designed to facilitate separating brain activation into encoding, maintenance and response phases.

Methods—Fourteen patients with schizophrenia (4 medication-free) and twelve healthy comparison participants completed functional magnetic resonance imaging while performing a spatial working memory task with two levels of memory load.

Results—Task accuracy was similar in patients and healthy participants. However, patients showed reductions in brain activation during maintenance and response phases, but not during the encoding phase. The reduced prefrontal activity during the maintenance phase of working memory was attributed to a greater rate of decay of prefrontal activity over time in patients. Also, in patients, but not in healthy subjects, the time-dependent reduction in prefrontal activity during working memory maintenance correlated with poorer performance on the memory task. Cortical deficits in patients did not appear to be related to antipsychotic treatment.

Conclusions—Overall, these data highlight that basic research insights into the distinct neurobiologies of the maintenance and response phases of working memory are of potential importance for understanding the neurobiology of cognitive impairment in schizophrenia and advancing its treatment.

Keywords

functional magnetic resonance imaging; working memory; schizophrenia; prefrontal cortex; timecourse analysis; event-related analysis

Introduction

Working memory (WM) involves the temporary storage of items for use in current mental operations and the guidance of ongoing behavior (1). Cognitive neuroscientists often view WM as involving an initial phase of encoding percepts; a middle phase of maintaining, updating, scanning and manipulating the WM contents; and a final phase of selecting and enacting responses. Preclinical research provides insights into WM neurobiology. Single-cell recordings in non-human primates indicate that some neurons in lateral prefrontal cortex (PFC) fire throughout the time period during which information is maintained in WM (2,3). A somewhat distinct, but partially overlapping, population of PFC neurons fire in the response phase (4).

Functional neuroimaging studies have generally supported the hypothesis that WM deficits in schizophrenia are related to PFC dysfunction. However, some investigators report that patients with schizophrenia (SZS) have deficient activation in PFC (5–7), and others report no difference or even increased activation (8–11). These conflicting findings may be related to the differential impact of increasing WM load on PFC activation in SZS and healthy comparison subjects (HCS) (9,12,13).

The three phases of WM have distinct neurobiologies that may help to inform our understanding of cortical dysfunction in schizophrenia. Preclinical data suggest that the distinctive kinetics of N-methyl-D-aspartate (NMDA) glutamate receptor activation, facilitated by D1 receptor activity, allow prefrontal cortical networks to produce sustained, modulated activation necessary for WM maintenance (14–19). In contrast, dopamine D2 receptors appear to destabilize PFC activity associated with WM maintenance (Seamans and Yang 2004) and may modulate activity associated with the response phase (18). Deficits in NMDA and D1 receptor function may contribute to schizophrenia pathophysiology (15,20–24). Anti-psychotic medication treatment which blocks the D2 receptor may further complicate the clinical picture. Thus, using WM phases to parse abnormalities in PFC activity associated with schizophrenia may shed light on the disorder's neurobiology.

Based on the studies reviewed above, we hypothesized that SZS would display reduced PFC activation during the maintenance phase of WM. We further sought preliminary evidence that reduced persistence would be related to poor performance. In addition, we hypothesized that PFC activity during the response phase would be reduced in SZS.

In order to distinguish PFC activity associated with WM phases in humans using functional magnetic resonance imaging (fMRI), one must specially design WM paradigms and analytic techniques to compensate for the limited temporal resolution of the blood-oxygenated level-dependent (BOLD) signal. We selected an fMRI paradigm that was designed to resemble the ocular delayed response task, a paradigm often used in non-human primate WM studies, and has been shown to be sensitive to PFC maintenance activity in healthy human volunteers (25). It includes a relatively long retention interval of 16s to separate initial responses, termed cue or encoding-related activity, from brain activity related to maintenance.

