Abnormal Parietal Cortex Activation During Working Memory in Schizophrenia: Verbal Phonological Coding Disturbances versus Domain General Executive Dysfunction

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Abstract

Objective: The goal of this study was to determine whether the regions of parietal cortex showing abnormal activation among individuals with schizophrenia during working memory tasks were those associated with either: 1) phonological coding processes that may be specific to verbal tasks (i.e., ventral inferior parietal cortex); or 2) domain general executive processes engaged by verbal and non-verbal tasks (i.e., dorsal inferior parietal cortex). Method: Participants were 57 medicated individuals with schizophrenia and 120 healthy controls matched to patients on age, gender and parental education. FMRI was used to scan all participants during the performance of both verbal (word) and non-verbal (faces) 2-back working memory tasks. Results: In healthy controls there was bilateral dorsal inferior parietal cortex activation during the verbal and non-verbal working memory tasks, but left greater than right ventral parietal cortex activation during verbal as compared to non-verbal working memory. Individuals with schizophrenia as compared to healthy controls showed bilateral deficits in activation of dorsal parietal regions during both verbal and non-verbal working memory tasks. There were no significant group differences in the activation of the left ventral parietal cortex and the individuals with schizophrenia demonstrated the typical pattern of greater activity to verbal as compared to non-verbal working memory in this region. Conclusions: These results support the hypothesis that working memory deficits in individuals with schizophrenia reflect deficits in the activation of brain regions associated with the central executive components of working memory rather than domain specific storage buffers such as the articulatory loop.
Introduction

Individuals with schizophrenia have deficits in working memory (WM) (1), defined as the ability to maintain and manipulation information over a short period of time (2). However, there is still controversy as to whether a deficit in central executive processing or domain specific storage buffers underlies the deficit in WM (1, 3). A number of studies have examined the integrity of brain systems necessary for WM in schizophrenia, using a variety of functional imaging techniques. One of the most consistent findings is the presence of abnormal activation of the dorsolateral prefrontal cortex (4). However, abnormal activation of the parietal cortex has also been observed in individuals with schizophrenia during WM tasks (4), and a more detailed examination of this region may help to resolve the controversy regarding the underlying basis of WM deficits in individuals with schizophrenia. In healthy individuals, there are at least two functionally dissociable subregions of the parietal cortex that can be activated during verbal WM tasks, which likely support different subcomponents of WM. The goal of this study was to identify which of these parietal subregions has abnormal activation during WM tasks in schizophrenia and therefore to determine which subcomponent of WM is abnormal in individuals with schizophrenia.

An influential model of WM but forth by Baddeley (2) postulates that WM has subcomponents that include; 1) a short-term storage buffer for visual information that is often referred to as the visuo-spatial scratch pad; 2) a short-term storage buffer for verbal information referred to as the phonological loop; and 3) a central executive component that guides the manipulation and transformation of information held within the storage buffers. The phonological loop (as well as the other components) can be further subdivided into at least two subcomponents: 1) the articulatory rehearsal of phonologically based representations; and 2) the
processing, coding, or storage of phonological representations. A number of studies suggest that articulatory rehearsal is particularly dependent on regions of left ventrolateral prefrontal cortex (VLPFC), including Brodmann’s areas 44 and 45 (5-10). In contrast, the processing, coding, or storage of phonological representations is thought to be dependent on regions of left posterior parietal cortex (e.g.,11, 12-16).

There may also be at least two functionally dissociable regions of the left posterior parietal cortex that are responsive during WM tasks (10). One of these regions, referred to as left ventral inferior parietal cortex (VIPC) by Fiez and colleagues, is thought to be a region that supports coding of phonological representations (10). This region is significantly more responsive in verbal as compared to non-verbal WM tasks (10, 17), is responsive in non-WM tasks that do require phonological coding (6, 18), and does not show increased activity as WM load increases (10). According to Fiez and colleagues (10), the location of this region (using coordinates in Talairach Space) is: 1) a \( z \) between 10 to 30 mm; a \( y \) of –27 mm (+-15mm), and a \( x \) –52 (+-15mm). If individuals with schizophrenia were to have functional activation disturbances in this VIPC region, it would suggest an impairment in language related processes that may not be specific to WM. A second more dorsal region of left parietal cortex, referred to as DIPC, is also responsive in verbal WM tasks. However, this region is also responsive to non-verbal WM tasks (as is its right homologue), does not consistently show greater activity for words than faces, increases activity as a function of WM load (10, 19), and is also responsive in tasks thought to require executive function more generally (10, 20-22). According to Fiez and colleagues (10), the location of this region is: 1) a \( z \) between 32 to 52 mm; a \( y \) of -51 mm (+-15mm), and a \( x \) –34 (+-15mm). If individuals with schizophrenia were to show functional
activation deficits in this DIPC region, it would suggest central executive related disturbances
that may impair both verbal and non-verbal WM function.

A recent meta-analysis concluded that individuals with schizophrenia show consistent
impairments across material types within WM (1), and a number of researchers have suggested
that the primary dysfunction leading to WM disturbances in schizophrenia arises from a defect of
central executive function (13, 23, 24). However, other researchers have suggested that
individuals with schizophrenia show a differential impairment in verbal WM, possibly caused by
a disturbance in the phonological loop (25, 26). Functional neuroimaging studies of WM in
individuals with schizophrenia consistently report abnormal dorsolateral prefrontal cortex
activation (4). Given that many researchers believe that this brain region is critical for a number
of executive functions, such findings are consistent with the hypothesis that WM impairments in
schizophrenia reflect, at least in part, deficits in central executive function. Further, few studies
of WM report impaired activation in left ventrolateral prefrontal cortex (VLPFC), region
associated with articulatory rehearsal. However, as reviewed in (4), many (11-16, 27), but not
all (28-36), WM studies in schizophrenia also report abnormal activation of the posterior
parietal cortex.

To date, it has not been clear whether the parietal regions that show abnormal activation
in schizophrenia correspond to the DIPC or VIPC (or both). Barch (4) plotted the coordinates of
the parietal regions showing abnormal activation in WM studies in schizophrenia in relationship
to the DIPC and VIPC regions characterized in (10), but the regions of abnormal activation in
schizophrenia did not clearly fall into either of these regions. There are a number of reasons why
prior studies of WM in schizophrenia have not clearly shown which parietal regions are
abnormally active in schizophrenia during WM tasks. Most relevant is that fact that the majority
of WM studies in schizophrenia have used only one material type, precluding the ability to identify parietal regions that are sensitive to material type (e.g., greater activation for verbal as compared to non-verbal WM). In three studies that did compare verbal and non-verbal WM, it was also not possible to implicate either the DIPC or the VIPC. Walter and colleagues did not find any parietal regions that showed group differences in activation during WM (31). Barch and colleagues found bilateral parietal regions that showed impaired activation in both working and episodic memory tasks, but these regions were somewhat inferior to the canonical coordinates for DIPC, and more posterior and medial than the canonical coordinates for VIPC (13).

The goal of the current study was provide further evidence regarding the pattern of parietal cortex activation (i.e., DIPC versus VIPC) during WM in individuals with schizophrenia. Using data from two prior studies of verbal and non-verbal WM in schizophrenia, we first sought to replicate previous findings of left VIPC activation in healthy individuals that was more responsive to verbal than non-verbal WM as well as DIPFC activation (either left or bilateral) that was equally responsive to both verbal and non-verbal WM. Second, we examined whether individuals with schizophrenia showed abnormal parietal activation in response to both verbal and non-verbal WM demands. Lastly, we examined whether individuals with schizophrenia showed the material sensitive activation in left VIPC.

**Methods**

**Participants**

Participants were 120 healthy controls and 57 individuals with DSM-IV schizophrenia, drawn from two prior studies of WM related changes in brain activation in schizophrenia (37). Participants with schizophrenia were recruited from the St. Louis Metropolitan Psychiatric Center and its outpatient clinics. Healthy control participants were recruited using local
advertisements in the same community as the individuals with schizophrenia. Potential participants were also excluded for presence of any of the following: (a) meeting DSM-IV criteria for substance abuse (severe) or dependence (any type) within the past 3 months; (b) the presence of any clinically unstable or severe medical disorder, or a medical disorder that would confound the assessment of psychiatric diagnosis or render research participation dangerous; (c) head injury (past or present) with documented neurological sequelae or resulting in loss of consciousness; (d) meeting DSM-IV criteria for mental retardation (mild or greater in severity); and (e) lifetime history of Axis I psychiatric disorder or any first-degree relative with a psychotic disorder (for controls). Demographic information is displayed in Table 1, which shows that the controls and the individuals with schizophrenia did not differ in parental education, or handedness. Controls were slightly younger than individuals with schizophrenia (mean of 4 years). However, analyses conducted on a subsample of 112 controls and 56 individuals with schizophrenia matched on age did not differ from the results with the full sample described below.