To analyze the results of our experiment we used an approach which we term “empirical timepoints” that involves calculating percent signal change from the BOLD timecourse data and requires fewer mathematical assumptions than traditional fMRI analysis. However, our hypotheses specified a decrease or decay of the BOLD signal over the course of the retention interval. This decay was best modeled by using a hemodynamic response function (hrf). Accordingly, on our major analyses we complemented the empirical timepoints approach with an analysis that deconvolved the hemodynamic response.

Methods and Materials

Participants

As detailed in Table 1, participants were 14 psychiatrically stable outpatients (10 medicated and 4 medication-free) who were well-known to the research team and diagnosed with schizophrenia or schizoaffective disorder according to a structured interview (SCID-I/P) (26). Detailed information regarding participant criteria is provided in Supplemental information 1. Psychiatric medication for each patient is supplied in Supplemental information 2. HCS (n = 12) with no history of neurological, substance or psychiatric disorder were matched to patients on age and parents' education. All participants gave written, informed consent in accordance with Yale Human Investigation Committee procedures.

Procedure

Patients were referred by outpatient research clinics which completed a structured diagnostic interview and assessed substance use via the SCID-I/P and/or the Addiction Severity Index (27). Healthy controls were recruited by community advertisement and were screened with a semi-structured phone interview based on the SCID. All participants were trained on the experimental task, performed it in the scanner and were debriefed after scanning. Patients returned for a one-hour rating session in which a single rater (ND) completed negative and positive symptom scales (28,29).

Imaging Task

Stimuli were projected onto a screen which participants viewed via a mirror. For the 4-target task, illustrated in figure 1, stimuli were four solid circles presented sequentially in locations ranging from $\pm 3.6^\circ$ to $\pm 11.5^\circ$ from the center of the screen. Target locations were selected from a set of 36 locations and the sets of locations used had been previously piloted and matched for difficulty. Participants fixated on a dot at the center of the visual field for 3,250 ms. Each circle was presented for 1s with a 250 ms interstimulus interval. After a 16 s retention interval, a ring, serving as a probe, appeared on the screen for 1 s. Approximately half of the time, the probe matched one of the previous circles. The subject pressed one button to indicate that the

probe location matched one of the previously presented circles and another button to indicate a non-match. After subjects responded to the probe, the fixation dot changed into a cross, which changed back to a dot at the start of the next trial. The inter-trial interval (ITI) was 14 s. The 2-target task was the same as the 4-target task except only two targets were presented and an additional 2,500 ms were added to the ITI to make the 4-target and 2-target trials the same length. Three 4-target and three 2-target trials alternated in each run. Scanning was performed on a 1.5T Signa LX system (General Electric Corp., Milwaukee, WI), equipped with the standard quadrature coil. Acquisition parameters are provided in Supplemental information 3.

Image Processing

Pre-processing and t-maps—Images acquired were motion corrected (30) and those with motion greater than 2 mm in the x, y or z direction or more than three degrees of pitch, yaw or roll were eliminated. Data were smoothed in the spatial domain with a 6.25mm Gaussian filter and corrected for slice acquisition time.

Images were divided into 26 image (39 s) trial blocks. The first and last two images of each block (images 1, 25, 26) served as the baseline and images 10 through 13 constituted the maintenance phase. A signal-change map was then derived for each run comparing the baseline and task and the maps averaged. Individual signal-change maps were transformed into Talairach space using piece-wise linear interpolation, and group composite t-map images were computed.

ROI Analysis—Using the Talairach grid, we defined 3–7 cm³ regions of interest (ROIs) in the PFC based on those employed by Leung and colleagues (2002). The ROIs are displayed in Figure 2. We then computed timecourses for each ROI and trial type as described in Supplemental Information 4. The resulting average timecourses were used to construct two types of analyses: 1) a timepoint analysis and 2) an analysis based on convolving a hemodynamic response function (hrf).

Defining timepoints—We selected an encoding peak, maintenance trough and response peak with a computer program so that the encoding peak was always first, then the maintenance trough, then the response peak. Figure 1 illustrates the timing of the events in the behavioral task and the periods used for defining encoding and response peaks and maintenance troughs. A rater, blind to group membership, reviewed each timecourse and the chosen peaks and troughs. Image ranges were expanded slightly for an individual curve when the program missed a peak or trough by a few images. We deleted two ROI curves for one control subject on the 2-target task because there was no clear peak or trough.