Diagnostic information was collected by a Master’s level research assistant using the Structured Clinical Interview for DSM-IV (SCID-IV; Spitzer et al., 1990) and all available information from hospital records and corroborative family sources. In addition, an expert clinician conducted a semi-structured interview, also using DSM-IV criteria and all available records. A consensus meeting between the SCID-IV interviewer and the expert clinician determined the participant’s final diagnosis. Handedness was assessed using the Edinburgh Handedness Inventory (Oldfield, 1971).

Tasks and Materials
Participants in both studies performed the same version of the “2-back” task while being scanned (13, 37). Stimuli appeared one at a time on the screen and participants were told to push one button any time they saw a stimulus that was the same as the stimulus they saw two trials back, and a different button if not. Stimuli for the verbal tasks were concrete visually presented words, 3-10 letters in length, presented in 48 point Geneva font. Stimuli for the non-verbal tasks were non-nameable faces. Each WM task run lasted 4.25 minutes, and included 4 task blocks of 16 trials each (40 seconds) and 3 fixation blocks of 10 trials (25 seconds) each interleaved in alternating order. There were also 4 fixation trials at the beginning of each run that were discarded in the analysis of the data (used to allow MR signal to reach steady state) and 4 additional fixations at the end. Participants also completed verbal and non-verbal encoding tasks, which we used as low WM load conditions against which to compare the 2back conditions. In study 1, this was intentional encoding task, in which participants were told to remember a series of items for a later memory test. In study 2, this was an incidental task in which participants were told to either make abstract/concrete judgments (words) or gender judgments (faces). The results in terms of the 2back-encoding comparisons were similar for study 1 and study 2. Thus, data from the two studies were combined. The order in which participants performed the verbal versus non-verbal version of the n-back task was counterbalanced across participants.

Scanning

All scanning was performed on the 1.5T Siemens VISION system at the Research Imaging Center of the Mallinkrodt Institute of Radiology at the Washington University Medical School. In both studies, the functional data were collected in runs using an asymmetric spin-echo echo-planar sequence sensitive to blood oxygenation level-dependent (BOLD) contrast (T2*) (TR = 2500ms, TE = 50ms, FOV = 24cm, flip=90°). During each functional run, 102 sets of
Oblique axial images were acquired parallel to the anterior-posterior commissure plane (3.75x3.75 mm in plane resolution). In study 1, sixteen 8 mm think slices were acquired in each image and the imaging parameters were: For study 2, nineteen 7 mm thick slices were acquired in each image. The imaging parameters were: TR = 2500 ms; TE = 50 ms; FOV = 24 cm; flip=90°. Structural images were acquired using a coronal MP-RAGE 3D T1-weighted sequence (TR=9.7 ms, TE=4 ms, flip=10°; voxel size=1x1x1.2 mm). These structural images were used for between subject registration (as described below) and anatomic localization.

A number of preprocessing steps were completed prior to statistical analyses: (1) compensation for slice-dependent time shifts; (2) elimination of odd/even slice intensity differences due to interpolated acquisition; (3) realignment of all data acquired in each participant within and across runs to compensate for rigid body motion (39); (4) intensity normalization to a whole brain mode value of 1000; and (5) spatial smoothing with an 8-mm FWHM Gaussian kernel. The functional data were transformed into the stereotaxic atlas space of Talairach and Tournoux (1988) by computing a sequence of affine transforms and then resampled to 3 mm cubic voxels.