Statistical analysis

Distributions were examined and screened for outlying values. We employed a mixed model approach to data analysis which is a relatively new statistical technique that allows for intercorrelated dependent variables (32,33). Unless otherwise specified in the text, all possible interactions were fitted. Only statistically significant effects are reported in this manuscript.

We report here both analyses based on empirically derived timepoints and analyses based on a deconvolved hemodynamic response. For all of the empirical timepoint analyses, amplitude of the BOLD response as compared to baseline serves as the dependent variable. In terms of the analyses on empirically derived timepoints, the hypothesis that SZS would have reduced activation at maintenance and at response would be supported by a statistically significant group x timepoint effect. Follow-up analyses would indicate reduced activation during maintenance and response. We tested the hypothesis that sustained activity (the encoding peak minus the maintenance trough) is related to performance through simple correlations.

The principal hypothesis that SZS would have reduced activation at maintenance and response was also tested with a more traditional model that fitted a hrf. It should be noted that the empirical and hemodynamic models are parallel but not entirely equivalent, particularly in the maintenance phase. The empirical model assesses the nadir BOLD response during a particular maintenance time window. In contrast, the hemodynamic model assesses the slope of the activation during the maintenance phase. We refer to this slope as decay of activation.

For all follow-up analyses, we provide uncorrected p-values that were significant after Bonferroni correction for multiple comparisons within but not between hypotheses. If the right hemisphere had greater amplitudes than the left and there was no statistically significant interaction between hemisphere and group, we fitted a model with only right ROIs for all primary analyses. Thus, we were able to compare 2- and 4-target versions of the task within the same model. Further details regarding our statistical analyses including calculation of the hrf and the exact statistical models used are contained in supplemental information 5.

Results

Behavioral Data

Performance scores on the spatial working memory task are displayed in Table 2. Participants performed more accurately on the 2-target than on the 4-target task, $F(1,21) = 6.10$, $p = .022$. The group difference in accuracy was not statistically significant, nor was the interaction between diagnosis and load. Additional analyses of hits, misses, false alarms and correct rejections revealed no statistically significant group differences. The patients were slower than HCS, $F(1,21) = 8.57$, $p = .008$. In both groups, reaction times were slower on the 4-target than on the 2-target task, $F(1,21) = 17.2$, $p = .0005$. Average reaction times were related to chlorpromazine (CPZ) equivalents, $r(13) = -.64$, $p < .05$.

Peak and Trough Activation Latencies—Timepoint latency did not differ significantly between groups.

Peak and Trough Amplitude Differences—Prefrontal activation differences between groups varied with timepoint, group by time interaction, $F(2,579) = 5.49$, $p = .004$. Group timecourses are displayed in Figure 3 and timepoint values are given in Supplemental information 6. No statistically significant group differences were found at the encoding peak, $F(1,579) = .09$, $p = .764$. Patients had lower maintenance troughs than controls, $F(1,579) = 4.81$, $p = .029$, though this result did not survive correction for multiple comparisons. Percent BOLD signal change from baseline at the trough was .09 for HCS and $-.02$ for SZS. Patient trough amplitude did not differ significantly from 0 ($p = .53$). Patients also had lower amplitudes than HCS at the response peak, $.34$ vs. $.46$, $F(1,579) = 5.56$, $p = .019$. This result was still statistically significant after multiple comparison correction.

Differences between the 2-target and the 4-target varied by timepoint, (timepoint by load interaction: $F(2,579) = 3.39$, $p = .034$). There were no group by load or group by timepoint by load interactions. Load effects were largest at the encoding peak, $F(1,579) = 20.47$, $p = .00001$, which was still statistically significant after multiple comparison correction. Percent change from baseline during encoding was greater on the 4-target task than on the 2-target task, $.39$ vs. $.31$. Response peak on the 4-target task was also higher than that associated with the 2-target task, $.42$ vs. $.38$, $F(2,579) = 4.87$, $p = .008$, though this result was not statistically significant after multiple comparison correction. No significant trough differences between the 4-target and 2-target tasks were observed.

Regional differences varied by timepoint, $F(6,579) = 11.13$, $p < .000001$, and these differences did not vary significantly between groups. Regional differences in the total sample were

significant at the encoding and response peaks but not at the maintenance trough and persisted after multiple comparison correction. During the encoding peak, BA 46/44 (MFG) was significantly higher than the average of the other regions, $F(1,579) = 11.39$, $p = .0008$. This difference remained after correction for multiple comparisons. In contrast, BA47, located in the ventral inferior frontal gyrus (IFG), was lower than the average of the other regions, $F(1, 579) = 52.87$, $p < .000001$, and significance persisted after multiple comparison correction. During the response peak, BA 45 (IFG) was higher than the average of the other regions, $F(1,579) = 76.68$, $p < .000001$, with significance persisting after multiple comparison correction. In contrast, BA 47 (ventral IFG) and BA 6/8, located in the superior middle frontal gyrus (MFG), were lower than average, $F(1,579) = 42.27$, $p < .000001$ and $F(1,579) = 8.95$, $p = .004$, respectively. Statistical significance remained after multiple comparison correction.

Relationship between Encoding Peak and Maintenance Trough Timepoints—

The association between encoding peak and maintenance trough was significant in both groups and varied with diagnosis, $F(1,165) = 9.39$, $p = .003$. In healthy subjects, a one unit increase in encoding peak resulted in an average $.57 \pm .07$ increase in the maintenance trough. In patients, a one unit increase in encoding peak resulted in an average $.32 \pm .06$ unit increase in maintenance trough. These relationships are illustrated in Figure 4.

Relationship between Response Peak and Previous Timepoints—The analysis indicated that the relationship between the maintenance trough and response peak varied by diagnosis and task load. In the 2-target task, the relationship between trough and response was strong and did not differ significantly between the groups. Averaging over all participants and controlling for the effect of encoding peak, a one unit change in maintenance trough produced a $.29 \pm .12$ change in response peak, $t(144) = 2.47$, $p = .015$. However, differences emerged during the 4-target task and are illustrated in Figure 5. On the 4-target task in healthy subjects maintenance trough amplitude was highly related to response peak amplitude, $\beta = .59 \pm .17$, $t(144) = 3.4$, $p = .001$. This finding was still statistically significant after multiple comparison correction. It was unrelated in patients with schizophrenia. The relationship between maintenance trough and response peak was also affected by region, $F(3,144) = 5.16$, $p = .0021$.

Relationship between Persistent Activity and Performance—The average difference in amplitude between the encoding peak and the maintenance trough was correlated with percent correct. For the 4-target task, This difference score was correlated with percent correct, $-.42$ ($p = .046$), but the correlation was not significant after correction for multiple comparisons. For the 2-target task, the correlation was $-.56$ ($p = .007$), which was statistically significant after multiple comparison correction. Trends were noted for the SZS to achieve higher correlations than the HCS but these did not reach statistical significance.

Chlorpromazine Equivalent Analyses—In both the 2-target and 4-target task, there was a significant interaction between timepoint and CPZ, (2-target: $F(4,289) = 2.96$, $p = .02$ and 4-target: $F(4, 304) = 3.12$, $p = .015$). The patients on lower doses of anti-psychotic medication had greater encoding peak amplitudes than those on higher doses or no anti-psychotic medication at all, (2-target: $F(2,289) = 3.66$, $p = .027$ and 4-target: $F(2,304) = 3.60$, $p = .028$). The CPZ findings at encoding were not significant after Bonferroni correction and there were no CPZ differences at maintenance or response.