**Statistical Analysis**

For each participant, we estimated the magnitude of task-related activation in each voxel using a general linear model (GLM) using a box-car function convolved with a canonical hemodynamic response, with separate estimates for each material type (e.g., WM-words, WM-faces). These estimates were then entered into appropriately designed ANOVAs and t-tests (described in more detail below) that treated subjects as a random factor. Images were subjected to a stringent threshold to control for false-positive rate. We used a cluster-size threshold of 10 contiguous voxels and a per-voxel alpha of .000625 or less. The analyses presented below were
conjunction analyses, in which we required multiple effects to be significant simultaneously. Each effect was required to be significant at a p-value threshold of .025, resulting in a combined significance of 0.000625 (.025*.025) for each voxel when two conjunctions were required, and a combined significance of 0.000016 (.025*.025*.025) when three were required. Such procedures have been used previously on a number of occasions and are described in detail elsewhere (40).

Results

Behavioral Data

The results of analyses of the behavioral data for the WM tasks have been reported previously (13, 37). For both studies, the individuals with schizophrenia performed less accurately than the controls on both the verbal and non-verbal WM tasks, with no interaction with material type (i.e., equally impaired accuracy for verbal and non-verbal WM).

Material Sensitive Parietal Activations

To identify regions that were more responsive to verbal than non-verbal processing demands, we used the conjunction of three effects: 1) the region was significantly more responsive to task as compared to fixation for verbal WM, using voxel-wise dependent sample t-tests; 2) the region was significantly more responsive to verbal compared to non-verbal WM, using voxel-wise dependent sample t-tests; and 3) no significant differences between WM and encoding. We first conducted these analyses for controls alone. As shown in Table 2 and Figure 1, we found clear evidence for a number of parietal regions that were more active for verbal as compared to verbal WM, two of which clearly correspond to the left VIPC area identified by Fiez. However, we also found additional more dorsal parietal regions showing similar patterns of activity. We repeated these same analyses in the individuals with schizophrenia. As shown in
Table 2 and Figure 1, the individuals with schizophrenia also showed a number of parietal regions that were more responsive verbal than non-verbal WM, one in VIPC and one in DIPC.

To identify regions that were responsive to WM load, we used the conjunction of four effects: 1) the region was significantly more responsive to task as compared to fixation for verbal WM; 2) the region was significantly more responsive to task as compared to fixation for non-verbal WM; 3) the region was significantly more responsive to verbal WM as compared to verbal encoding; and 4) the region was significantly more responsive to nonverbal WM than nonverbal encoding. As shown in Table 3 and Figure 2, we found robust activity for this analysis in both left and right DIPC among controls, although we also found a small right VIPC region showing a similar pattern. We repeated these analyses on the individuals with schizophrenia and again found bilateral DIPC regions that showed significantly greater activity in both verbal and non-verbal WM.

To look for group differences in the regions identified above that were more responsive to verbal as compared to non-verbal WM, we used the conjunction of the following three effects: 1) the region showed significantly different activity between individuals with schizophrenia and controls in verbal WM (using independent sample t-tests); 2) the region was significantly more responsive to verbal as compared to non-verbal WM in either controls or individuals with schizophrenia.
schizophrenia; and 3) the region was significantly more responsive to task as compared to fixation for verbal WM in either controls or individuals with schizophrenia. Given that the later two effects were identical to those used to identify VIPC regions within each group separately, this analysis essentially examined group differences in the regions presented in Table 2. This analysis revealed only one region in which activity differed significantly between individuals with schizophrenia and controls (BA 40, X = -24, Y = -59, Z = 32). This region was the left DIPC, which showed greater activity in individuals with schizophrenia as compared to controls.

To look for group differences in the DIPC regions identified above that were equally responsive to verbal and non-verbal WM, we used the conjunction of the following three effects: 1) the region showed significantly different activity in individuals with schizophrenia and controls in verbal WM; 2) the region showed significantly different activity in individuals with schizophrenia and controls in non-verbal WM; 3) the region was significantly more responsive to task than fixation in both verbal and non-verbal WM, in either individuals with schizophrenia or controls and 4) the region was significantly more responsive to WM than encoding for both verbal and non-verbal materials, in either controls or individuals with schizophrenia. Given that the later two effects were identical to those used to identify DIPC regions within each group separately, this analyses examined group differences in the regions presented in Table 3. This analysis revealed two regions whose activity differed significantly between individuals with schizophrenia and controls; i.e., the left DIPC (BA 40, X = -24, Y = -61, Z = 33) and right DIPC (BA 40; X = 23, Y = -60), Z = 36). In both regions, controls exhibited significantly greater task related activity than individuals with schizophrenia for both verbal and non-verbal WM.