Analysis with HRF—We also modeled the timecourse by convolving a hrf and computing beta weights (see supplemental information 4). Generally, the results of this analysis paralleled those derived from timepoints. Prefrontal activation differences between groups varied with timepoint, (group by time interaction: $F(2,587) = 3.39$, $p = .034$). SZS and HCS participants had similar peaks during the encoding period. SZS had greater decay of activation (i.e. a steeper

downward slope) than HCS during the maintenance period, $F(1,587) = 8.65$, $p = .003$. They had lower peaks during the response period, $F(1,587) = 5.67$, $p = .018$. Both effects survived multiple comparison correction.

In the beta weight analysis, there was a region by diagnosis interaction that did not emerge in the timepoint analysis, $F(3, 587) = 3.89$, $p = .009$. In the ventral IFG (BA47), activation was greater across time periods in HCS than in SZS, $F(1, 587) = 10.47$, $p = .001$. This result survived correction for multiple comparisons.

Discussion

This paper presents two principal findings related to prefrontal cortical dysfunction in schizophrenia. First, this study shows that PFC activity associated with the maintenance of WM is reduced in SZS relative to HCS. In the empirical timepoints analysis, there was an initial finding that was non-significant after adjustment for multiple comparisons. This indicated that nadir response phase activity was reduced in SZS even when activation at encoding was held constant. In the analysis which convolved a hrf we were able to assess decay of PFC activity over time. This analysis was also consistent with a maintenance deficit. Furthermore, we found that reduced maintenance activity was associated with poor performance. Second, both empirical and hemodynamic models indicated reduced response phase PFC activity in SZS. The findings were made possible because the paradigm and analytic techniques employed were specially designed to isolate PFC activity associated with the phases of WM.

Performance

Performance accuracy was similar in the two groups, but the SZS responded more slowly than the HCS. Reaction time (RT) was related to medication dose. Observed group differences in RT did not appear to affect the latency of the BOLD timepoints.

Decay of Maintenance Activity

In healthy subjects, encoding peaks in PFC activity are substantially sustained during the maintenance and response phases of WM. In contrast, in schizophrenic individuals, there is a greater decay in PFC activity that would normally contribute to the maintenance of information in working memory. Thus, in patients, cortical activity associated with encoding peaks is not well sustained in the delay period.

This deficit did not appear to be related to SZS having more difficulty with the study task. First of all, we did not find performance accuracy differences between the two groups. Secondly, we used a load manipulation to better understand how task difficulty might influence findings. The more difficult, 4-target task increased encoding and response peak amplitudes in both patients and healthy subjects. Thus, maintenance activity was not related to load in either group. Furthermore, our load analysis supports the assertion that the task presented similar difficulty for both groups. Since increased load was associated with higher encoding and response peaks in both groups, we would expect that, if the patients were experiencing greater task difficulty, they would have higher encoding *and* response peaks than HCS. This was not the pattern found.

Reduced Response Peaks

SZS obtained lower response peaks than their healthy counterparts. Since, in general, lower maintenance troughs predict lower response peaks, the lower response peaks observed in SZS largely reflect their inability to sustain activation during maintenance. However, an additional deficit was noted during the more difficult, 4-target task. In SZS, the relationship between maintenance trough and response peak was so compromised that there was no statistically significant relationship found between the two timepoints. Our observation parallels a recent

report by Johnson and colleagues (34). In an fMRI paradigm, they found that during encoding both SZS and HCS had increased dorsal lateral pre-frontal cortex (DLPFC) activation in response to increased load. However, during the response period, an almost flat response to load was observed in patients. Our data suggest that the patients' reduced response to load may be related to a deteriorating relationship between maintenance and response that occurs in situations of increased demand.

Deficits and Medication

Previous research indicates that anti-psychotic medication blocks D2 receptors and, with chronic administration, reduces D1 receptors in PFC (18,35). Thus, D1 and D2 deficits related to medication could possibly explain the reduced brain activation observed in this study during the response and maintenance phases respectively. CPZ equivalents are a very rough way of equating antipsychotic medication which only takes into account the relative potency of drugs at D2 receptors and dose. However, using this approach allowed us to provide preliminary evidence that the effects observed during maintenance and response were not simply medication effects. In regards to the reduced delay-related PFC activity observed, there was no association between anti-psychotic medication dose and decay of PFC activity during the maintenance phase of WM. In addition, the deficits in maintenance-related PFC activity appeared to be similar in medication-free and medicated patients.

Relationship to Previous WM Studies in Schizophrenia

A meta-analysis (36) and several recent studies implicate encoding as a primary WM deficiency in schizophrenia (37–39). Thus, some may be surprised that we did not find deficient activation in the first peak, a time period commonly viewed as relating to encoding processes (40,41). There is a great deal of evidence that individuals with schizophrenia are deficient in attention and early perceptual processing (42–44). However, we chose a task that would minimize encoding demands and allow us to focus on possible deficits in maintenance activity. Thus, our work does not suggest that WM encoding is intact in schizophrenia, but rather that the relationship between encoding, maintenance and response is compromised.

Our protocol was designed to assess simple maintenance of spatial locations. Though tasks that only require basic maintenance processes rather than extensive manipulation of WM contents tend to produce smaller group differences (45), maintenance deficits in schizophrenia are often reported (39,46,47).

The maintenance period was quite long which raises the possibility that the two groups might have had time to engage in different cognitive processes during that time. We did not manipulate motivation and therefore we cannot account for motivation-related effects. In addition, we did not control for active processes related to memory maintenance such as rehearsal. These two effects require further study. However, a recent study provided an especially provocative examination of active maintenance processes in schizophrenia (48). The investigators asked SZS and HCS to “refresh” presented words i.e. bring the words back into conscious awareness. They found that, even though the patients' longer term memory benefited from refreshing, they were differentially slower at this basic maintenance operation.

A limitation of our study was that in order to facilitate a thorough investigation we concentrated on a pre-selected set of PFC ROIs. Perhaps restricting our selection to ROIs known to be elevated during maintenance contributed to the weak regional findings in this study. In general, we found no regional differences in group effects within the PFC. However, in an analysis that fitted the hrf, we found that ventral IFG was more activated across the three phases in HCS than in SZS.

There is strong evidence that spatial working memory involves a network of brain areas beyond the prefrontal cortex including anterior cingulate, the frontal eye fields, premotor areas, inferior parietal lobule, and superior parietal lobule (25,49–52). Thus, it is important to note that the dysfunctions we report may result from brain activity outside the ROIs we studied.

Along with limitations associated with the brain areas selected, the implications of our research are also constrained by our participants. Our sample size was relatively small which reduced our power to detect differences. For example, we did not find any group differences in accuracy on our spatial working memory task. However, trends can be observed in the data, and it is possible that group effects would have been found with a larger sample. Another issue was that we did not have any control over the medication regime of our patients. Thus, it is very likely that medication and clinical characteristics are confounded in this sample. For this reason, our analyses involving medication should be viewed cautiously and in an exploratory manner.

Conclusion

This investigation allowed an in-depth analysis of timecourse data in a carefully chosen set of ROIs. It may provide a useful lens for better understanding the interplay between PFC areas and other brain areas that underlie working memory and the alteration of that connectivity in schizophrenia. Our investigation revealed an orderly relationship between phases of WM in healthy subjects. These relationships can be seen as a physical instantiation of the transfer of information necessary to successfully accomplish each phase of the WM process. From the neuronal perspective, each phase is accomplished by partially overlapping populations of neurons, so information needs to be communicated from neuron to neuron in a complex manner that we are only beginning to understand (4,53). Our results indicate these relationships become fractured in schizophrenia. Specifically, SZS fail to sustain activity during the maintenance period. Their activations during the response phase are also reduced. Since maintenance trough and response peak are linked, the loss of response phase activation may partially reflect the failure to sustain activity during maintenance. In addition, under the demands of a higher load level, it was found that the relationship between maintenance trough and response peak disintegrated. The group differences observed were not associated with performance differences or medication status.