Discussion
The results of the current study provide further evidence for the presence of at least two regions of the parietal cortex that play different roles in WM. Like Fiez and colleagues (10), we found that the bilateral DIPC showed greater activity in high versus low WM load conditions, but did not consistently show greater activity in verbal than non-verbal WM. In contrast, the left VIPC showed robustly stronger activity in verbal as compared to non-verbal WM, but did not show greater activity for high load as compared to low load conditions. These findings are consistent with the suggestion that the VIPC plays a role in phonological processing (10), while the DIPC is associated with a frontal-parietal executive system (10, 20-22, 41).

Our results also suggest that the VIPC and DIPC show differential impairments in individuals with schizophrenia. In individuals with schizophrenia, we found a left VIPC region that was more responsive to verbal than non-verbal WM, but not more responsive to high than load WM loads. In addition, small bilateral regions of DIPC were more responsive to high than low WM loads, though not necessarily more response to verbal than non-verbal WM. When we conducted direct group contrasts, however, we only found evidence for altered task-related activation in the bilateral DIPC regions and not in the left VIPC. More specifically, the bilateral DIPC regions showed reduced activation among individuals with schizophrenia during both the verbal and non-verbal WM tasks as compared to controls. Given hypotheses that the DIPC is involved in a frontal-parietal executive system, such results are consistent with the hypothesis that the primary WM deficit in individuals with schizophrenia involves a disturbance of central executive function (1, 13, 42, 43). Further, the fact that individuals with schizophrenia and healthy controls showed the same pattern of VIPC activation suggests that schizophrenia does not involve a specific deficit in the verbal aspects of WM, as suggested by others (3, 26).
Finding impaired activation among individuals with schizophrenia in a region of parietal cortex thought to be part of a frontal-parietal executive system is consistent with numerous prior reports of altered functional connectivity between frontal and parietal regions among individuals with schizophrenia (11, 44-46). Notably, the regions of parietal cortex showing altered functional connectivity with frontal cortex in these prior studies were in the DIPC area described by Fiez (10) and identified as impaired in schizophrenia in the current study. Taken together, such findings raise interesting questions about the role of a disturbance of DIPC function and executive control processes during WM tasks in schizophrenia. One hypothesis is that the DIPC makes a specific contribution to the temporal coding of items within WM using magnitude codes (20) in coordination with the dorsolateral prefrontal cortex (47) and that it is this coordinated activity of the DIPC and dorsolateral prefrontal cortex that is disturbed in schizophrenia. Such a hypothesis is supported by recent evidence that individuals with schizophrenia have difficulties coding the temporal order of items within a WM task (37). However, further work will be needed to establish a tighter link between deficits in the temporal coding of order in WM among individuals with schizophrenia and disturbances in the functional activation and connectivity of DIPC.

There were several limitations to the current study. First, we did not have an explicit manipulation of load within the WM task, such as directly comparing 0, 1 and 2 back levels of the Nback task. Inclusion of such a parametric manipulation of load along with a manipulation of material type in future studies would help to further establish the presence (or absence) of differential deficits in DIPC versus VIPC among individuals with schizophrenia. A second limitation was that all individuals with schizophrenia were currently taking antipsychotic medications, and it is not clear what influences this could have on parietal cortex activity.
However, *a priori* one would not necessarily predict that DIPC versus VIPC regions of parietal cortex should be differentially sensitive to the influence of antipsychotic medication. A third potential limitation was that there were more males among the individuals with schizophrenia than among the controls. However, reanalysis of the data with gender as an addition factor did not change the results, and gender did not interact with group. Further, recent work from our lab has demonstrated that males and females show the same patterns of material sensitive activation in both frontal and parietal cortex (48), suggesting that sex differences should not alter patterns of material sensitive activity.