The enhanced decay of PFC activity observed in this study is consistent with neurobiological hypotheses related to the neuropathology of schizophrenia, particularly reduced dopamine D1 and NMDA glutamate receptor function. Reduced response peaks in SZS may implicate D2 receptor dysfunction. However, the lack of association between anti-psychotic medication and response peaks may throw doubt on this hypothesis. Further experimentation with patients randomized to treatment and dose may help elucidate the role of D2 receptors in response peak deficits.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.

Timing of trial events for the 4-target task. Colored rectangles show sampling periods for the encoding peak (blue, 6–21s after trial start), the maintenance trough (green, 13.5–28.5s), the response peak (yellow, 21–36s) and the baseline (orange, 0–1.5 and 37.5–39). The peaks were defined as the image with the highest percent signal change from baseline during the sampling period and the trough was defined as the image with the lowest percent signal change from baseline during the sampling period. Note that, because of the hemodynamic delay, sampling periods lag behind trial events. ITI = intertrial interval.

Figure 2.

Regions of interest used in analysis. R=right. SMFG = superior middle frontal gyrus, MFG = middle frontal gyrus, IFG = inferior frontal gyrus, VIFG = ventral inferior frontal gyrus.

Figure 3.

Timecourses of all regions of interest used in analysis by group and task. Blue represents the stimulus encoding period when participants are viewing targets and yellow the probe period. Timecourses are normalized by subtracting the mean baseline from each timepoint shown. SMFG = superior middle frontal gyrus, MFG = middle frontal gyrus, IFG = inferior frontal gyrus, VIFG = ventral inferior frontal gyrus. SZS = patients with schizophrenia. HCS = healthy comparison subjects.

Figure 4.

Correlation between encoding peak and maintenance trough in HCS (top) and in SZS (bottom) averaging over the 2-target and 4-target tasks. SMFG = superior middle frontal gyrus, MFG = middle frontal gyrus, IFG = inferior frontal gyrus, VIFG = ventral inferior frontal gyrus. SZS = patients with schizophrenia. HCS = healthy comparison subjects.

Figure 5. Correlation between response peak and maintenance trough in HCS (left) and SZS (right) during the 2-target (top) and 4-target tasks (bottom). SMFG = superior middle frontal gyrus, MFG = middle frontal gyrus, IFG = inferior frontal gyrus, VIFG = ventral inferior frontal gyrus. SZS = patients with schizophrenia. HCS = healthy comparison subjects.

Table 1

Participant Characteristics

	Controls (n= 12)	Patients (n=14)
Age^b	35.83 (9.05)	42.36 (7.50)
Sex	6 males/6 females	9 males/5 females
Ethnicity	2 AA/1 Asian/9 Caucasian	2 AA/1 Asian/11 Caucasian
Education Self	15.8 (2.6)	14.1(2.3)
Education Father^a	13.4 (2.8)	14.4(4.2)
Education Mother^a	13.3 (2.1)	13.9(3.5)
SANS (mean,sd)^a		5.67(2.74)
SAPS (mean,s.d.)^a		6.08 (3.15)
Antipsychotic Medication		4 Med-free/7 2nd Generation/3 1st Generation
DSM-IV Diagnosis		1 295.1/5 295.3/6 295.7/2 295.9

Note: AA = African- American, 2nd Generation Medication included olanzapine, risperidone, and clozapine.

^aInformation was unavailable for two patients.

^bThough there was some age range in the participants, no statistically significant age effects were found in any of the data analyses.

Table 2
Performance (Means and Standard Deviations) on the Spatial WM Task: Reaction Time (RT) and Percent Correct

	Controls (11)	Patients(13) [†]
RT (ms)		
2-target task	1348(339)	1845(593)
4-target task	1465(390)	2119(657)
% Correct		
2-target task	.85 (.12)	.77 (.15)
4-target task	.77(.05)	.71 (.13)

[†] Note that one patient only did the 4-target task.