In summary, the current study replicated previous findings that the DIPC is sensitive to load in a WM task, but not to material type effects, and that the VIPC is sensitive to material type but not load. Further, the current study provided evidence that the regions of parietal cortex impaired during WM tasks among individuals with schizophrenia correspond to the DIPC, which is thought to be involved in a frontal-parietal executive control network that supports that temporal coding of items within WM. Further research is needed to establish whether or not DIPC activation deficits among individuals with schizophrenia are specifically related to deficits in the temporal orders of items in WM.
Table 1

**Clinical and Demographic Characteristics**

<table>
<thead>
<tr>
<th>Group</th>
<th>Healthy Controls</th>
<th>Patients with Schizophrenia</th>
<th>T-Test ($X^2$)</th>
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</thead>
<tbody>
<tr>
<td>M</td>
<td>SD</td>
<td>M</td>
<td>SD</td>
</tr>
<tr>
<td>---</td>
<td>----</td>
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<td>----</td>
</tr>
<tr>
<td>Age (in years)</td>
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<td>31.5</td>
<td>t(175) = 2.48, $p &lt; .05$</td>
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<td>72</td>
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<tr>
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<td>85.7</td>
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<tr>
<td>Parent's Education (in years)</td>
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<td>13.7</td>
<td>t(175) = 1.6, $p &gt; .10$</td>
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<tr>
<td>Education (in years)</td>
<td>14.0</td>
<td>12.5</td>
<td>t(175) = 3.37, $p &lt; .01$</td>
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<td>Disorganization Symptoms</td>
<td>-----</td>
<td>2.3</td>
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</tr>
<tr>
<td>Reality Distortion Symptoms</td>
<td>-----</td>
<td>3.3</td>
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<tr>
<td>Poverty Symptoms</td>
<td>-----</td>
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Table 2. Left Parietal Regions Demonstrating Greater Activity in Verbal than Nonverbal Working Memory

<table>
<thead>
<tr>
<th>Regions of Interest</th>
<th>Brodmann Area(s)</th>
<th>Xa</th>
<th>Ya</th>
<th>Za</th>
<th>Volume In 3mm³ voxels</th>
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<td>Healthy Controls</td>
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<tr>
<td>Left Dorsal Parietal Cortex (DIPC)</td>
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<td>-43</td>
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a X, Y, and Z are coordinates in a standard stereotactic space (49)(47)(47)(48)(46)(49) in which positive values refer to regions right of (X), anterior to (Y), and superior to (Z) the anterior commissure (AC).
Table 3. Left Parietal Regions Demonstrating Greater Activity in Working Memory than Encoding

<table>
<thead>
<tr>
<th>Regions of Interest</th>
<th>Brodmann Area(s)</th>
<th>Xa</th>
<th>Ya</th>
<th>Za</th>
<th>Volume In 3mm³ voxels</th>
</tr>
</thead>
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<td>Healthy Controls</td>
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<td>Individuals with Schizophrenia</td>
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a X, Y, and Z are coordinates in a standard stereotactic space (49)(47)(47)(48)(46)(49) in which positive values refer to regions right of (X), anterior to (Y), and superior to (Z) the anterior commissure (AC).
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**Figure Captions**

Figure 1: Regions demonstrating greater activity in word than face working memory, but which did not show greater activity in high than low working memory load. The top row shows regions identified in healthy controls, the middle rows show regions identified in individuals with schizophrenia, and the bottom row shows regions that demonstrated significantly different activity between controls and individuals with schizophrenia. Slices are oblique axial slices through the brain, and the Z coordinates at the top of the figure represent mm above the AC/PC line in Talairach space.

Figure 2: Regions demonstrating greater activity in high than low working memory load. The top row shows regions identified in healthy controls, the middle rows show regions identified in individuals with schizophrenia, and the bottom row shows regions that demonstrated significantly different activity between controls and individuals with schizophrenia. Slices are oblique axial slices through the brain, and the Z coordinates at the top of the figure represent mm above the AC/PC line in Talairach space.
Z = +30  Z = +24  Z = +18  Z = +12  Z = +6

Controls

Schizophrenia

Control > Schizophrenia
Z = +48  Z = +42  Z = +36  Z = +38

Controls

Schizophrenia

Control > Schizophrenia